

# OECD principles of GLP: what is working and what needs work

**Chidambaram T. Viswanathan**

*Food and Drug Administration,*

*Center for Drug Evaluation and Research, Rockville, Maryland, USA*

**Summary.** The Organisation for Economic Co-operation and Development (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 the principles of GLP are indeed accepted in other member countries for purposes of assessment. Regulatory authorities (RA) routinely further assess such studies to determine their applicability to specific regulatory decisions. In the experience of the author, the procedures laid out by the OECD GLP principles often support and complement the collection of robust data and aptly address complexities such as multisite study conduct. Perspectives on what works and what might benefit by further optimization are discussed.

*Key words:* good laboratory practice, regulatory authorities, mutual acceptance of data, multisite studies.

**Riassunto** (*I principi di BPL dell'OCSE: cosa è adeguato e cosa necessita di ulteriore adeguamento*). I principi di buona pratica di laboratorio (BPL) dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) hanno lo scopo di assicurare l'integrità e la qualità dei dati. I dati di sicurezza preclinici in un paese membro dell'OCSE in conformità ai principi di buona pratica di laboratorio (BPL) sono effettivamente accettati negli altri paesi membri. Le autorità regolatorie (AR) valutano ulteriormente tali studi in maniera sistematica per verificare se essi rispettino decisioni normative specifiche. L'esperienza dell'autore conferma che le procedure messe a punto in base ai principi di BPL spesso favoriscono e completano l'ottenimento di dati robusti e ben si prestano alla gestione di situazione complesse come la conduzione di studi multisito. Vengono infine presentate alcune considerazioni su quanto non presenta problemi e su cosa invece trarrebbe vantaggio da una migliore ottimizzazione.

*Parole chiave:* buona pratica di laboratorio, autorità regolatorie, accettazione reciproca dei dati, ispezioni, studi multisito.

## INTRODUCTION

The principles of good laboratory practice (GLP) of the Organisation for Economic Co-operation and Development (OECD) are intended to assure the quality and integrity of data [1]. Pre-clinical safety data generated in an OECD member country in accordance with the OECD principles of GLP are indeed accepted in other member countries for purposes of assessment. Such studies are routinely further assessed by regulatory authorities (RA) to determine their applicability to specific regulatory decisions. In our experience, procedures defined by the OECD GLP principles often encourage the collection of relevant data and address complexities such as multisite study conduct. As discussed during the recent "OECD industry event, multilateral symposium between monitoring authorities, regulatory authorities and test facilities on the implementation of the OECD principles of GLP", held in Villa Tuscolana, Frascati (Rome, Italy) from April 10-11, 2008, this article provides perspectives on fundamentals that work and opportunities that exist for optimization [2].

## FUNDAMENTALS THAT WORK

As an example, the OECD principles of GLP address the conduct of multisite studies through a robust consensus document on the topic [3]. Recognizing the global nature of drug development activities and a defined trend in the conduct of individual studies across multiple facilities, the consensus document provides considerations for increased complexity in study design, overall study management, and risks to data integrity. It also establishes the need for clear lines of communication between all involved parties as a mechanism to assure that individuals with the need to know have access to critical study details and data. Thus, this document has facilitated the much needed lines of communication among the principalities and improved the atmosphere across multiple facilities to follow standard criteria of GLP.

## OPPORTUNITIES FOR OPTIMIZATION

Over time, various inspections conducted by the US Food and Drug Administration (FDA) have

revealed a multitude of issues that might benefit from optimization and a strengthened approach for study conduct and reporting. The findings of such inspections bring to the forefront considerations intended to assure data integrity and the utility of the safety studies for review purposes. Certain cases of interest can be related to the adequate training of study personnel, degree of transparency of expert scientist findings and conclusions, and specific confirmation of test article dosing formulations, as follows:

#### **Example 1**

FDA review of certain reprotoxicity data found that many submitted studies had unexpectedly low incidences of spontaneous variations and malformations in both control and treated animals. The incidence rate reported by the test facility (TF) in the studies submitted to FDA was approximately 0.15%. This rate was in stark contrast to published, spontaneous abnormality rates that ranged from approximately 4-7%. Although an audit of the archived data found no explanation for the low rate of abnormalities reported, it was observed that study personnel at the responsible facility had less or negligible training than similar counterparts at other facilities that also conduct reprotoxicity studies. In light of this concern regarding observational sensitivity, more than 100 studies were deemed unreliable for review purposes.

Because inspections are not feasible for each and every study submitted for regulatory review, they should not be considered a primary mechanism for assuring and determining data integrity. In this context, RA must rely on other well-defined processes to confirm with certainty that safety assessments are valid in preparation of human exposure to test articles. The ability of study personnel to carry out their assigned functions so that protocol requirements are met and the resulting data are reliable is a significant component of a well-controlled study. Thus, considerations for assuring the adequate training of study personnel are critical. Strengthening the provisions for a qualified study staff are positive and can lead to the existence of appropriate controls that will likely support data quality, instead of the rejection of multiple studies and applications.

#### **Example 2**

It is recognized that study directors (SD) frequently rely on expert pathologists for the evaluation of histology slides. The evaluations and opinions made by such expert individuals can clearly have significant impact on the assessment of a test article in terms of human safety. Although the critical nature of this study component is wholly apparent, FDA inspec-

tions have revealed that the findings and conclusions of expert scientists involved with the conduct of the study were not documented. For example, in some instances, signed and dated histopathology reports were not archived with the study file.

As the single point of study control, the SD needs documentary evidence of communications of critical study data. Signed and dated expert scientist reports fulfill this need. Furthermore, such reports allow RA to verify that the conclusions made by the SD for the study overall accurately reflect and include the findings of the individual experts. In this regard, it is worthwhile to consider the transparency of expert scientist contributions as critical to the evaluations made by SD. The assurance of such transparency will benefit sponsors and RA alike, in understanding first hand the expert findings.

#### **Example 3**

FDA has found that SD sometimes lack the results necessary to confirm accurate dosing. In such circumstances, the SD cannot make a meaningful assessment of study outcomes, as there is no confirmation that the intended dose of test article was the actual dose administered to the test system. For example, instead of providing the results of dosing formulation testing to the SD, sponsors sometimes bypass the SD and submit this critical information to FDA separately.

When SD lack critical data, they are not afforded the opportunity to make informed evaluations regarding overall study reliability and outcomes. Without assuring the actual dose, how can the SD as the single point of study control draw conclusions regarding toxicity, or the lack thereof, at a given dose? In this regard, optimization should consider highlighting the central role of the SD and the need of direct access to critical study data.

## **CONCLUSIONS**

In our experience, accountability is a critical component in generating robust safety data and reliable study outcomes. The inspectional examples provided suggest that opportunities for optimizing study conduct and reporting exist. In this regard, it is worthwhile to consider optimization as a welcome advancement of the good foundation and infrastructure already in place for the OECD principles of GLP. Continued teamwork to address such opportunities will surely support data quality and integrity.

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