ISTITUTO SUPERIORE DI SANITÀ

OECD Event.
The implementation of the OECD Principles of Good Laboratory Practice

Villa Tuscolana
Frascati (Rome), April 10-11, 2008

ABSTRACT BOOK

Edited by
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Reliable experimental information on chemical substances is pivotal for a sound assessment of the risk they pose. In this context, the Principles of Good Laboratory Practice (GLP) developed by the Organisation for Economic Co-operation and Development (OECD) must be adopted whenever non-clinical safety studies are undertaken by Test Facilities (TFs) for regulatory purposes. Nowadays the mutual recognition of studies performed according to those Principles ensues in undeniable benefits, primarily better protection of human health and the environment and substantial saving of financial resources. This Conference provides both public authorities and industry with an opportunity to assess the progress made so far at the international level in the application of the Principles of GLP, discuss new challenges and promote further reciprocal understanding.
Key words: Good Laboratory Practice, Non-clinical safety studies, Test Facilities, Monitoring Authorities, Regulatory Authorities.

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Informazioni sperimentali attendibili sulle sostanze chimiche sono indispensabili per una valutazione corretta del rapporto rischio-beneficio. In quest'ambito, l'effettuazione di studi non clinici di sicurezza intrapresi dai Centri di Saggio (CdS) per fini regolatori deve essere condotta in conformità ai Principi di Buona Pratica di Laboratorio (BPL) sviluppati dall'Organizzazione per la Cooperazione Economica e lo Sviluppo (OCSE). Oggi il mutuo riconoscimento degli studi condotti in accordo ai Principio di BPL ha prodotto benefici innegabili, in primo luogo una migliore protezione della salute umana ed un consistente risparmio di risorse economiche. Questo Convegno offre alle Autorità pubbliche ed all'industria un'occasione per valutare il progresso finora fatto nell'applicazione dei Principi di BPL a livello internazionale, esaminare le sfide emergenti e favorire l'ulteriore comprensione reciproca.
Parole chiave: Buona Pratica di Laboratorio, Studi non clinici di sicurezza, Centri di Saggio, Autorità di Monitoraggio, Autorità Riceventi.

Chairpersons of the OECD Event: Sergio Caroli (ISS), Dian Turnheim (OECD)

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PROGRAMME

Thursday, April 10, 2008

8.00 Registration of participants

9.00 *Opening of the Conference and welcome address*
Sergio Caroli, Francisca E. Liem, Maik Schmahl, Dian Turnheim

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THE POINT OF VIEW OF THE OECD AND MAS

Chairpersons: **Andrew Gray, Helen Liddy**

9.30 *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

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

10.30 *Future issues including broadening the scope of the GLP Principles*
Francisca E. Liem

11.00 Coffee break

11.30 *OECD Principles of GLP: what is working and what needs work*
Chidambaram T. Viswanathan

12.00 *Complying with different quality systems: GLP Principles and ISO/IEC 17025 accreditation*
Etty Feller

12.30 *Critical aspects in implementing the OECD Monograph no. 14 "The application of the Principles of GLP to* in vitro *studies"*
Hedwig Beernaert

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Session 2
THE POINT OF VIEW OF GLP RAS

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Brendan James Cuddy, Emer Cooke

15.00 *Collaboration between Monitoring Authorities, Regulatory Authorities and Test Facilities on GLP Principles provides confidence in data quality and an emphasis on sound science*
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Nobumasa Nakashima

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Shinoi Sakata

10.00 *Risk based assessment applied to QA GLP audits. How to fulfill regulatory requirements while making the best use of our common sense, knowledge, talents and resources?*
Alain Piton

10.30 *Critical aspects regarding the application of the GLP Principles to new compounds such as biotechnology products*
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11.30 *International GLP. Key issues from a Test Facility viewpoint*
Kathrin Ertz, Martina Preu

12.00 *Differences in the interpretation of the GLP Principles by OECD Monitoring Authorities: the point of view from the pharmaceutical industry*
Raymond K. Lowing

12.30 *OECD and US GLP applications*
Del W. Huntsinger

13.00 *Role and responsibilities of Test Facility management and sponsor related to studies performed according to the Good Laboratory Practice Principles*
Rik Hendriks, Werner Coussement

13.30 *Developments in consultation and training in the GLP arena: 1980 to 2020*
David Long

14.00 Lunch break

Session 4

Round Table

THE GLP PRINCIPLES AND CURRENT NEEDS. WHAT NEXT?

