

## The OECD policy for the implementation of the principles of good laboratory practice

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**Summary.** - OECD has been involved in the harmonisation of policies and instruments for chemicals control since the late 1970's. The OECD principles of good laboratory practice (GLP) were developed and subsequently adopted by the Council in 1981. These principles have the primary objective of ensuring the generation of high quality test data. They set out managerial concepts covering the organisation of test laboratories as well as the conditions under which laboratory studies are planned, performed, monitored, recorded and reported. A system of compliance monitoring procedures has been established to ensure that laboratory studies are carried out in member countries according to the principles of GLP. The harmonization and mutual recognition of compliance monitoring methods among member countries have been a crucial step in ensuring the international acceptability of data. This undertaking involved the development of consistent criteria for determining whether a laboratory conducts studies in accordance with the principles of GLP. Training courses are held for GLP inspectors, an activity which lies at the basis of harmonising monitoring procedures. Consensus workshops result in consensus documents on the harmonised application and interpretation of the GLP principles in specific areas or on specific points. This system makes it possible for countries to speak the same language when exchanging information about specific laboratories, and to have confidence in the quality and rigour of safety tests undertaken in a laboratory.

*Key words:* information systems, registers, toxicology, databases.

**Riassunto** (*La linea di condotta dell'OECD per l'adozione dei principi delle buone pratiche di laboratorio*). - Dalla fine degli anni settanta l'OECD si è interessato all'armonizzazione delle linee di condotta e degli strumenti per il controllo delle sostanze chimiche. I principi delle buone pratiche di laboratorio (good laboratory practice, GLP) furono sviluppati e quindi adottati dal Consiglio dell'OECD nel 1981. Questi principi, il cui obiettivo primario è quello di assicurare la produzione di dati sperimentali di alta qualità, partono dai concetti di gestione che interessano tanto l'organizzazione dei laboratori di analisi quanto le condizioni in cui gli esami di laboratorio sono pianificati, eseguiti, osservati, registrati e trascritti. È stato stabilito un sistema di procedure di monitoraggio della conformità allo scopo di assicurare che gli esami di laboratorio siano eseguiti nei paesi membri in accordo con i principi delle GLP. Cruciali per l'accettazione internazionale dei dati sono stati lo scambio e la mutua accettazione dei metodi di monitoraggio della conformità fra i paesi membri. Questo impegno ha comportato lo sviluppo di criteri coerenti per poter stabilire se le analisi eseguite da un determinato laboratorio siano in accordo con i principi delle GLP. I corsi di formazione sulle GLP, tenuti da ispettori dell'OECD, costituiscono una attività fondamentale dell'armonizzazione delle procedure di monitoraggio. Consensus documents sull'applicazione e sull'interpretazione dei principi delle GLP in specifiche aree o su specifici problemi originano da consensus workshops. Questo sistema fa sì che paesi diversi possano parlare lo stesso linguaggio allorché si verifichi uno scambio di informazioni fra laboratori e che si abbia certezza della qualità e del rigore con cui sono stati eseguiti gli esami.

*Parole chiave:* sistemi di informazione, registri, tossicologia, database.

### Introduction

OECD has been involved in the harmonisation of policies and instruments for chemicals control since the late 1970's. The guidelines for the testing of chemicals and the principles of good laboratory practice were developed at that time in the broader context of the concept of mutual acceptance of data (MAD). Both of

these instruments for ensuring harmonised data generation and data quality are an integral part of the 1981 Council decision on MAD. OECD's 24 member countries agreed to implement the decision, which states that "data generated in the testing of chemicals in an OECD member country in accordance with OECD test guidelines and OECD principles of good laboratory practice shall be accepted in other member countries for purposes of

(\*) The opinions expressed in this paper are those of the author and do not necessarily represent the views of the OECD or of the governments of the member countries.

assessment and other uses relating to the protection of man and the environment". The practical consequence of this decision is that data, developed in a member country under these conditions and submitted for fulfilling regulatory requirements in another country, cannot be refused, and thus need not be developed a second time.

With the adoption of the GLP principles and the test guidelines in 1981 and, shortly thereafter, the updating programme, the basis for harmonised standards was established. Implementation of the test guidelines and the principles in laboratories in member countries was straightforward. Verification by receiving authorities that data were generated in agreement with the test guidelines is relatively simple; however, verification that it was done in compliance with GLP called for another set of procedures to be developed. Here, too, OECD took the lead by adopting a Council recommendation on mutual recognition of compliance with GLP in 1983. This Council recommendation was subsequently replaced by a decision in 1989 which called for the implementation of harmonised national GLP compliance monitoring procedures and made provisions for the mutual recognition of compliance among member countries [1-8].

