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Good laboratory practice in the European Community. Role of the Commission and the member states: external aspects

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Summary. - The paper recalls the history of the development of the OECD principles of good laboratory practice (GLP) and explains why the European Community has a role to play in the area of GLP. It presents briefly the current legal framework in the European Community (Directives 87/18/EEC and 88/320/EEC) and describes the role of the Commission and the member states in the practical implementation of the GLP principles within the European Community. Impacts of GLP on the relations of the European Community with third countries, both within the framework of the OECD and through bilateral trade agreements (mutual recognition agreements, MRA) based on article 133 of the treaty establishing the European Community, are then examined in greater detail.

Key words: good laboratory practice, OECD, principles, European Community, mutual recognition agreements, internal market.

Riassunto *(Buona pratica di laboratorio nella Comunità Europea. Ruolo della Commissione e degli stati membri: aspetti esterni).* - Viene tratteggiata la storia dello sviluppo dei principi di buona pratica di laboratorio (BPL) dell'OECD e si delinea la funzione svolta dalla Comunità Europea in quest'ambito. Si riportano l'attuale quadro normativo (Direttive 87/18/EEC e 88/320/EEC) ed i compiti della Commissione e degli stati membri per l'effettiva adozione dei principi di BPL all'interno della Comunità Europea. Vengono infine descritti gli effetti del sistema BPL sulle relazioni tra la Comunità Europea ed i paesi terzi, sia attraverso l'OECD che per mezzo degli accordi commerciali bilaterali (mutual recognition agreements, MRA) basati sull'articolo 133 del trattato che istituisce la Comunità Europea.

Parole chiave: buona pratica di laboratorio, OECD, Comunità Europea, riconoscimento reciproco, mercato interno.

Introduction

The principles of good laboratory practice. History

The OECD principles of good laboratory practice (GLP) were adopted in 1981 in Annex II of the Decision of the OECD Council on mutual acceptance of data (MAD) [C(81) 30 (Final)]. Their objective is to create an internationally recognised system of quality assurance for test data that are to be used in the evaluation of chemicals with regard to their effects on human health and the environment. The importance of the GLP principles in the international arena is obvious: the assurance of the quality of test data will facilitate the recognition of their validity by the authorities in different countries. This has immediate benefits for companies, which operate in different countries, for all authorities concerned and, last but not least, is a big contribution to animal welfare through the avoidance of multiple testing. After 15 years of application in practice, modifications to the GLP principles were adopted in 1997 [C(97) 186 (Final)].

After the adoption of the MAD Decision, it became clear very quickly that the existence of the OECD principles of GLP alone was not sufficient to actually ensure the acceptance of data. Further measures to enhance the confidence of the authorities in the reliability of the work of the others was necessary, especially regarding the monitoring of the compliance of the test facilities with GLP.

In 1989 *Guides for compliance monitoring procedures for GLP* were adopted and annexed to the OECD Decision-Recommendation on compliance with the principles of GLP [C(89) 87 (Final)]. Annex I contains the *Guides for compliance monitoring procedures of GLP*, which defines the basic elements for national monitoring programmes, and Annex II contains detailed *Guidance for the conduct of laboratory inspections and study audits*. Modifications were adopted in 1995 [1].

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Reasons for the involvement of the European Community

Internal market

From the very beginning, the European Community, all member states of which are also members of the OECD, has participated in the development of the principles of GLP and compliance monitoring for two main reasons, *i.e.*, the creation of the internal market and the common policy for external trade.

Since 1967 the Community has legislative competence in the area of chemicals. The adoption of Directive 67/548/EEC created the internal market for chemicals [2]. The directive has been amended on several occasions and in the course of time a very elaborate system for the testing of chemicals for their effects on human health and the environment was incorporated. Already in 1979, the directive required the testing to be carried out according to "the principles of existing high quality laboratory procedures", which meant the principles of GLP (still under development at that time). This has been made very explicit in subsequent amendments: all tests on chemical substances for whatever regulatory purpose must be carried out according to the OECD principles of GLP and using OECD test guidelines. The objectives of this requirement are twofold:

a) a high level of protection of human health and the environment based on test data of high quality; and

b) the proper functioning of the internal market for chemicals, for which the recognition of data among the member states is of prime importance.

These testing requirements have been extended to all preparations, *i.e.*, mixtures of substances (Directive 1999/45/EC) [3]. They also apply during the testing of the so-called existing substances (chemicals placed on the market before september 1981) in the framework of the risk assessments according to Regulation 793/93 [4]. In the course of time a number of Community directives concerning chemicals for special purposes have been adopted. Many of these require pre-market authorisation or approval, a process in which the assessment of their effects on human health and the environment plays an important role. Such chemicals are, among others, medicinal products for human and veterinary use, plant protection products, biocides, feed additives, chemicals used in foodstuff and cosmetics.