Chairpersons: **Maria Mercede Brunetti, Sergio Caroli, Mark Goodwin, Theo Helder, Francisca E. Liem, Alain Piton, Katariina Rautalahti, Shinoi Sakata, Maik Schmahl, Dian Turnheim**

17.00 Closure of the second day and of the Conference

PREFACE

This Symposium aims at providing an open forum where the public sector and the private sector can informally meet and discuss current Good Laboratory Practice (GLP) issues of interest to all partners involved. The event is meant to be the first one of a series of conferences of similar approach to be held regularly. An overview is given of the degree of implementation of the OECD Principles of GLP in Member and non-Member Countries, promotion of better co-operation among Monitoring Authorities (MAs), Regulatory Authorities (RAs) and Test Facilities (TFs) in respect to Part II of the 1989 Council Decision and the Mutual Acceptance of Data (MAD) and achievement of better understanding and interaction among all partners. This event is organized by the OECD GLP Working Group (WG) and features the participation of selected representatives of the public sector (MAs, RAs and relevant agencies and scientific institutions such as EMEA), of the private sector (TFs and relevant industrial organisations), as well as of other interested parties.

Sergio Caroli and Dian Turnheim

Session 1

The point of view of the OECD and MAs

Chairpersons
Andrew Gray, Helen Liddy

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, Paris, France

This paper describes the current situation as regards implementation of the 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 GLP compliance monitoring programmes which guarantee the acceptability of non-clinical environment and health safety data on chemicals and chemical products tested in these countries.

The Pilot Project of Mutual Joint Visits (MJVs) undertaken by the OECD Working Group on Good Laboratory Practice (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 Approximately 50 monitoring programmes will be examined during the first ten-year cycle which began in 2008.

The MJV project, its results and the evaluation 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.

QUEST FOR HARMONISATION: DIFFERENCES AND SIMILARITIES IN NATIONAL PROGRAMMES FOR GLP MONITORING. A SENIOR INSPECTOR'S VIEWPOINT

Theo Helder
Voedsel en Waren Autoriteit (VWA), Den Haag, The Netherlands

The conditions under which safety data may be accepted by Regulatory Authorities in OECD Member 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 OECD system for Mutual Acceptance of Data (MAD), establish a Monitoring Programme (MP) to ensure proper application of the GLP Principles. Detailed guidance how to set up an MP as well as how to perform inspections and study audits, is given in the OECD GLP Documents Nos. 2 and 3.

Nevertheless, this guidance permits countries quite some freedom where it concerns the organisation of their programmes. MPs may be embedded in governmental as well as private structures and, with the enlargement of the MAD system with new economies in the last and coming years, 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 MP is diverging: in some countries the programme is fully or partly paid by the inspected Test Facilities through a fee or retribution system, while in other countries the financing comes from the national treasury. The pros and cons of these situations are discussed. Is there a need for harmonisation in this area, as there is and was in the interpretation of the GLP Principles themselves?

The OECD Working Group on GLP has always put much effort in global harmonisation of the GLP Principles. Over the years more than ten consensus and advisory documents have been published. The very existence of these documents is however no guarantee that the interpretation of GLP by inspectors is similar let alone identical. But does it matter? Is not the most important criterion: is there any harm for human health and the environment? I am intending to present and discuss these and some related issues.

FUTURE ISSUES INCLUDING BROADENING THE SCOPE OF THE GLP PRINCIPLES

Francisca E. Liem
Laboratory Data Integrity Branch, United States Environmental Protection Agency, Washington, D.C., USA

When the Principles of Good Laboratory Practice (GLP) were drafted in 1982 by the Organisation for Economic Co-operation and Development (OECD), many issues to be discussed in this presentation were not anticipated. The electronic era was in its infant stages and many of the issues surrounding what may affect the environment and human health was not expected. Today, advances in technology for capturing and recording data for the reconstruction of a study are presently available and are being developed operating at speeds which could not have been known or understood in years past.

Since that time, the United States Environmental Protection Agency (US EPA) has required the conduct of additional studies in support of a pesticide registration in accordance with the GLP regulations. However, not all of these studies are required in other countries, and those studies that are required, may not require adherence to the Principles of GLP. There are new types of products, such as biotechnological pesticides (plant-incorporated-protectants), biological pesticides, biocides and pesticides for eradicating public health pests (insecticides, rodenticides, avicides).

Many companies are submitting underlying studies in support of a registration of a pesticide based on publications in scientific journals. Companies are using computer models as virtual studies instead of inlife or bench-type regulated research. Studies are many times conducted at institutions of higher learning, because of the academic expertise they offer. Do these institutions have to be in compliance with the Principles of GLP? Will they be inspected by the GLP compliance Monitoring Authorities (MAs)? Do the Principles of GLP have an effect on nanotechnology? What is the overall impact advancing technology has on the Principles of GLP? And, the basic question - Are we ready?

The medical products field faces similar issues, *e.g.*, medical devices, biological products, biotechnological products, bioanalysis, just to mention a few. Development and testing of these products and devices is being conducted similar to development and testing in the pesticide arena.

