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The OECD pilot project of mutual joint visits: state of the art and need for further action

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Summary. - This paper describes the ongoing pilot project to examine the organisation and procedures of the 33 national good laboratory practice (GLP) compliance monitoring programmes in OECD to determine the extent to which they comply with the recommendations of the 1989 Council Decision-Recommendation on compliance with GLP. The project is based on mutual joint visits (MJV) of peer review teams representing other monitoring authorities. At the time of this paper all 33 MJV had been completed and the reports were being reviewed by the OECD Working group on GLP. A full evaluation of the pilot project will take place in 2002, after which a policy decision will be made regarding the need to continue such a programme and in what form.

Key words: good laboratory practice, mutual joint visits, monitoring authorities.

Riassunto *(Il progetto pilota dell'OECD di "visite congiunte reciproche": stato dell'arte e prospettive).* - Viene descritto il progetto pilota che intende esaminare l'organizzazione e le procedure dei 33 programmi nazionali di verifica della conformità ai principi di buona pratica di laboratorio (BPL) dell'OECD, al fine di accertarne il grado di adesione alle raccomandazioni della Decisione-Raccomandazione del Consiglio del 1989 circa l'adesione ai principi stessi. Il progetto si basa su "visite congiunte reciproche" (*mutual joint visits, MJV*) eseguite da squadre di osservatori in rappresentanza di altre autorità di monitoraggio. Al momento in cui questo lavoro viene redatto, tutte le 33 MJV sono state completate ed i rapporti sono stati esaminati dal Gruppo di lavoro OECD per la BPL. Una valutazione completa del progetto pilota avrà luogo nel 2002. Verrà successivamente presa una decisione circa la necessità di continuare tale programma ed eventualmente in che modo.

Parole chiave: buona pratica di laboratorio, visite congiunte reciproche, autorità di monitoraggio.

Background

In 1997 the OECD Joint meeting of the Chemicals committee and Working party on chemicals, pesticides and biotechnology requested the Working group on good laboratory practice (GLP) to undertake a four-year pilot project to examine the compliance monitoring procedures in member countries through a system of mutual joint visits (MJV). Based on a similar programme carried out in the European Union a few years earlier, the idea behind the project was to provide a mechanism to examine the extent of adoption and implementation by national GLP monitoring authorities of the OECD Council Decisions related to GLP. These include the 1981 Council Decision on the mutual acceptance of data, with the annexed OECD principles of GLP [C(81)30/Final] and the Guidelines for the testing of chemicals, and the 1989 Council Decision-Recommendation on compliance with principles of GLP [C(89)87(Final)], with its associated revised annexes and guidance documents in the *OECD Series on principles of good laboratory practice and compliance monitoring* [1].

Member countries considered that such an examination of national GLP compliance monitoring programmes was needed if the necessary assurance was to be had that countries were indeed implementing the OECD Council acts related to the mutual acceptance of data (MAD). The brief overview of the MAD system which follows is given as background.

Mutual acceptance of data

The *OECD Guidelines for the testing of chemicals and principles of GLP* were developed for ensuring harmonised data generation and data quality and are an integral part of the 1981 Council Decision on MAD. OECD's 29 member countries agreed to implement the

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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 test facilities 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, *e.g.*, 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.

OECD has therefore worked 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. 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 to achieve 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, 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 good reason exists. The annexes to the 1989 Council Act include the technical and administrative guidance developed by the Working group. These *Guides for compliance monitoring procedures* and the *Guidance for the conduct of laboratory inspections and study audits* were revised in 1992 and have been published in the *OECD Series on principles of good laboratory practice and compliance monitoring* (no. 2 and 3) [2, 3].

