Current state of the implementation of the OECD GLP principles in the OECD member countries and non-member economies in light of the outcome of the 1998-2002 pilot project of mutual joint visits

Dian Turnheim

Environment, Health and Safety Division, Environment Directorate, Organisation for Economic Co-operation and Development (OECD), Paris, France

Summary. This paper describes the current situation as regards implementation of the Organisation for Economic Co-operation and Development (OECD) Council Decisions related to the mutual acceptance of data (MAD) in the assessment of chemicals in the 30 OECD member countries as well as in several non-member countries which adhere to the Council Acts. The cornerstone of MAD is the knowledge of and ensuing confidence in national good laboratory practice (GLP) compliance monitoring programmes which guarantees the acceptability for regulatory purposes of non-clinical environment and health safety data on chemicals and chemical products tested in these countries. The pilot project of mutual joint visits (MJV) undertaken by the OECD working group on GLP between 1998 and 2002 to observe and understand the way compliance monitoring is carried out in member countries was the successful basis for evaluation of the readiness of non-members to become full members of the OECD system on MAD and for a continuing on-site evaluation programme which began in 2008. The MJV project, its results and follow up by the Chemicals Committee and the continuing programme on on-site evaluations are described. Details are given on the work with non-member economies in the area of MAD and the status of their GLP compliance monitoring programmes.

Key words: good laboratory practice, test facilities, mutual acceptance of data, inspections.

Riassunto *(Stato attuale dell'adozione dei principi di buona pratica di laboratorio dell'OCSE nei paesi membri dell'OCSE e nelle economie non ancora aderenti alla luce degli esiti del Progetto Pilota di Visite Congiunte reciproche del 1998-2002)*. Questo lavoro espone la situazione attuale per quanto riguarda l'adozione delle Decisioni del Consiglio dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE), per quanto riguarda la reciproca accettazione dei dati (RAD) (*mutual acceptance of data*, MAD) nella valutazione delle sostanze chimiche nei 30 paesi membri dell'OCSE, nonché in diversi altri paesi non membri che tuttavia accettano gli Atti del Consiglio. La base del RAD è la conoscenza dei programmi nazionali di verifica della conformità ai principi di buona pratica di laboratorio e la fiducia nella loro idoneità che ne consegue. Ciò garantisce l'accettabilità a fini regolatori dei dati di sicurezza non clinici per la sicurezza della salute e dell'ambiente relativi alle sostanze ed ai prodotti chimici esaminati in questi paesi. Il progetto pilota per le visite congiunte reciproche (VCR) (in inglese *mutual joint visits*, MJV) intrapreso dal gruppo di lavoro dell'OCSE per la BPL tra il 1998 ed il 2002 per osservare e comprendere le modalità per la verifica di conformità attuate nei paesi membri è stata la chiave del successo per la valutazione del grado di preparazione dei paesi non membri ai fini dell'accettazione come membri a pieno titolo del sistema dell'OCSE per la RAD e del programma permanente di visite in loco iniziato nel 2008. Il progetto di VCR, i suoi risultati e le azioni che ne sono conseguite da parte del Comitato Sostanze Chimiche *(Chemicals Committee)* vengono infine descritte in dettaglio le attività svolte con le economie non appartenenti all'OCSE e lo stato dei loro programmi di verifica della conformità ai principi di BPL.

Parole chiave: buona pratica di laboratorio, centri di saggio, accettazione reciproca dei dati, ispezioni.

INTRODUCTION

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organization grouping 30 industrialized countries. Its main tasks are to monitor economic trends in those countries and to promote policies in order to achieve the highest sustainable economic growth and employment and a rising standard of living in member countries and to

Address for correspondence: Dian Turnheim, Environment, Health and Safety Division, Environment Directorate, OECD, 2 rue André Pascal, 75775 Paris Cedex 16, France. E-mail: dian.turnheim@oecd.org.

contribute to the development of the world economy and the expansion of world trade on a multilateral, non-discriminatory basis in accordance with international obligations. Increasing attention is being paid by OECD to promoting sound and environmentally sustainable economic expansion of non-member economies in the process of economic development [1].

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 co-ordinated action. Problems related to contamination of the environment by chemicals are dealt with in OECD through a specific programme on chemicals, which carries 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 safety of nanomaterials and pesticides, biosafety and food safety and chemical accidents.

MUTUAL ACCEPTANCE OF DATA

As one of the first priorities in their work on chemicals in OECD, in the late 1970s 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 quality standards for safety testing, were also recognised and this led to the adoption over the years of three cornerstone legally binding OECD Decisions related to the mutual acceptance of data (MAD) in the assessment of chemicals [2-4].

The OECD system of MAD is intended to promote the efficient and effective protection of public health and the environment. Successful implementation of MAD depends on non-clinical health and environmental safety studies being designed and conducted according to internationally recognized scientific and quality standards that assure that studies are scientifically valid and that data are reliable. Standards for the scientific validity are established through the development of OECD Guidelines for the testing of chemicals [5]:

- Section 1: Physical chemical properties;
- Section 2: Effects on biotic systems;
- Section 3: Degradation and accumulation;
- Section 4: Health effects;
- Section 5: Other test guidelines.