As we continue toward a global economy, we will face many new challenges. To build confidence and garner trust in Mutual Acceptance of Data, each participating nation must adhere to practices that ensure the highest standards of quality and integrity. The GLP inspector will need to have a good understanding of the science supporting the study conduct and the electronic systems that generate process and maintain study records. This presentation discusses future issues that may broaden the scope of the Principles of GLP.

OECD PRINCIPLES OF GLP: WHAT IS WORKING AND WHAT NEEDS WORK

Chidambaram T. Viswanathan
Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD, USA

OECD Principles of Good Laboratory Practice (GLP) are intended to assure data quality and integrity. The pre-clinical safety data generated in an OECD Member country in accordance with OECD Principles of GLP are indeed accepted in other Member countries for purposes of assessment. Regulatory Authorities routinely further assess such studies to determine their applicability to specific regulatory decisions.

In our experience, the procedures laid out by the OECD GLP Principles often support and complement the collection of robust data and aptly address complexities such as multi-site study conduct.

This presentation discuss our perspectives on what works and what might benefit by further optimization.

COMPLYING WITH DIFFERENT QUALITY SYSTEMS: GLP PRINCIPLES AND ISO/IEC 17025 ACCREDITATION

Etty Feller
Israel Laboratory Accreditation Authority, Ramat, Israel

Test Facilities (TFs)/Laboratories with a quality system accredited to ISO/IEC 17025 have a definite advantage, compared to non-accredited laboratories, when preparing their facilities for recognition according to OECD Good Laboratory Practice (GLP) directives and *vice versa*.

Accredited laboratories have an established quality system covering the administrative and technical issues specified in the standard (ISO/IEC 17025 or ISO 15189). The quality system of these laboratories relate to many issues including: internal audits, job descriptions and responsibilities, procedures for equipment/instrument maintenance and calibration, document control, handling of reagents, chemicals and reference materials, sampling and sample reception, validation of test methods, traceability and uncertainty of the test results, training of personnel, handling of client complaints, corrective and preventive actions *etc*.

Several of these issues are also required for OECD GLP recognition either with a different emphasis and/or with additional requirements.

This presentation addresses the question of whether it is suitable to comply with either or both sets of criteria on the basis of the needs of the clients and whether their choice fits their purposes.

CRITICAL ASPECTS IN IMPLEMENTING THE OECD MONOGRAPH NO. 14 "THE APPLICATION OF THE PRINCIPLES OF GLP TO *IN VITRO* STUDIES"

Hedwig Beernaert
Bureau of Quality Assurance, Scientific Institute of Public Health, Brussels, Belgium

The Principles of Good Laboratory Practice (GLP) were originally written for the application of animal-based toxicology studies. However, more and more studies involving *in vitro* test systems are performed to produce data on the safety of chemicals with respect to human health and the environment. Therefore, national legislation usually requires that the *in vitro* studies are conducted in accordance with GLP requirements. Furthermore, developments in the area of toxicogenomics, toxicoproteomics, toxicometabonomics and various high throughput screening techniques will also enhance the importance of *in vitro* methodologies for safety testing.

The OECD Principles of GLP require that safety studies, independent of their type, are planned, conducted, recorded, reported and archived in a way that they can be totally and accurately inspected by the GLP Monitoring Authorities and scientifically evaluated by the Receiving Authorities. Therefore, the GLP Principles and the associated Consensus Documents describe requirements for and provide general guidance on the conduct of all non-clinical health and environmental safety studies, including *in vitro* studies.

The purpose of this presentation is to discuss some critical aspects and pitfalls related to the proper application and interpretation of the GLP Principles for the organisation and management of *in vitro* studies. Organisational charts and responsibilities of Test Facilities (TFs) involved in single or multi-site studies are sometimes dysfunctioning because there is a lack of traceability in reporting and communication lines.

The Quality Assurance (QA) programme is not clearly scheduled as regards the critical phases to be followed. Manipulation of cell and tissue cultures of different test systems should be separated and performed under aseptic conditions to prevent cross-contamination. These conditions may also be very important during the handling and use of test and reference items. Certain equipments, such as microbalances, micropipettes, laminar air flow cabinets or incubators, are not regularly maintained, monitored and calibrated.

Characterization and environmental conditions under which the test systems are manipulated and stored are critical in *in vitro* studies. Another important pitfall is the lack of description in the experimental design concerning the use of any internal control items to control bias and to evaluate the performance of the test system. Finally, it is observed that samples of long-term preservable test systems are not always retained or only for a short time which can lead to a lack of confirmation of test system identity and/or reconstructability of the study.