The MAD system has allowed OECD countries to avoid non-tariff trade barriers which can be created by different national regulations while improving protection of human health and the environment. Duplication of expensive safety testing is avoided by the industry and time to market for new chemicals is shortened, saving further resources. In light of the World Trade Organisation agreements which require the use of relevant international standards as the basis for national technical regulations, the OECD system has taken on a more global aspect. Since 1997 the OECD system for the mutual acceptance of data in the assessment of chemicals as described above has been opened up to membership by non-OECD countries. By making the system accessible to non-member countries who adopt the same test methods and quality standards for chemical safety testing as OECD countries, the same level of protection of health and the environment is ensured. Access to markets is furthered by harmonisation and mutual recognition of standards for development of safety data.

Organisation of mutual joint visits

Mutual acceptance of test data as called for in the Council Acts described above is only possible if genuine mutual confidence exists in the manner in which inspections and study audits are carried out. This mutual confidence can only be obtained through the transparency resulting from site visits by teams of expert, objective observers. In the MJV pilot project the organisation and operation of national GLP monitoring programmes are examined by peer review teams.

From 1998 to early 2001, 33 national monitoring authorities were visited by teams comprising representatives of three other monitoring authorities. The teams were composed of either the heads of the monitoring authorities themselves or experienced senior inspectors. In drawing up the schedule of visits, care was taken to ensure geographical distribution of the countries represented in each team, as well as preferences expressed by monitoring authorities to visit a specific country. A team leader coordinated the finalisation of the report of the visit. Travel and subsistence costs were carried by the visiting monitoring authorities; these included all costs of the visit such as travel to and from the authority and facility visited, hotels and meals.

The Working group on GLP developed guidance to be followed during the pilot project. The guidance set down the documentation required by the team prior to and during the MJV as well as the areas that needed to be formally examined during the visit. Teams spent one week for each MJV, which included a visit to the offices of the national monitoring programme and an on-site visit to a test facility. The latter usually covered three days during which time the team could observe the inspectors during an inspection and study audits. The conduct of the GLP inspection and study audits was reviewed according to the criteria outlined in the revised OECD Guidance document no. 3 and Guidance document no. 9 in the series on GLP and compliance monitoring, *Revised guidance for the conduct of laboratory inspections and study audits* and *Guidance for the preparation of GLP inspection reports* [3, 4].

Flexibility was required as to the language used during the site visit. Arrangements concerning the language to be used were made between the visited monitoring authority and the MJV team. Interpreters were used if the inspection at the test facility was to be held using a language which was not understandable by the members of the team. In virtually all cases, English was the language used.

On day one of the MJV, the host GLP monitoring authority introduced and explained the operation of its national GLP monitoring programme, providing the team of observers an opportunity to discuss the material documenting the programme. The host authority had provided the documentation described in Annex III to the 1989 Council Act to the evaluation team prior to the visit, with translations where necessary. Documentation on the national GLP monitoring authority's organisation and operation was reviewed using criteria outlined in the OECD revised Guidance Document no. 2 in the series on GLP and compliance monitoring, *Revised guides for compliance monitoring procedures for good laboratory practice* [2]. The areas for formal examination were:

- programme administration, including relationship with the regulatory/receiving authority;
- maintenance of confidentiality of commercially valuable information;
- number of programme personnel, personnel qualifications and personnel training;
- elements of the national GLP compliance programme, including inspection reports;
- follow-up to test facility inspections and study audits;
- appeal procedures.

Days two through five were devoted to the observation of an actual GLP inspection and study audits at a covered test facility, with the last day being devoted primarily to the conclusions and discussion of the visit. The host monitoring authority selected the test facility or facilities to be inspected and assured access by the MJV team. The conduct of the GLP inspection and study audits was reviewed according to the criteria outlined in the revised OECD Guidance document no. 3 and Guidance document no. 9 in the series on GLP and compliance monitoring, *Revised guidance for the conduct of laboratory inspections and study audits* and *Guidance for the preparation of GLP inspection reports* [3, 4]. These include:

- pre-inspection procedures;
- starting conference;
- test facility organisation and personnel;
- quality assurance programme;
- facilities;
- apparatus, materials, reagents and specimens;
- test systems;
- test and reference substances;
- standard operating procedures;
- performance of the study;
- reporting of study results;
- storage and retention of records;
- closing conference;
- preparation of the inspection report.

