Quest for harmonisation: differences and similarities in national programmes for GLP monitoring. A senior inspector's viewpoint

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Summary. The conditions under which safety data may be accepted by regulatory authorities (RAs) in OECD Countries do not only include the obligation to apply the principles of good laboratory practice (GLP) while producing these data, but also must countries, partaking in the Organisation for Economic Cooperation and Development (OECD) system for mutual acceptance of data (MAD), establish a monitoring programme to ensure proper application of the GLP principles. Detailed guidance to this end is given in the OECD GLP documents No. 2 and 3. Nevertheless, this guidance permits countries quite some freedom where it concerns the organisation of their programmes. Monitoring programmes may be embedded in governmental as well as private structures. It appears that GLP compliance monitoring is increasingly charged to accreditation bodies. Inspectors may be full-time or part-time workers, and there are differences in scheduling and performing inspections and study audits. Also the financing of the monitoring programmes is diverging: in some countries the programme is fully or partly paid by the inspected test facilities (TFs), while in other countries the financing comes from the national treasury. Is there a need for harmonisation in this area, as there is and was in the interpretation of the GLP principles themselves? Over the years more than ten consensus and advisory documents have been published by the OECD working group on GLP. The very existence of these documents is however no guarantee that the interpretation of the GLP principles by inspectors is similar, let alone identical. The most important criterion is, in fact, that there be no harm for human health and the environment.

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

Riassunto *(La ricerca dell'armonizzazione: differenze e somiglianze nei programmi nazionali di verifica della BPL. Il punto di vista di un ispettore senior)*. Le condizioni sotto cui i dati di sicurezza possono essere accettati dalle autorità regolatorie (AR) nei paesi dell' Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) non solo includono l'obbligo di applicare i principi di buona pratica di laboratorio (BPL) nella generazione di tali dati, ma anche che i paesi partecipanti al sistema dell'OCSE per la mutua accettazione dei dati (MAD) realizzino un programma di monitoraggio atto a garantire l'applicazione corretta dei principi di BPL. I documenti dell'OCSE sulla BPL No. 2 e 3 forniscono una guida dettagliata a questo proposito. Nondimeno, questa guida consente ai paesi interessati una notevole libertà nella organizzazione dei loro programmi. I programmi di monitoraggio possono essere gestiti da strutture tanto governative quanto private. La verifica di conformità ai principi di BPL è sempre più affidata agli enti di accreditamento. Gli ispettori possono essere a tempo parziale o a tempo pieno e ci sono pure differenze nella programmazione e nella conduzione delle ispezioni e delle audizioni degli studi. Anche la copertura economica del programma di monitoraggio è diversificata: in alcuni paesi il programma è sostenuto del tutto o in parte dai centri di saggio (CdS) ispezionati, mentre in altri paesi la copertura economica viene da fondi pubblici. C'è necessità di armonizzazione in questo settore come c'è e c'è stata nella interpretazione dei principi di BPL stessi? Nel corso degli anni sono stati pubblicati più di dieci tra documenti di consenso e di consultazione da parte del gruppo di lavoro dell'OCSE per la BPL. La mera disponibilità di questi documenti, tuttavia, non garantisce che l'interpretazione dei principi di BPL da parte degli ispettori sia simile o, meno che mai, identica. Il criterio più importante è infatti che non vi sia alcun pericolo per la salute umana e l'ambiente.

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

INTRODUCTION

The first publication of the Organisation for Economic Cooperation and Development (OECD) on good laboratory practice (GLP), entitled good laboratory practice in the testing of chemicals, now a collector's item, was published in 1982 [1]. Although this booklet has been replaced and superseded by later publications, it offers some more background information on the early history of OECD good laborato-

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ry practice and its monitoring. Quoted verbatim from this book is the following: "On May 12, 1981, on the proposal of the High level meeting of the chemicals group, endorsed by the Environment Committee, the OECD Council adopted the Decision concerning the mutual acceptance of data in the assessment of chemicals [C(81)30 (Final)]. Under the overall objective of internationally harmonizing practices and procedures in chemicals control, the OECD Council decided: that data generated in the testing of chemicals in an OECD 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 environment. In support of this Decision, the Council recommended that member countries apply the OECD test guidelines and principles of GLP, when testing chemicals. Further, the Management Committee was instructed to develop internationally harmonized approaches to assure compliance with the OECD principles of GLP".