All of these practical instruments and policy statements have played a significant role in international harmonisation. However, the mutual acceptance of data is based on a concept that cannot be defined in Council acts and national legislation, i.e. confidence in the procedures used in monitoring compliance with GLP in the country of origin of the data. This confidence can only be had through knowledge and understanding of these procedures. Since the mid-eighties OECD has taken on the task of promoting the flow of information which will lead to this knowledge and understanding.

Various fora have been established in OECD to exchange information on specific technical and administrative matters related to the application of GLP principles and the implementation of compliance monitoring procedures. A Panel on GLP comprising representatives of national monitoring authorities for GLP compliance in the fields of industrial chemicals, pharmaceuticals, pesticides, etc. meets at least once a year to oversee the programme on GLP and to develop common positions on administrative issues related to compliance monitoring. Training courses are held for GLP inspectors, an activity which lies at the basis of harmonising monitoring procedures. Consensus workshops result in consensus documents on the harmonised application and interpretation of the GLP principles in specific areas (such as field or short-term studies) or on specific points (such as quality assurance or the role of suppliers). Recently a new aspect has been added to OECD activities on GLP: outreach to eastern Europe and other non-member countries, based on training seminars held by the GLP Panel for industry and government on implementation of GLP principles and compliance monitoring procedures.

In addition to these technical aspects of GLP compliance, the Panel endeavours to find solutions to problems related to acceptance of the results of compliance monitoring between member countries. In this context, the Panel is currently developing criteria and procedures to review implementation in member countries of the 1989 Council act on compliance with GLP.

## OECD

The OECD is an intergovernmental organisation grouping 24 industrialised countries. Its main task is to monitor economic trends in those countries. The basic aims of the OECD are described in the first article of its founding convention signed in 1960. They are "to promote policies designed: a) to achieve the highest sustainable economic growth and employment and a rising standard of living in member countries, while maintaining financial stability, and thus to contribute to the development of the world economy; b) to contribute to sound economic expansion in member as well as non-member countries in the process of economic development; and c) to contribute to the expansion of world trade on a multilateral, non-discriminatory basis, in accordance with international obligations".

At first glance, differences and disparities among the 24 member countries of the OECD may seem quite marked. The United States, for example, have a thousand times as many inhabitants as Iceland. Belgium and Luxembourg rely on exports of goods and services for 60 per cent of their national income, the United States for only 10 per cent. Thirty per cent of the labour force in Greece works on farms as against less than 3 per cent in the United Kingdom. But member countries are linked by a community of interests, common problems, a commitment to the market economy, a democratic system and - because of their combined economic weight - common responsibilities to the world at large.

Reflecting shared views and strong historic ties, the Organisation acts through consensus. The common approach to public policy of the OECD countries means that their discussions generally yield consensus. The OECD's supreme authority is the Council, in which representatives of all member countries participate under the chairmanship of the OECD Secretary-General. Meetings of the Council are normally attended by each country's permanent representative, who has the rank of ambassador. The Commission of the European Communities also takes part in these meetings. Once a year, the Council meets at ministerial level, chaired by one member country, and brings together ministers of foreign affairs, finance, trade and other leaders. Actions are taken concerning the main economic and social issues facing member countries. These serve as a guide for the Organisation's future work and give it political impetus.

OECD is not a supranational organisation, but a center for discussion where governments express their points of view, share their experiences and search for common ground. The Secretariat provides the basis by setting forth the problems and possible remedies.

More specifically, what the OECD does is:

- to clarify through quantitative and qualitative analyses, the economic and social problems facing its member countries;
- to exchange information on how the problems are being approached in country so that the experience of one can inform the actions of the others;
- to analyze the effectiveness of economic and social policies;
- through discussion, to make countries aware of the impact of their actions on the others;
- to search for common solutions or strategies.

Within OECD, many of the agreements reached are informal and unpublicised, but, if member countries consider it appropriate, the accord can be embodied in more formal actions provided for in OECD's convention or developed since. Generally, these actions are taken unanimously by consensus. "Rules of the game" are established as are codes of behaviour to which participating countries formally bind themselves. An example of a binding decision of the Council is the 1981 decision on the mutual acceptance of data, with its test guidelines and GLP principles, which will be discussed below.