Session 2

The point of view of GLP RAs

Chairpersons
Sergio Caroli, Katariina Rautalahti

RELATIONSHIP BETWEEN RECEIVING AUTHORITIES AND MONITORING AUTHORITIES. THE EMEA EXPERIENCE

Brendan James Cuddy, Emer Cooke
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The presentation describes the European Medicines Agency's approach to Good Laboratory Practice (GLP) inspections in the context of authorization of medicinal products. It covers the EMEA's experience as a Receiving Authority (RA), the procedures it has in place for the reporting and follow-up of GLP inspections, and the role of the *ad hoc* GLP Inspectors working group.

It also examines the relationship between the EU Monitoring Authorities (MAs) and the EMEA as a specific RA and how inspections outside the EU are handled and identifies some issues (exchange of information, handling of non-compliance, triggers for inspection) that have been raised during recent inspections.

COLLABORATION BETWEEN MONITORING AUTHORITIES, REGULATORY AUTHORITIES AND TEST FACILITIES ON GLP PRINCIPLES PROVIDES CONFIDENCE IN DATA QUALITY AND AN EMPHASIS ON SOUND SCIENCE

Betsy Grim, Thomas Steeger
Office of Pesticide Programs, United States Environmental Protection Agency, Washington, D.C., USA

The US Environmental Protection Agency (EPA) gets its authority to regulate pesticides from the Federal Insecticide Fungicide Act (FIFRA) and the Food, Drug and Cosmetic Act (FDCA). Regulations on Data Requirements for Registration of Pesticides are codified in the US Code of Regulations 40 (CFR) Part 158. The 40 CFR Part 160 prescribes Good Laboratory Practice (GLP) Principles for conducting studies that support or are intended to support applications for research or marketing permits.

As well as the established process that allows the Regulatory Authority, Office of Pesticide Programs (OPP), to request audits by the Monitoring Authority, EPA's Office of Enforcement, Compliance and Assurance (OECA) of a Test Facility (TF) when data quality of a submitted study is in question, there have been special requests for audits of studies by OPP because the studies are key to its scientific assessments. The herbicide atrazine has been the subject of numerous studies investigating its potential effects on the survival, growth, metamorphosis and gonadal development in African clawed frogs (*Xenopus Laevis)* and other species of amphibians. EPA required the atrazine registrant to conduct a tiered study approach. Tier I of the studies involved laboratory studies to determine whether atrazine affects amphibian gonadal development.

Several GLP audits were conducted during the Tier 1 atrazine amphibian study entitled *Response of Larval Xenopus laevis to Atrazine Exposure: Assessment of Metamorphosis and Gonadal Morphology*. These audits were conducted on each of the in-life (Phase 1) TFs*, i.e.*, Wildlife International (WLI) Ltd., Easton, MD, USA and the Leibniz Institute of Freshwater Ecology and Inland Fisheries (IGB), Berlin, Germany. All of the audits were conducted in conjunction with the EPA GLP Monitoring Authority (MA), the Office of Enforcement, Compliance and Assurance (OECA) as well as auditors from the Regulatory Authority (RA) (OPP). The audit of the German facility also included representatives of the German equivalent of OECA.

In Phase II of the Tier 1 study, tissue samples collected (by both IGB and WLI) during Phase I were prepared for histology and reviewed by a veterinary pathologist at the Experimental Pathology Laboratory, Vienna, Virginia, USA. This inspection included personnel from OPP, OECA and EPA's Office of Research and Development (ORD).

During each of the inspections, representatives of the primary technical registrant for atrazine (Syngenta) and their Quality Assurance/Quality Control (QA/QC/) staff along with the TF QA/QC personnel were present.

The above skill mix and cooperation between the MA, RA and the TFs allowed OPP to ensure the GLP Principles were being followed as well as allowing everyone involved to bring up some higher level science issues associated with the study execution. There was an overall emphasis on sound science by everyone involved in the inspection.

NATIONAL GLP PROGRAMMES AND IMPLICATION OF PHARMACEUTICALS, PESTICIDES AND OTHER CHEMICALS REGULATORY AUTHORITIES

Nobumasa Nakashima
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There are various kinds and types of Good Laboratory Practice (GLP) Monitoring Authorities (MAs) among countries. For example, some countries have only one MA and others, including Japan, have more than one MA. In addition, each MA has its own relationship with Regulatory Authorities (RAs) and industries based on the internal regulatory systems.

Japan has six GLP programmes. The number is likely the largest in the world. We have been making efforts to establish a close link between programmes to apply and implement them effectively and efficiently as described below.