Data quality, integrity and reproducibility are assured by compliance with the OECD principles of good laboratory practice (GLP) and by national GLP compliance monitoring programmes which implement the guidance established by OECD in the series on the GLP principles and compliance monitoring [6]:

- No. 1, OECD principles of good laboratory practice (as revised in 1997);
- No. 2, Revised guides for compliance monitoring procedures for good laboratory practice (1995);
- No. 3, Revised guidance for the conduct of laboratory inspections and study audits (1995);
- No. 4, Quality Assurance and GLP (as revised in 1999);
- No. 5, Compliance of laboratory suppliers with GLP principles (as revised in 1999);
- No. 6, The application of the GLP principles to field studies (as revised in 1999);
- No. 7, The application of the GLP principles to short term studies (as revised in 1999);
- No. 8, The role and responsibilities of the study director in GLP studies (as revised in 1999);
- No. 9, Guidance for the preparation of GLP inspection reports (1995);
- No. 10, The application of the principles of GLP to computerised systems (1995);
- No. 11, The role and responsibilities of the sponsor in the application of the principles GLP (1999);
- No. 12, Requesting and carrying out inspections and study audits in another country (2000);
- No. 13, The application of the OECD principles of GLP to the organisation and management of multi-site studies (2002);
- No. 14, The application of the OECD GLP principles to *in vitro* studies (2004);
- No. 15, Guidance on the establishment and control of archives that operate in compliance with the principles of good laboratory practice.

Ultimately public health and environmental protection can only be attained when there is a concerted effort to assure that both scientific validity and data quality standards are fulfilled. For example, a study that is planned according to valid scientific principles, but is poorly conducted and inadequately documented, cannot provide assurance of safety of a chemical or chemical product. Likewise, a properly executed and documented study is of little value to regulatory scientists if the design is flawed.

Scientific validity of a non-clinical safety study can be assessed during the pre-marketing or pre-manufacturing review which is part of the process for registration or notification of chemicals and chemical products. However, assessment of study conduct and data quality and integrity can only be done at the facility where the study was conducted, with the facility personnel and with the records that document the conduct and results of the study.

By using the standards set out in these MAD Council Decisions – the OECD guidelines for the testing of chemicals and principles of good laboratory practice – test facilities can ensure harmonised data generation

and data quality so that "data generated in the testing of chemicals in an OECD member country in accordance with OECD test guidelines and OECD principles of GLP shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment". This means non-clinical health and environmental safety data, developed in one 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.

Beyond a set of standards for safety testing and test facility management set out in the 1981 Decision, the 1989 Council Decision calls for a countries to harmonise their systems for verification of compliance with the GLP principles, so that they are speaking a common language when they are exchanging information about test facilities and studies 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 – for instance, field studies – and with more and more multi-site studies being undertaken, it is not only not very efficient; it is virtually impossible for national monitoring programmes to personally verify the compliance of foreign facilities with GLP, except in special situations.

OECD promotes international – indeed global – harmonisation of the whole GLP system, including the GLP principles, their implementation, the performance of compliance monitoring and information exchange among national monitoring programmes, the evaluation of national compliance monitoring programmes, and opening system to non-OECD countries. This is the only way in which the quality, and mutual acceptability, of test data can be assured on a global scale.

By making the system accessible to non-members 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 the OECD standards for development of safety data. Since 1997 the MAD system has been opened up to membership by non-OECD economies with a major chemical, pesticide and/or pharmaceutical industry via a Decision of the Council.

That Council decision sets out a step-wise procedure for non-OECD countries with a major chemical industry to take part in the work of OECD, at both the technical and policy level, eventually leading to full membership in that part of OECD related to the Mutual Acceptance of Data in the assessment of chemicals. South Africa was the first non-OECD country to have completed this process and to have been invited to join the system as a full member. Slovenia and Israel are also now full members; and Argentina, Brazil, India and Singapore participate in the work as provisional adherents. The provisional adherence procedures have begun for Thailand and Malaysia; and China and Chinese Taipei are expected to provisionally adhere in the near future.

ON-SITE EVALUATION OF COMPLIANCE MONITORING PROGRAMMES

Full membership is granted by the OECD Council once the provisionally adhering non-member economy has fully implemented the 1981 and 1989 Council Acts and has shown that it has a GLP compliance monitoring programme which is compatible with those of OECD countries, by undergoing a successful on-site evaluation visit by a team representing the OECD working group on GLP. This policy body, comprising the heads of national GLP compliance monitoring programmes, oversees the all work in OECD on GLP and compliance monitoring in order to ensure common positions on policy, administrative and technical issues, and, thus, mutual acceptability of data. It reports to the chemicals committee. An evaluation team comprised of three members of the working group performs an on-site evaluation visit to the non-member economy when they feel they have satisfactorily implemented the 1989 Council Decision and its recommended guidance documents.