More often, the consensus will be reflected in a recommendation of OECD's Council. The 1989 act on compliance with GLP is an example of a decision-recommendation. Member countries may also adopt declarations such as the 1979 "Declaration on anticipatory environmental policies", which gave impetus to the subsequent development of instruments to anticipate and control the effects of new chemicals (like the minimum premarketing set of data, the test guidelines and the GLP principles).

Within the OECD are more than 150 committees, working parties and expert groups, covering a wide range of subjects, some broad in scope, others technical and highly specialised. Countries are usually represented on the over 20 Committees by delegates from various parts of their national administrations who travel to Paris for meetings. These experts from capitals become part of a broad international multidisciplinary network.

An independent corps of experts drawn from the 24 member countries and from many disciplines, OECD's Paris-based secretariat supports the Council and Committees in their work. The Secretary-General is assisted by three deputies and a staff of over 1,800 of which about 600 are professionals. They are organised into specialised directorates and support staff, supplemented by consultants drawn from universities, business, banks and governments.

The Commission of the European Union generally participates in the work of OECD under a protocol signed at the same time as the OECD convention. The European Free Trade Association (EFTA) may also send representatives to OECD meetings. There are also official relations with International Labour Organisation (ILO), Food and Agriculture Organisation (FAO), International Monetary Fund (IMF), World Bank, General Agreement on Tariffs and Trade (GATT), International Atomic Energy Agency (IAEA) and a large number of United Nations organisations (like the International Programme on Chemical Safety). Special arrangements establishing close links with Council of Europe were concluded in 1962.

International non-governmental organisations (NGOs) deemed to be widely representative in general economic matters or in a specific economic sector can be granted consultative status, under a decision of the Council of 13 March 1962. This enables them to discuss subjects of common interest with a Liaison Committee chaired by the Secretary-General; they may also be consulted in a particular activity by the relevant OECD Committee or its officials. To date, this consultative status has been granted to: the Business and Industry Advisory Committee to the OECD (BIAC), the Trade Union Advisory Committee to the OECD (TUAC), the International Association of Crafts and Small and Medium-sized Enterprises, the International Federation of Agricultural Producers, and the European Confederation of Agriculture.

Since 1989, OECD has begun several programmes to assist central and Eastern European economies in transition. A special "Partners in transition" programme has been established with Poland, Hungary and Czechoslovakia. Representatives of those countries can participate as observers in the OECD committees and working groups.

#### *Environmental Policy Committee*

In recent years, OECD countries have increasingly developed policies legislation and institutions to maintain and improve the environment, in order to ensure a high qualitative (as well as quantitative) standard of living. The variety and potential magnitude of effects on the local, national and global environment stemming from activities in OECD countries have underscored their special responsibility in regard to the state of the environment and the need for coordinated action. In 1970, the Council, realizing the need for cooperation of governments to promote environmental quality, established the Environmental Committee (which since 1992 is called the Environmental Policy Committee).

Since then, governments have responded individually with new laws and regulations and through OECD have taken a common position on a number of key issues.

The Council has made specific recommendations and decisions on the economic, legal and scientific aspects of environmental management. The well-known "polluter-pays" principle, which originated in OECD, has been accepted by all OECD member countries, as has the concept of "prevention is better than repair".

OECD has also urged its members to reduce air pollution which leads to acid rain, photochemical smog and global warming, and has been providing member countries information on the costs of abatement and the benefits in the form of reduced damage.

OECD has also made recommendations or decisions on noise abatement, water management, transfrontier pollution and the control of international shipment of hazardous wastes and has developed a series of environmental indicators which include positive marks for prudent management of resources. Since OECD member countries produce the lion's share of the world's chemicals, the Organisation has proved to be one of the most effective fora for international efforts to deal with the hazards created by these substances.

The Environmental Policy Committee now has four main subsidiary groups, each with its own array of expert groups, advisory bodies, panels, etc. The structure continues to evolve in response to member countries' major environmental concerns. Some of the subsidiary bodies are long-standing and address general areas of environmental knowledge and experience of the member countries, and direct them towards the analysis of common problems and the identification of practical solutions. The Chemicals group is, of course, one of these. There are also groups on pollution prevention and control, state of the environment and economics and the environment.

### Chemicals programme

Problems related to contamination of the environment by chemicals are dealt with in OECD through a specific programme on chemicals. This work began in 1971 under the Chemicals group, which at that time concentrated on concerted action by member countries on the control of several specific, very persistent, chemicals (PCBs, mercury, cadmium, CFCs).