- Establishment of the Inter-Ministerial Meeting on GLP. It is essential to establish a system for information exchange and decision making when there are a number of GLP programmes such as in Japan. We have established the Inter-Ministerial Meeting on GLP between GLP programmes to share the information from OECD and foreign countries and make a national decision as a whole country.
- Joint training programme. With a goal of training the inspectors and narrowing the difference with inspection over programmes, we have initiated the joint training programme including joint visit to the Test Facilities and attending the evaluation committees at other programmes. We have also started the Joint Mutual Evaluation programme by using the OECD Working Template to prepare for the OECD on-site evaluation visit project.
- Joint translation programme of the OECD documents. To avoid unnecessary confusion due to the difference of the interpretation and translation of OECD documents between programmes, we translated the OECD documents jointly in cooperation with the industry. It also has substantial merits such as cost cutting and time saving for all stakeholders in Japan.
- Others. Each authority play mutual roles as both for RA and MA. It means that there are close relationships between RA and MA. Communication with partners from industries is also greatly facilitated.

We know that some countries, including non-Member countries, have also established multi-GLP-programmes. We would be pleased if our experience could be useful to to them.

Session 3

The point of view of TFs

Chairpersons
Dominique Abdon, Hans-Peter Saxer

GLP 30 YEARS ON: CHALLENGES FOR INDUSTRY

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The Principles of Good Laboratory Practice (GLP) have undergone little change since they were established 30 years ago. Conversely, there have been huge advances in science and technology during this time. Test Facilities (TFs) have embraced these changes to enhance the quality of their programmes of non-clinical safety testing. As a consequence, practices are very different today compared with the late 1970s. Working in the modern day environment has led to a divergence of opinion in the application of the GLP Principles.

The Principles themselves are still fundamentally sound and so on the one hand industry must take into account these Principles before applying new science and technology and, on the other hand, the GLP Monitoring Authorities (MAs) should recognise the impact of technology on the quality of data to allow for a pragmatic approach without compromising compliance. Advances in science has led to new study types, new study designs, increased interest in biological entities, increased scientific methodology and the ability to measure more parameters. The GLP Principles could be perceived as a barrier for such changes due to the risk or effort required to transfer novel research techniques into the safety testing environment. Industry should not move too quickly ensuring that appropriate validation has taken place and GLP MAs should readily accept valid models for safety testing.

Advances in technology have been of great benefit to the industry, for example, allowing data to be captured electronically and in a number of formats. These changes have enhanced the quality of data and should promote the application of risk management Principles; however this is somewhat constrained by the GLP Principles, *e.g.*, the requirement for Quality Assurance (QA) to audit every final report.

The advancements in science and technology have also influenced the organisation and strategy of TFs. With improvements in communications and development of specialist areas, the industry can now fully operate on a global basis rather than having a number of separate entities operating within the same organisation. The challenge here is to harmonise procedures when there are parochial GLP MA interpretations. The improvement in communications and capacity to perform specialised or focussed areas of work has also contributed to a significant increase in multi-site studies. Multi-site studies present more compliance risk than single site studies due to their complex nature.

A specific challenge for QA unit is maintaining their independence. The auditees perception of the QA unit being the "police force" has been replaced by QA unit now being considered a partner. This has greatly enhanced compliance as auditees more readily seek consultation and advice from the QA unit. The QA unit must ensure that the relationship does not impact on their ability to monitor in an objective, independent manner.

The industry is faced with a number of challenges related to the conduct of non-clinical safety studies. The main challenges are the incorporation of new science/technology into the safety testing environment, globalisation in the face of parochial GLP interpretations, the management of multi-site studies, independence of the QA unit and the scope of the GLP Regulations themselves.

IMPLEMENTATION OF THE OECD GLP PRINCIPLES AT TEST FACILITIES IN JAPAN

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For the implementation of the OECD Good Laboratory Practice (GLP) Principles and performance of the studies according to worldwide regulatory requirements, Test Facilities (TFs) under multi-GLP-programmes in Japan need better understanding, much international information and good communication with Monitoring Authorities (MAs) and relevant Regulatory Authorities (Ras). The Japan Society of Quality Assurance (JSQA), which comprises most of TFs, has been spending big effort to improve communication with MAs and to ensure the international acceptance of data in accordance with OECD GLP Principles.