Furthermore, in addition to the on-site evaluation visits to non-member economies, the OECD Chemicals Committee established in 2006 a continuing programme of periodic evaluations to assess on a regular basis the extent to which member countries and fully adhering non-members implement the 1989 OECD Council Decision/Recommendation on Compliance with GLP. This programme is based on the outcome of a four-year pilot project which examined the compliance monitoring procedures in member countries from through a system of mutual joint visits (MJV). From 1998 to early 2001, 33 national monitoring programmes were visited by teams comprising representatives of three other monitoring programmes. The teams were composed of either the heads of the monitoring programmes or experienced senior inspectors from different OECD regions. A team leader co-ordinated the finalisation of the report of the visit, which was then examined by the working group on GLP. These on-site evaluations are the means by which member countries and fully adhering non-member economies ensure continuing mutual confidence in one another's GLP compliance monitoring programmes.

The working group 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 Annexes to the 1989 Council Act.

The objective of the periodic on-site evaluation programme is to ensure continued confidence that data receiving authorities are provided accurate and complete assessments of the conduct of non-clinical health and environmental safety studies and of the quality and integrity of data used to support pre-marketing (pre-manufacturing) applications. Because studies are conducted and submitted throughout the world, it is difficult and expensive for a monitoring authority to perform inspections and audits of studies conducted outside its country. Therefore, confidence in other GLP compliance monitoring programmes is crucial to supporting regulatory submissions and for assuring public health and environmental protection. Such confidence permits monitoring programmes to provide timely and accurate compliance information about foreign test facilities to their respective data receiving authorities for their use in evaluating the quality of data submitted for their review and assessment.

The continuing on-site evaluation of GLP compliance monitoring programmes by the OECD working group is a concrete response to the mandate given by council to the chemicals Committee and the Environment Policy Committee in the 1989 decision to pursue a programme of work to facilitate implementation of the Council Act. As was the case with the MJV pilot project, the continuing on-site evaluation visit programme remains informal and flexible; it provides for an evaluation of each monitoring programme every ten years and is adaptable to the diverse character of the monitoring programmes that comprise the working group, designed to tailor the on-site evaluation process to the history, character and overall activities of the monitoring programme under review. The size of the teams have been reduced from three to two members and new, more detailed procedures for preparing, carrying out and reporting on the evaluation have been adopted. There is a mechanism for exceptional re-evaluation if there is evidence that changes in a programme may invalidate the findings of the last on-site evaluation visit and are of such magnitude that it is no longer certain that the Annexes to the 1989 Council Act are still being implemented and therefore that the data acceptance provisions of MAD are still applicable. There is also a provision for follow-up evaluations for monitoring programmes where a final conclusion on the adequate implementation of the annexes to the 1989 council act cannot be rendered on the basis of a single on-site evaluation visit. This flexibility provides additional credibility to the findings and greater confidence in the outcome of the on-site evaluation programme. The on-site evaluation programme, which began effectively in 2008, is funded by member countries and fully adhering non-members and is centrally managed by the Secretariat. The working group on GLP oversees the programme, draws conclusions on the adequacy of the implementation of the Annexes to the 1989 council act in countries, and monitors follow-up as appropriate.

CONCLUSIONS

The three OECD Council Acts related to MAD, complemented by the continuing programme of on-site evaluations of national GLP compliance monitoring, form the basis for a multilateral system which avoids trade barriers which could arise through differing requirements for regulatory submissions. Through OECD continued confidence in this system is ensured among participating member and non-member countries, thus reducing duplication, use of laboratory animals, and time to market of chemicals and chemical products, etc.

Acknowledgements

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.

Submitted on invitation.
Accepted on 22 September 2008.

References

1. Organisation for Economic Co-operation and Development. *For a better world economy*. Paris: OECD; 2008. Available from: www.oecd.org/home/0,3305,en_2649_201185_1_1_1_1_1,00.html.
2. Council Decision Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)]. Available from: www.oecd.org/document/47/0,3343,en_2649_34365_1817647_1_1_1_1,00.html.
3. Decision of the Council concerning the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals [C(81)30(Final)]. Available from: www.oecd.org/document/47/0,3343,en_2649_34365_1817647_1_1_1_1,00.html.
4. Council Decision concerning the Adherence of non-Member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(97) 114(Final)]. Available from: www.oecd.org/document/47/0,3343,en_2649_34365_1817647_1_1_1_1,00.html.
5. Organisation for Economic Co-operation and Development. OECD *Guidelines for the testing of chemicals. Section 1: Physical chemical properties; section 2: effects on biotic systems, section 3: Degradation and accumulation; section 4: Health effects; section 5: Other test guidelines*. Paris: OECD; 2008. Available from: www.oecd.org/document/40/0,3343, en_2649_34377_37051368_1_1_1_1,00.html.
6. Organisation for Economic Co-operation and Development. *OECD Principles of good laboratory practice (as revised in 1997)*. Paris: OECD; 2008. (Series on the GLP Principles and Compliance Monitoring. No. 1). Available from: www.oecd.org/env/glp.