It was soon recognised, however, that dealing with a few specific chemicals per year was not sufficient to protect man and the environment from exposure to those hazardous chemicals which were not already covered in a regulatory framework in member countries. In the early 1970's several countries were already developing policies for routine scrutiny of chemicals before marketing and use, in order to avoid the inadvertent loss of harmful chemicals to the environment. At this time countries began to be concerned that the emerging, and potentially differing, national chemicals policies might bring about distortions in international trade among OECD countries

and that the efforts in each country to assess a chemical's potential hazards might be unnecessarily duplicative. Thus, OECD work on chemicals soon moved away from reactive, concerted action on specific hazardous chemicals to the development of the policies and technical instruments needed to support more broadly-based proactive approaches to chemicals control.

This ambitious agenda led to the creation in 1978 of a larger special extra-budgetary programme on the control of chemicals in OECD. Together with the Chemicals group, the management committee of this special programme on the control of chemicals works under the umbrella of the Environmental Policy Committee to carry out the work related to the international dimensions of protecting health and the environment from the potential hazards of chemicals. It also oversees work on chemical accidents, safety in biotechnology and pesticides.

As one of the first priorities under the special programme, member countries recognised the need to encourage the generation of valid and high quality test data for chemicals assessments. This issue became central to the work of the chemicals programme. Countries were concerned about the cost burdens associated with testing and the need to utilise more effectively scarce test facilities and specialist manpower. The possible duplication of effort, as well as the potential barriers to trade, which could result if member countries had different test procedures and standards for laboratory conduct, were also recognised.

### MAD decision

OECD has been involved in the harmonisation of policies and instruments for chemicals control since the late 1970's. The guidelines for the testing of chemicals and the principles of good laboratory practice were developed at that time in the broader context of the concept of mutual acceptance of data (MAD). Both of these instruments for ensuring harmonised data generation and data quality are an integral part of the 1981 Council decision on MAD. OECD's 24 member countries agreed to implement the decision, which states that "data generated in the testing of chemicals in an OECD member country in accordance with OECD test guidelines and OECD principles of good laboratory practice shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment". The practical consequence of this decision is that data, developed in a member country under these conditions and submitted for fulfilling regulatory requirements in another country, cannot be refused, and thus need not be developed a second time.

"Harmonisation" means more than using the same standards for laboratory testing and management and having legal instruments on the books which state that data developed under these standards must be accepted.

It means that the whole system of verification of compliance with the GLP principles needs to be harmonised among countries, so that they are speaking a common language when they are exchanging information about laboratories and so that they understand and have confidence in the procedures used for monitoring compliance.

It is not very efficient for countries to carry out GLP inspections abroad to verify compliance with their own national legislation for their own national purposes. With more and more laboratories requesting entrance into national GLP programmes, with more and more countries establishing such programmes, and with more and more areas of testing being done under GLP - for instance, field studies - it is not only not very efficient; it is virtually impossible for national monitoring authorities to personally verify the compliance of foreign laboratories with GLP, except in special situations.

One of OECD's important activities in the past decade has been to promote international harmonisation of the whole GLP system - including the GLP principles, their implementation, the performance of compliance monitoring and information exchange among national monitoring authorities. Only when a working system is completely in place can the quality of test data be assured on an international scale. After adoption of the GLP principles in 1981, OECD began to concentrate on activities to facilitate internationally harmonised approaches to compliance monitoring and assurance.

### Compliance monitoring and assurance

Shortly after the adoption of the MAD decision, a second Council act related to GLP was endorsed. The 1983 recommendation on mutual recognition of compliance with GLP set out the kinds of requirements national GLP compliance monitoring programmes would need to fulfil if they were to be acceptable to other countries. As in all subsequent work in OECD in this area, to be acceptable to other countries was understood as being able to offer guarantees concerning the quality and rigour of test data. This Council act recommended several characteristics to be met in national compliance monitoring programmes; such as their being based on inspections and study audits, designation of a national authority to monitor compliance, and certification by test facilities that studies were carried out under GLP.

This recommendation, together with the MAD decision, provided a good policy basis for ensuring the confidence in the comparability, quality and rigour of national procedures that is necessary for mutual recognition. However, a great deal still needed to be done to assist countries to implement these acts and to actually establish the guarantees necessary for mutual recognition. Common approaches to the technical and administrative issues that underlie GLP compliance and its monitoring

needed to be developed and implemented. A working group on mutual recognition of compliance with GLP began this task in 1985.