In order to establish international quality networks, JSQA has international activities with EU, USA and Asian countries as follows:

- *improvement of communication with MAs*. JSQA has communicated and cooperated with some MAs in promoting the development of quality test data. As an example, regarding Pharmaceutical GLP, Pharmaceutical and Medical Devices Agency (PMDA) answers questions on interpretation of GLP from JSQA at annual GLP training courses. The Questions & Answers presented in the training course are published in the GLP Guide Book every year and shared with all parties concerned. Furthermore, we have put together our opinions and discussed with PMDA on the following specific issues: 1) use of digital camera in GLP studies; 2) procedures and records of general clinical observation using a computerised system;
- *establishment of global quality network*. JSQA concluded Memoranda of Understanding with the Society of Quality Assurance in USA and the British Association of Research Quality Assurance to promote the communication among the societies in October 2002. These three societies had held the 1st Global Quality Assurance Conference (GQAC) in Florida, USA in February 2005 to share views, knowledge and experiences in QA. International projects such as "Comparison of the practical GLP interpretation among tripartite countries" are in progress among these societies now. The project results will be presented at the 2nd GQAC in Edinburgh, UK in October 2008. It is planned to hold the 3rd GQAC in Kyoto, Japan in November 2011, expecting a more internationally harmonized approach in GLP issues.

RISK BASED ASSESSMENT APPLIED TO QA GLP AUDITS. HOW TO FULFILL REGULATORY REQUIREMENTS WHILE MAKING THE BEST USE OF OUR COMMON SENSE, KNOWLEDGE, TALENTS AND RESOURCES?

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For ages the standard plan of internal Good Laboratory Practice (GLP) audits has been designed according to the study critical phases' concept. A decade ago the concept of facility-based and process-based audits came in force, mostly under the influence of short term and *in vitro* study design. For unclear reasons, probably dictated by an unchanged interpretation of FDA GLP Principles, the quarterly inspection scheme has been the prevailing rule. Nowadays, the emerging concept of risk management reaches the field of GLP. This communication intends to address the following items.

- The nature of risks associated with the GLP Principles and GLP studies.
  What is a risk in a GLP environment and what are the criteria used to characterize a risk in laboratory and R&D environment.
  Quality and integrity of data, study results and scientific conclusions. Which risks are associated to the processes and which are associated to the product.
  Workers safety.
  Consumers safety.
- The variety of tools available for assessment of those specific risks.
  The Principles of risk assessment – the five steps approach.
  The standard and specific risk assessment tools. Who should assess the risk? The Quality Assurance (QA) unit? The management? The organization as a whole?
  The required level of accuracy.
- The use of risk assessment results for the elaboration of audit plans.
  Nature of information obtained.
  Prioritization.
  Intrinsic Risk versus available resources.
- The potential caveats from a regulatory standpoint.
  Compatibility of risk approach with the GLP regulatory requirements.
  How to demonstrate the GLP goals are fulfilled although some of the GLP specific requirements may not be.
- The benefits of this approach for the audits efficiency and the quality systems improvement.
  What the risk approach provides to the organization.
  How does risk approach efficiency compare to standard efficacy.
  The use of metrics for continuous improvement.

CRITICAL ASPECTS REGARDING THE APPLICATION OF THE GLP PRINCIPLES TO NEW COMPOUNDS SUCH AS BIOTECHNOLOGY PRODUCTS

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The safety evaluation of new products such as the biotechnology-derived pharmaceuticals (biopharmaceuticals) requires a less standardised and more flexible strategic approach, to be defined on a case by case basis. In fact, conventional approach to toxicity testing is not appropriate. This is due basically to the biological and structural properties that are specific for each product, especially regarding aspects like species specificity and immunogenicity activity. Thus, it is necessary to select the relevant animal species for toxicity testing, evaluate the effects on the immune system, considering both the humoral and cell-mediated immune responses, and then develop new types of tests (*e.g.*, *in vitro* tests, analytical methods).

Any test performed for the safety evaluation of a new product shall be carried out in compliance with the Good Laboratory Practice (GLP) Principles. Nevertheless, also Regulatory Authorities recognise that some studies/tests may be part of the registration dossier, although not full GLP compliance can be claimed. Of course, the non-compliance areas/aspects need to be clearly identified as well as their impact on the overall safety evaluation.

The application of GLP Principles to new tests/methods always requires their re-interpretation and adaptation and, as usual, new doubts and questions arise. Examples of problematic aspects regard the availability, need and extension of the characterisation of the reference items, including the blank matrices, as well as the feasibility, need and extension of the validation of any new test/method developed.

Difficulties are well evident, for example, if we consider as mandatory the application of the GLP standard requirements in the case of classic analytical methods (HPLC methods, MS/MS and so forth) to these new tests/methods, especially to the non-quantitative ones. Regarding the reference item, *e.g.*, it can be an antibody prepared in house through an *in vivo* study. How to manage the preparation phase? How to characterise this product. What is the minimal information required? It is neither easy nor foreseen to reply to such questions, especially keeping in mind that such reference item could be used only for one analytical test/method carried out as part of a toxicology study in order to get supporting information.

Therefore, it seems necessary to evaluate the issue more in depth in order to establish a dialogue among involved parties, colleagues from other companies as well as Regulatory Authority (RA) representatives, for a harmonised understanding and application of GLP Principles in this field.