Good laboratory practice in the European Community

Legal framework and practicalities

The legal framework for GLP in the EC has been established through two basic directives:

a) Directive 87/18/EEC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of GLP and the verification of their applications for tests on chemical substances [5]. The Directive makes the principles of GLP compulsory for the member states during the testing of chemicals and already stipulates certain minimum requirements for compliance monitoring. The directive was amended in 1999, taking into account the modifications of the GLP principles adopted by the OECD in 1997 [6];

b) Directive 88/320/EEC on the inspection and verification of GLP [7]. The Directive defines with greater precision the obligations of the member states regarding GLP compliance monitoring and in its Annex contains the OECD guidance documents on this matter. This Directive was also last amended in 1999, following the Acts of the OECD from 1995 [8].

As always in the application of EU legislation, the Commission has to ensure the correct and uniform application in all member states of the directives and to this end a number of activities have been started, *i.e.*:

a) regular meetings of the experts from the member states in the so-called Working group on GLP. This group meets to discuss all aspects of implementation of the directives, especially those where deviations and problems are observed, but also more technical aspects of the principles themselves;

b) maintenance of common data bases: a list of inspected test facilities, a list of all addresses and contact points to facilitate information exchange and a so-called vademecum, which contains for the Commission and each member state a short description of the legal and administrative system chosen for implementation of the directives. Most of this information is now also available on the website: http://europa.eu.int/comm/enterprise/chemicals/glp/glp.htm, which also contains links to the relevant websites of the member states monitoring authorities. However, because of confidentiality issues, not all member states have agreed to put the lists of inspected test facilities on the web. In fact, some are worried about the possibility that animal rights activists would use that information to take actions against test facilities carrying out tests on animals. Therefore, links were made to those member states which have such lists publicly available, *e.g.*, Italy, whereas for the others, anyone interested in finding out more about the test facilities in the national monitoring programme has to contact the authorities;

c) finally, with the support of the members of the Working group, a very thorough exercise of confidence building was launched, the so-called mutual joint visits (MJV) programme, where in each case inspectors from three member states have examined the compliance monitoring programme of a fourth one. The MJV exercise was carried out in 1995 and 1996 and has helped to confirm that most of the member states had correctly implemented the two directives to a large degree. The deviations and flaws that could be identified have lead

to the adoption of corrective measures. Overall, a lot of improvements have been made and mutual confidence has increased considerably. The successful scheme, which was purely intra-EC/EEA, has been taken up in the meantime by the OECD, which extended it to the greater framework of its member countries. This is illustrated in full detail elsewhere in this special issue (D. Turnheim).

Overall, the major objective of the various activities of the Commission is to facilitate the acceptance of test data among the member states through enhanced co-operation, exchange of information and other appropriate means of confidence building.

Good laboratory practice

Role of the member states

The member states have certainly also their part to play in the implementation of GLP in the European Community. In fact, like with most other pieces of Community legislation, it is the member states which have to carry out the major part of the practical work. They have to adopt the necessary legislative and administrative measures to transpose the Community directives into national law. The legal instruments by which the member states transpose Community directives are actually quite diverse.

The member states have to create the national programmes for compliance monitoring in accordance with the Community directives and the OECD guides. This entails much practical work starting with the designation of the necessary monitoring authorities, hiring and training of inspection personnel, publication of documents on the functioning of the national programme, etc. The practical arrangements and the scope of the monitoring activities in the member states are actually widely different.

The most important task of the monitoring authorities is the inspections of the test facilities at regular intervals to ensure their compliance with the GLP principles. They also have to carry out additional study audits and inspections if requested to do so. There are in total some 600 inspected test facilities in the EU. However, there are significant differences in numbers between the member states. Based on their inspection activities, the monitoring authorities have to establish annual reports, which are to be transmitted to the European Commission and constitute the basis for updating the Community data bases.

Also, the receiving regulatory authorities in the member states are obliged, in general, to accept data submitted to them as part of the regulatory process, provided that these data have been produced in accordance with the GLP principles. Unjustified refusal of data by the member states' authorities would severely disturb the internal market for chemicals.

Finally, the member states, through their technical experts and based on their practical experience, contribute to the further development of the GLP principles and guides for compliance monitoring in the OECD. This leads to the other important reason why the Community is so much involved in the area of GLP, *i.e.*, the implications on external trade.

External impacts of good laboratory practice

Based on article 133 of the treaty establishing the European Community, the Community has the exclusive competence for a common commercial policy particularly in regard to the conclusion of tariff and trade agreements and the achievement of uniformity in measures of liberalisation and measures to protect trade. It is obvious that GLP has implications for trade of chemicals with third countries.

The Commission therefore has a major role in the area of GLP in the relations with third countries and international organisations. Within the OECD and if appropriate in other international fora, the Commission should ensure co-ordinated views of the member states. As the group of member states as a whole has a considerable weight in the OECD, co-ordination and uniform positions can be used as a very powerful tool to shape the policy of these organisations in a way that is desirable for the member states.

The Commission also has to work towards the correct application of the MAD Decision between member states of the EC and other OECD member countries. This means, if necessary and requested, intervention and support in cases where test data from a member state are refused by authorities in a third country.

The Commission has also negotiated legally binding formal agreements with other countries to reinforce the acceptance of test data beyond what is guaranteed by the MAD Decision alone.