From a legal point of view, one of the first things that needed to be done was to strengthen the 1983 Council recommendation. In 1989 a new Council act on compliance with GLP principles was adopted which superseded and replaced the earlier one. Essentially, it requires the implementation of the characteristics of national compliance programmes which were merely recommended in 1983. It also deals with the international aspects of GLP compliance monitoring. It requires designation of authorities for international liaison and exchange of information concerning monitoring procedures and establishes a system whereby information concerning compliance of a specific test facility can be sought by another member country where a good reason exists.

The annexes to the 1989 Council act include the technical and administrative guidance developed by the working group. The first two of these - the *Guidance for GLP monitoring authorities. Guides for compliance monitoring procedures for good laboratory practice*, 2, and the *Guidance for GLP monitoring authorities. Guidance for the conduct of laboratory inspections and study audits*, 3 - have been reprinted in the OECD publication series on GLP [9, 10].

### Current activities

Currently, the work on GLP in OECD is directed primarily at the information exchange aspect of mutual recognition. The philosophy behind this is that the key to recognition of the assurance by a member country that GLP principles have been complied with in generating specific test data is confidence in the procedures used by that country for monitoring compliance. This confidence can, in turn, only be had by knowledge and understanding of these procedures. The role of OECD is to promote the flow of information which will lead to this knowledge and understanding.

This is done through various fora and mechanisms. The OECD Panel on GLP, which comprises representatives of national monitoring authorities dealing with chemicals, pesticides, pharmaceuticals, etc., meets regularly and exchanges information on, e.g., the compliance status of laboratories in their countries. It also oversees the work on the interpretation and application of the GLP principles, harmonisation of compliance monitoring procedures and training of inspectors. Items on the current Panel agenda include discussion, for example, of criteria and procedures for assessing the implementation in member countries of the 1989 Council act in order to further mutual recognition of GLP compliance monitoring procedures; definition of the scope of GLP and its relationship to laboratory accreditation schemes and other issues of a policy nature.

As with most of our work on chemicals, we have found that it is the personal communication among the people in the field from the different areas involved as well as from different countries that is significant. Probably the most important of the fora for information exchange are now the consensus workshops. These workshops are aimed at reaching a common understanding on the content of GLP principles and their application. The workshops have been attended not only by GLP inspectors and representatives of national monitoring authorities, but also by representatives of industry management and quality assurance units. The workshops ultimately result in so-called consensus documents, which undergo a peer review process and are finally endorsed by the OECD Environmental Policy Committee and made public. By establishing a consensus on points to be considered when evaluating various kinds of operations for compliance with GLP, a major step forward is made in international harmonisation.

The first consensus workshop was held in Germany in October 1990, followed by one in the USA in May 1991 and a third one in Switzerland in October 1992. Various areas were identified where clarity needed to be established and agreement reached among the various players involved in assuring and monitoring compliance with GLP principles - industry management and quality assurance units, GLP inspectors and national authorities: quality assurance, compliance of suppliers with GLP and application of GLP to field studies.

Each of the areas needed to be treated in a different way and the resulting consensus documents which resulted show this very well. The consensus document on quality assurance sets out guidance for management to effectively implement the vague GLP requirement to establish documented quality assurance programmes, including such issues as the status, qualifications and training of QA staff, the responsibilities of the QA unit and the content of QA statements.

The consensus document on compliance of suppliers with GLP is a brief one, but it includes an important policy statement on the responsibility of management for the materials and services supplied from outside the laboratory. It helps draw the lines between accreditation schemes and GLP compliance monitoring. The consensus document on the role and responsibilities of the study director in GLP studies discusses the role of management in the appointment and training and the Study Director's qualifications and responsibilities.

The consensus document on application of GLP principles to field studies is much more specific and detailed than the above two. It sets out the OECD principles of GLP and annotates them where there is a need for interpretation in respect to field studies. The document deals with definitions of such concepts as "study", "test facility" and "test system", discusses management's responsibilities in the special context of

field studies; and deals, among others, with the issues of study director and principal investigator, quality assurance in field studies and temporary test sites.

The consensus document on the application of GLP principles to short-term studies deals with a specific interpretation for short-term biological and physical-chemical studies which are repeatedly done by the laboratory and for which single general study plans and standardised final reports are acceptable under certain conditions.

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