INTERNATIONAL GLP. KEY ISSUES FROM A TEST FACILITY VIEWPOINT

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The implementation of the Good Laboratory Practice (GLP) Principles on an international level is well advanced. However, GLP Guidelines leave room for interpretation and working in GLP environments in several countries represents a challenge. Some experiences highlighting key issues are presented.

- National GLP interpretation.
  The interpretation of GLP roles, responsibilities and rules in different countries lacks consistency.
  Multi-site studies conducted at test sites in different countries cross the "GLP-borders". Issues vary from differing interpretation of the OECD Guidelines to differences in the content of the OECD Guidelines in different language versions.
  From a company viewpoint, it is desirable to organize Test Facilities across regional or national "GLP-borders". A more harmonized approach by the international GLP monitoring community would be helpful.
- Archiving. In spite of the new OECD Guidance Document No. 15 on Archiving, some important issues still have not been harmonized on an international level.
  Different required archiving periods in different countries are problematic, especially when working with Contract Research Organizations (CROs) in several countries.
  There is no international systematic approach (or recommendation) for dealing with archived data if CROs close down.

GLP and Information Technology (IT). Due to the speed of technical development in the area of IT, the gap to GLP is constantly widening. As a consequence, Test Facilities (TFs) frequently face the challenge of using new IT techniques in the GLP environment in accordance with the GLP rules. In addition, the tendency towards global IT strategies and systems also applies to IT tools in the GLP area. This again crosses the "GLP-borders".

List of GLP TFs. Most countries maintain a list of all currently certified GLP TFs. However, if the GLP certificate of a TF is not renewed or even revoked, there is no official system in place to circulate this information on an international level.

Import tolerance studies. Import tolerance studies must be conducted according to the GLP Principles (field and analytical part). This rule also applies if the studies are performed in "non-GLP" countries. This entails enormous time, effort and cost for the TF "exporting" its GLP competence and the complete GLP infrastructure including a Quality Assurance (QA) system has to be brought along for each individual study.

This study-by-study approach does not contribute to building a sustainable GLP base in these “non-GLP” countries.

DIFFERENCES IN THE INTERPRETATION OF THE GLP PRINCIPLES BY OECD MONITORING AUTHORITIES: THE POINT OF VIEW FROM THE PHARMACEUTICAL INDUSTRY

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The need to harmonise the Good Laboratory Practice (GLP) Principles, their application and their monitoring was seen very early on with the publication of the set of OECD documents, the joint meetings and training of the inspectors and the system of Joint Mutual Visits. Even though some challenges were encountered in the preparation of the text of the initial OECD documents and the update of the Principles in 1997, the texts are now, for the most part, aligned. However, often the expectations behind the text are different and sometimes even opposite.

In my company we have an almost unique position having 12 research and development sites in 8 different countries, all performing phases of studies which can be used by any of the other sites and all inspected by OECD GLP Monitoring Authorities.

As you will all - I think - agree in such a global organization to ensure the maximum quality, it is always best to follow the same practices and processes. In this presentation I identify some of the challenges which are encountered when we try and establish a global system of high quality which will satisfy all the expectations of the multiple Monitoring Authorities (MAs).

In this presentation I identify the diversity of origins of the requirements which we need to be aware of including international and national GLP Principles, specific guidance documents on GLP, question and answer sessions on GLP interpretations, annex requirements on specific areas (21 CFR part 11, veterinary legislation *etc.*) and conference presentations by Regulatory Authorities (RAs).

I concentrate then on some of the more important variations in expectations and interpretations concerning:

- perimeter of application of the GLP Principles;
- metabolism and pharmacokinetics;
- multi-site studies;
- metrology;
- computer-related systems;
- master schedules;
- Quality Assurance (QA) programme and responsibilities;
- control article in bioanalytical phases;
- extra work to signed off studies;
- terminated compounds.

In the time given, however, it obviously is not possible to discuss in detail all of the differences in the expectations and unfortunately we are not able to discuss the very great

and interesting variations in the classification of the severity of the same observation by different MAs which can go from “no criticism” to “critical observation”.

It is important to realize that even though there might be some interpretations that we in the industry have some difficulty in understanding, the objective of this presentation is not to complain or to criticize one or other of the MAs. Rather, the objective is to try to be constructive and to show where there are differences so that you can then help us in our goal which is to give you the highest possible level of quality. This obviously will be much easier if we in industry have a single set of expectations to which we need to adhere.

OECD AND US GLP APPLICATIONS

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Since the inception of the FDA Good Laboratory Practice (GLP) in 1979, the OECD Principles of GLP in 1981 and the finalization of the EPA GLP in 1983 there have been recognizable differences between the compliance programmes.