An expert group, set up earlier by the OECD Management Committee after a preparatory meeting in Stockholm in 1978, had completed the principles of GLP by March 1980, which were revised and republished in 1995 [2] and proceeded to draft the Implementation of the OECD principles of good laboratory practice, representing the elements necessary for the establishment of effective national compliance monitoring programmes and their mutual recognition. This Implementation was published as chapter 3 in the above mentioned book in 1982 and was later rewritten as an Annex I to Council Decision C(89)87 (Final) and revised in 1995 [3]. Chapter 4 of the same book contains the "OECD Guidelines for national GLP inspections and study audits", later also rewritten as the Guidance for the "Conduct of laboratory inspections and study audits", being Annex II to Council Decision C(89)87 (Final) and also revised in 1995 [4]. These three documents are the corner stones of national monitoring programmes.

ORGANISATION FORMS

As for the set-up of monitoring programmes, it is clear that governments are responsible for their establishment. In the early years of the GLP principles most monitoring authorities (MAs) were set up as governmental bodies, sometimes associated with receiving authorities (RAs). That has been done in the USA, the United Kingdom, Germany, Japan, The Netherlands and some other countries. But more and more member countries assigned the tasks of monitoring to already existing accreditation bodies. Those countries that joined the OECD GLP/mutual acceptance of data (MAD) system in about the last ten years have almost exclusively charged accreditation bodies with the task of GLP compliance monitoring. Has that posed a problem? First of all, it should be noted that the expert group mentioned above got its mandate from the OECD Council with the Council Decision C(78)127(Final), which says, inter alia:

"it is proposed to examine: i) systems of accreditation and /or inspection of laboratories existing or proposed in each country and by international organizations; and ii) means of harmonizing such systems" [1].

This indicates that the Management Committee was quite open-minded and had no strong preferences for the organisation and positioning of the monitoring systems. The Expert Committee followed its mandate and eventually came up with the monitoring system known today, where the MAs are set up nationally and where the procedures are a mixture of practices employed by accreditation bodies and governmental inspectorates and are based on two instruments, namely TF inspections and study audits.

The OECD GLP panel, later renamed as the working group on GLP, has always been quite adamant where it concerned laboratory accreditation. In the early 1990's there was quite some pressure from various sides, including the European Union, to come to some kind of cooperation. A position paper on the use of laboratory accreditation with reference to GLP compliance was issued, which clarified the differences between GLP monitoring and laboratory accreditation [5]. Till now the situation is such that, whatever the status of a MA is, governmental inspectorate or accreditation body, GLP monitoring is done according the OECD requirements as laid down in Annexes II and I. It should be strongly underlined that MAs might differ organisationally, although their monitoring practices are similar.

It must be emphasized that the pilot project of mutual joint visits (MJVs) has greatly contributed to a better understanding of programmes, run by the various countries, and also has been a learning experience for quite some member countries. The same is true for the assessment visits for those countries that wish to adhere to the OECD Council Decisions on MAD. These visits also have helped considerably to a better harmonisation of organizations and procedures.

A complicating factor in some countries is the number of MAs. There are at least 5 member countries that have three or more MAs. Although the situation, in which CROs have to deal with only one Inspectorate is preferable, the OECD's guidance however permits member countries the freedom to have more than one. This might lead to embarrassing situations where test facilities (TFs) are visited more than once a year by GLP inspectors, who might come up with different outcomes of their inspections. In practice this seems hardly to be the case. Most of these countries have established joint programmes or have found other ways to cooperate and harmonise. Again, there are differences in the national programmes, but solutions have been found.

FINANCING

The OECD guidance documents are completely silent in relationship with financing the national

GLP monitoring programmes. Since governments are known for the fact that they are always short of money, many inspectorates were forced to ask money for their services and TFs in quite some countries are forced to pay up to € 10 000 for their inspections. In The Netherlands fees are not levied, as it is also not done for instance in the French, Swedish and Portuguese medicines monitoring programmes and in the USA.

It is debatable that inspections imposed upon TFs should be paid by these last. On the one hand, it is up to TFs to conduct their studies in agreement with the GLP principles, while, on the other hand, it is the task of the governments to assess the rightfulness of their GLP claims. The fact that TF inspections often have to be paid per man-hour spent, might tempt a TF management to speed up the inspection. Inspectors might feel themselves curtailed in time, which will not be beneficial for a proper inspection. Furthermore, the financing of study audits requested by other MAs might become a point of severe disagreement. The question of who is paying for study audits is still not resolved definitely.