The team of observers examined not only whether the host GLP monitoring authority's inspectors covered each of the points, but also the thoroughness of the coverage. In addition, the quality of the study audit(s) was reviewed.

The observers then prepared consensus reports of the MJV in English, outlining strong and weak points with reference to the guidance documents cited above. The draft reports were submitted to the host monitoring authorities for comment. The final MJV reports, including comments by the host country, were to be finished within five months of the visit.

The reports covered the following aspects of the national GLP compliance monitoring programmes:

1) Administration
- monitoring authority and legal framework (including the relationship with the regulatory/ receiving authority);
- written documentation of the programme;
- programme statistics and records.

2) Confidentiality

3) Personnel and training
- number of inspectors;
- qualification requirements and training;
- independence;
- identification during inspections.

4) Monitoring programme
- scope and coverage;
- registration of test facilities;
- category of inspections/study audits;
- access to test facilities;
- procedures for inspections and study audits.

5) Follow-up to inspections and study audits

6) Appeal procedures

7) Findings regarding the observed inspection
- pre-inspection;
- starting conference;
- test facility organisation and personnel;
- quality assurance programme;
- facilities;
- care, housing and containment of biological systems;
- apparatus, materials, reagents, specimens;
- test systems;
- test and reference substances;
- standard operating procedures;
- closing conference.

8) Findings regarding the conduct of study audits
- performance of the study;
- reporting of study results;
- storage and retention of records;
- closing conference.

9) Findings regarding the inspection report
- the consensus report also included an examination of the inspection report resulting from the site visit to a test facility. The inspection report was made available to the MJV team after the visit, with any information considered confidential under national law removed.

Mutual joint visits reports

The MJV reports and the reactions to them by the visited authority are reviewed first by a small Steering group, which, after hearing the report from the team leader, draws conclusions and recommendations on the results of the MJV for discussion by the full Working group on GLP, as well as recommendations on the way MJV were carried out and evaluated. The Working group then reviews the reports, holds a discussion with the team leader and the host country and considers the conclusions and recommendations of the Steering group. The latter relate to the extent to which the group considered that the organisation and practices of the visited authority met the requirements of the OECD guidance documents for GLP monitoring authorities. The discussions in the Steering group and in the Working group are confidential and not subject to a written record.

The MJV reports themselves are considered the property of the evaluation team and/or the Working group, and therefore are not subject to public release outside the OECD Working group on GLP. They are considered the property of the evaluation team and/or the Working group only. The purpose of the reports is to provide a means that national GLP monitoring authorities can use to strengthen their compliance programmes. The reports do not constitute a formal assessment of national compliance with the OECD Council Decisions on GLP, but rather an informal means to enhance mutual acceptance of data through greater harmonisation of national programmes. Attendant to this result is less testing, a reduction in testing costs and more rapid introduction of products of enhanced quality. It is also hoped that the interface between GLP monitoring authorities and their national receiving authorities will be improved. MJV reports can also enhance bilateral arrangements between OECD member country GLP monitoring authorities, where these exist.

Next steps

The overall objective of the pilot project is to assess the feasibility and desirability of implementing such a process on a permanent basis after evaluating the results of the pilot phase. Once all 33 MJV reports have been examined by the Working group (by December 2001), the final step is that of the evaluation of the pilot phase as a whole. That process will take up the first part of 2002, with the objective of recommending to the Joint meeting whether the project should: a) continue on a permanent basis as in the same way as the pilot project; b) continue on a permanent basis with modified procedures based on experience gained in the pilot project; or c) be discontinued. An interim discussion by the Working group at its last meeting in December 2000 showed that all participants - teams and visited authorities - felt that the pilot phase to date had resulted in increased understanding of compliance monitoring procedures and confidence in test data. Since the Working group has only considered half of the MJV reports at this time, it is too early to know what the final recommendation about the need to continue this sort of evaluation will be.

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 member countries.

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