All have been revised since their initial publication and there remain differences in verbiage, and in some cases content, between the FDA, EPA and OECD GLP Principles, but the end result for each is the assurance that the data generated under each programme is of sufficient quality and integrity to support the reports for the various studies.

These differences, while not affecting the data quality, can result in issues when submitting studies globally.

This presentation looks at some of the differences that exist between the US and OECD GLP Principles and the challenges global companies face when making regulatory submissions.

ROLE AND RESPONSIBILITIES OF TEST FACILITY MANAGEMENT AND SPONSOR RELATED TO STUDIES PERFORMED ACCORDING TO THE GOOD LABORATORY PRACTICE PRINCIPLES

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The focus of this presentation is based on the OECD series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring.

In particular, the managements' responsibilities during a regular onsite study compared to the responsibilities in a global multi-site study are illustrated. Other issues of interest in this context are dealt with, such as the qualification and training for professionals and technicians, the meaning of "validity of Standard Operating Procedures (SOPs)", what is the relation between management and Quality Assurance (QA), the role played by study plans, test and reference items, archives, master schedule, communication lines, validation of methods and calibration, and related activities.

Furthermore, the consequences for the test facility management and sponsors during global multi-site studies are discussed, with particular regard to the existence of "other" responsibilities set forward by Health Authorities in countries with deviating rules.

Hence, the major question on the floor is whether one global set of GLP Principles can be agreed upon which in turn can lead to one global submission file. It is firmly hoped that Health Authorities and Industry, hand in hand, can actually optimize their interaction to the overall benefit of human health.

DEVELOPMENTS IN CONSULTATION AND TRAINING IN THE GLP ARENA: 1980 TO 2020

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This presentation is divided into two parts; the shorter first part traces the development of Good Laboratory Practice (GLP) consultancy and training from the early 1980s to the present time, the longer second part goes on to discuss the present industrial needs in GLP consultancy and training and suggests what is likely to happen in these areas over the next ten years.

Part 1. Consultancy and training requirements from GLP inception to the present time. In common with many other industrial activities, the development of both GLP training and GLP consultancy have been subject to the normal constraints of the client-supplier relationship. When the GLP regulations of the FDA, followed by the OECD GLP Principles, were published in the early 1980's, they were new and worrisome for the Life Science industries. The primordial need, as seen by these industries, was simply to understand what was required of them to avoid regulatory hassle. As a result, a new profession, the "GLP expert", was born. Because GLP was completely new, GLP experts often combined basic training and consultancy in one package.

Training was concerned with helping trainees to understand the regulatory text of GLP and make them aware of their responsibilities in the successful management and conduct of GLP studies. Trainers stuck very closely to the "letter of the GLP Principles" with only the most imaginative stepping outside of the GLP regulatory mould to embrace relevant notions and fundamentals of quality already explored elsewhere.

Consultancy concentrated on using the GLP awareness training as a lever to implement compliant systems. Particular attention was devoted to the development of compliant prescriptive documents (*e.g.*, study plans, standard operative procedures) and descriptive documents (*e.g.*, raw data, reports).

With the development of the OECD GLP advisory and consensus documents, training and consultancy became much more complete; again, in response to the industrial needs of the time. Training was developed to cover the roles and responsibilities of specific actors (*e.g.*, management, study director, quality assurance). Consultation developed two main functions; the first to audit on behalf of the client company (both in-house and externally), the second to prepare companies for regulatory inspections (*e.g.*, mock inspections, inspection readiness).

Part 2. Consultancy and training GLP requirements over the next ten years. Few major companies are now worried about their GLP compliance status, although regulatory inspectors still find occasional major problems. However, there is a burgeoning of small, highly specialised companies, particularly in the biotechnology sector, that need the type of consultation services previously provided to larger companies. In addition to these, there are other areas which require servicing: analytical laboratories facing the problems of Registration, Evaluation, Approval of Chemicals (REACH), clinical analytical laboratories caught in the Good Clinical Practice (GCP) regulatory hiatus, *etc*. However, consultation

over the next ten years will also be focussing on the harmonisation of regulatory references used on the same site, such as Good Manufacturing Practice (GMP), GCP, GLP, ISO, and also on the incorporation of other quality concepts into the GLP laboratory (*e.g.*, risk analysis, quality indicators, continuous improvement).

Training will clearly be required in the areas mentioned above. But there will be two other important developments in training. The first is the thrust for training programmes which can serve as "certification" so that relevant staff can demonstrate the level they have attained, with the view to servicing their professional development. The second is the need to provide individualised training at distance.

This means that we will see important developments in Internet-based training programmes. Obviously these two developments are not mutually exclusive. Indeed, Internet training, followed by assessment modules, and covered by certification from an academic institution will be run-of-the-mill in the year 2020.

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