HOW TO ENTER A NATIONAL MONITORING PROGRAMME

At GLP training courses for quality assurance (QA) persons, study directors (SDs) etc., one of the questions often asked is: how does a TF enter a national GLP monitoring programme? In The Netherlands it is quite simple: if a TF is undertaking any testing in the regulated area, that work should be done according to the GLP principles, since that is required by law. The TF thus must claim adherence to the GLP principles and must notify the agency of their claim. The TF will then be included in the national monitoring programme and will be inspected. After the inspection, it will be acknowledged that it is operating or not operating in compliance with the principles of GLP and the counterparts will informed of this through the yearly inspection oversights. In some countries it is not allowed to claim adherence to GLP as long as a TF is not inspected and thus the situation becomes a chicken-and-egg situation as GLP studies cannot be inspected until the TF is inspected, whereas the TF will not be inspected if no GLP studies have been inspected. Luckily all kinds of ingenuous solutions have been found like the performance and inspection of mock studies, preliminary GLP certificates and so on.

CERTIFICATES

As regards certificates, again there can be found various situations. Neither the OECD guides nor the European Directives mention certificates. The text reads, verbatim: "The GLP monitoring authority may issue a statement that the test facility has been inspected and found to be operating in compliance with GLP principles. Such statement may be used to provide information to (National) GLP monitoring authorities in other member countries". Thus, first of all, there is no requirement to issue a statement; secondly, the statement is meant for official use, and not to serve as a certificate to be used for commercial purposes!

Some MAs even give these certificates expiration dates, as if it is known, that the TF will be in compliance till that date! It cannot be stressed enough that a TF cannot be accredited for GLP, although some certificates do suggest so. Moreover, it should be recognized that certificates are sought after, just for reasons of publicity.

THE INTERPRETATION OF THE GLP PRINCIPLES

The last question is now whether there are differences where it relates to the interpretation of the principles of GLP. Indeed, there are. There always have been. For instance, a matter that repeatedly comes up is about the characterization of test items: is it allowed to have the test item characterized in accordance with good manufacturing practice (GMP) requirements? It is actually allowed in many member countries. As the former head of the US-FDA MA, Jim McCormack, stated quite clearly at the SQA meeting in Orlando a few years ago: "Everything is allowed, as long as it is done under GLP". Since there were so many of these technical issues to be addressed at the OECD GLP working group meetings, it was decided to set up an electronic forum to deal with such matters. It is well used and there are often also minor issues. Where it concerns major issues, already a few years after the establishment of the GLP Panel, now working group on GLP, it became evident that the GLP community needed a harmonised approach to the interpretation of the GLP principles in important areas. The first so-called Consensus Workshop was held in Bad Dürkheim in 1990 produced the first Consensus document under the title Quality Assurance and GLP [6]. Many other documents followed, the last one being on archiving.

A recent survey on how national MAs deal with the consensus and advisory documents showed that: i) the OECD consensus and advisory documents were regarded by most respondents as equally important, although a minority regarded consensus documents to have a slightly higher status, since industry had been involved in their development; ii) industry and MAs are bound to follow the guidance (or its equivalence) given in these documents; iii) more than 90% of the inspectorates use both the GLP principles and the consensus and advisory documents as a reference; iv) the advisory and consensus documents remain valid, and provide useful and relevant guidance, which is internationally agreed upon.

So, although these documents are not strictly legally binding, they were endorsed by the working group on GLP and the Joint Meeting, thus indicat-

ing that there is consensus in governments on their content. They do not only offer guidance, but also present the interpretation of the GLP principles internationally agreed upon. It thus still stands that data developed in accordance with the GLP principles and de facto applying the advisory and consensus documents, cannot be refused on GLP grounds in OECD and MAD-adhering countries.

CONCLUSIONS

It must be admitted that all the monitoring programmes are different, sometimes considerably, and often also differ in their inspection procedures and approaches. The TFs, our clients, so to say, may consider this strange and sometimes unfair. But we have to recognize that we all live in different political systems and cultural environments. For the sake of clarity, the OECD working group on GLP should proceed to further harmonisation in inspection practices. Harmonization is obviously a priority whenever it is possible, although there will never be identical programmes. The most important issue in this context is: are data coming from these different programmes reliable and can the RAs use them for the assessment of the safety of chemical products? So far there are no grounds not to believe so.

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