This is a somewhat controversial issue, as the OECD Secretariat sees the MAD Decision already as legally binding and thus as a multilateral recognition agreement. However, this opinion was and still is not shared by all member states (neither in all OECD member countries, *e.g.*, Japan and USA). Also, many authorities were not really ready to accept the assurances of other authorities regarding compliance with the GLP principles, and thus the recognition of test data among the member countries did not work as smoothly in practice as should have been ensured by the MAD Decision.

In fact, not happy with the situation as it was, the GLP monitoring authorities in several member states had concluded the so-called "Memoranda of understanding" (MoU) with the GLP monitoring authorities in certain third countries, which were, however, not legally binding. As the Community has the exclusive

competence for external trade relations, it is, in principle, not acceptable that individual member states negotiate and conclude such MoU with the authorities in other countries. In addition, the fact that some member states did have MoU with certain third countries and others did not, constitute an obvious discrimination between the member states. As a result of this very unsatisfactory situation, most of the member states thought that the Community should include GLP in negotiations with other countries on the mutual recognition of technical standards (mutual recognition agreements, MRA) and a mandate in this sense was given by the Council to the Commission in the early 1990's.

So far, three MRA for GLP have been successfully concluded, two of them with other OECD countries, one with a non-OECD country, whereas two further attempts have failed. The MRA with Switzerland was finalised relatively quickly and was signed already in 1998, but it is still not in force. The reason for this is that the MRA, which covered already 15 different technical sectors, was part of a greater package of seven bilateral agreements between the EU and Switzerland on a number of issues (among them transport). These needed to be approved in Switzerland through referenda and then went through quite lengthy parliamentary procedures, both in Switzerland and the EU member states. The agreements are expected to enter into force very soon.

The MRA with Japan has been quite a different case. The negotiations between the Community and Japan were dragging on for more than five years and were quite tedious. This was due to many reasons: first, the scattered competence for implementation of GLP in Japan, involving 4 different Ministries and, secondly, because the MRA was to cover GLP, GMP and a number of other sectors in accreditation and standardisation. There were fundamentally different views on parallels between the role of authorities and test facilities in GLP (and GMP) in comparison to the accreditation and standardisation system. However, the agreement is now ready (it was signed at the beginning of April 2001). Ratification will probably take a while, as the procedures, in particular in Japan, are rather time-consuming. Still, it is a major step forward, as it is the first time that Japan has accepted a legally binding agreement in this area. This MRA will replace all existing MoU between various member states and individual Ministries in Japan that were not legally binding.

The Commission has also negotiated an MRA with one non-OECD country, *i.e.*, Israel. Obviously, it has to be made sure that the third country is adequately implementing the OECD principles of GLP and compliance monitoring, *e.g.*, through transition periods, where assistance is provided and confidence builds up through inspections carried out by the authorities from the member states in the country concerned. The agreement with Israel entered into force on 1 May 2000. The key element of the agreement is a two-year transition period during which the actual inspections of test facilities are carried out by teams of EU inspectors, whilst Israel is to build up its national monitoring programme. Five test facilities in Israel have been inspected by teams of inspectors from the EU member states and the first meeting of the Joint Committee surveying the implementation of the agreement took place in November 2000. Israel could demonstrate remarkable progress in the setting up of its national monitoring programme.

Furthermore, two attempts for negotiation of MRA in the area of GLP have failed so far: one with USA and one with Canada. In the case of USA, the major stumbling block were certain positions of the FDA regarding the possibilities to carry out inspections in all EU member states before concluding the agreement that were judged excessive by the Community. In the case of Canada, it was mostly the domestic legal situation, which would have made a legally binding MRA covering a large range of chemicals difficult to ratify for Canada. Last but not least, the Commission is very active in the preparation of the enlargement candidate countries, in various ways: through training workshops and through the so-called screening exercise which examines the situation of the legislation in the enlargement candidate countries in comparison to the "aquis-communautaire". In addition, the Commission has negotiated the so-called PECA (Protocol to the Europe Agreement on Conformity Assessment and Acceptance of Industrial Products) agreements, which are similar to MRA but are situated in the specific preparatory programmes for accession. Such PECA have been concluded with several candidate countries, but only one so far, with Hungary, covers also the sector of GLP. The agreement is not yet in force and in particular the annex on GLP will become applicable only after the final evaluation of the OECD MJV to Hungary. Similar negotiations with the Czech Republic had to be suspended, as the legal and practical situation regarding GLP was not completely clear yet, due to the many changes in the national legislation in the transition period from the old regime to the new situation. They will be resumed, once the Czech Republic has made substantial progress. The Commission is currently working with the Czech authorities to prepare the necessary changes.

Conclusions

The European Community has a strong interest in the effective and correct implementation of the GLP principles in its member states, as this is a pre-requisite for the functioning of the internal market for a large variety of chemical products and ensures enhanced protection of human health and the environment throughout the Community. Both the Commission and the

member states have important roles to play in the uniform implementation of the GLP principles. Finally, the European Community has an influential role in the international developments regarding the GLP principles, both within the OECD and through its commercial policy.

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