Relationship between receiving authorities and monitoring authorities. The EMEA experience

Brendan James Cuddy
European Medicines Agency, London, UK

Summary. The approach of the European Medicines Agency (EMEA) to good laboratory practice (GLP) inspections in the context of authorization of medicinal products is illustrated with particular reference to 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. Other key issues dealt with are the relationship between the EU monitoring authorities (MAs) and the EMEA as a specific RA, how inspections outside the EU are handled and some aspects (exchange of information, handling of non-compliance, triggers for inspection) that have been raised during recent inspections.

Key words: European Medicines Agency, good laboratory practice, monitoring authorities, receiving authorities.

Riassunto *(I rapporti tra le autorità riceventi e le autorità di monitoraggio. L'esperienza dell'EMEA).* Vengono illustrate le attività dell'Agenzia Europea per il Farmaco (EMEA) nel campo delle ispezioni di buona pratica di laboratorio (BPL) per quanto riguarda l'autorizzazione dei prodotti medicinali con specifico riferimento alla esperienza dell'EMEA come autorità ricevente (AR), alle procedure adottate per predisporre i rapporti ispettivi e le azioni che ne conseguono ed ai compiti del gruppo di lavoro *ad hoc* per la BPL. Altri aspetti di rilievo in quest'ambito sono i rapporti tra le autorità di monitoraggio (AM) della UE e l'EMEA come specifica AR, il modo in cui sono condotte le ispezioni al di fuori della UE ed altri problemi emersi durante recenti ispezioni (scambio di informazioni, gestione delle non-conformità, punti determinanti di una ispezione).

Parole chiave: Agenzia Europea per il Farmaco, buona pratica di laboratorio, autorità di monitoraggio, autorità riceventi.

INTRODUCTION

The European Medicines Agency (EMEA) is one of the fifteen independent European Community agencies. It is composed of a secretariat (EMEA staff), management board, scientific committees, working parties and expert groups, *i.e.*, members nominated by European Union (EU)/European Economic Area (EEA) member states (MS). The EMEA mobilises existing scientific and inspection resources for the evaluation of centralised medicinal products and to prepare guidelines on safety/quality/efficacy. In particular, the main activities of the EMEA in the inspections sector cover good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), pharmacovigilance compliance verification, mutual recognition agreements (MRA) and the Committe for Medicinal Products for Human Use (CHMP)/ Committee for Medicinal Products for Veterinary Use (CVMP) Quality Working Party (QWP). Other important aspects of the EMEA inspections sector in this field are the certification of medicinal products, sampling and testing (S&T), product defects (*i.e.*, quality problems), GMP aspects of applications/validations, chair of GXP (X = C, L and M) meetings and co-ordination of the EudraCT and EudraGMP projects.

VERIFICATION OF COMPLIANCE WITH THE PRINCIPLES OF GLP

The legal basis for inspection during the assessment of a marketing authorization application (MAA) is Regulation 726/2004, Article 57 (i) which states, *verbatim*: "co-ordination of the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations" [1].

The EMEA standard operating procedures (SOPs) cover co-ordination of GLP inspections of preclinical studies, human and veterinary applications, and pre-authorisation GLP inspections developed in collaboration with *ad hoc* GLP inspector groups. Inspection requests are triggered by assessors, prepared by EMEA and adopted by the relevant body. If the test facility (TF) belongs to the EEA, this responsibility lies with the GLP monitoring authority (MA) of the interested MS where the laboratory is

Address for correspondence: Brendan James Cuddy, European Medicines Agency, Inspections Sector, 7 Westferry Circus, Canary Wharf, London E14 4HB, United Kingdom. E-mail: Brendan.cuddy@emea.europa.eu.

located. On the other hand, for laboratories in third countries, the GLP MA of the (Co)- rapporteur MS should provide the inspection resources. Study audits and exceptionally facility audits are always possible. The assessor is responsible for evaluating the statements on GLP compliance provided in the application and the scientific content of each study. The assessor includes in the assessment report a standard statement that GLP audits are not considered necessary for the evaluation of the application or, if an audit is considered necessary, asks the inspections sector to prepare an inspection request for Day 90 or 120 from the application.

SUMMARY OF INSPECTION FACTS

An overview of the inspection requests received during these last 14 years is set forth in *Table 1*. Furthermore, 9 marketing authorisation applications for medicines for human use were entered for a total of 9 TFs (2 in EU, 4 in Canada, 3 in non-OECD countries) and 31 studies were audited (plus 10 outstanding). The average duration of an inspection is between 3 – 6 days. Of the 31 studies audited, 29 were found to be GLP-compliant whereas 2 were found not to be GLP-compliant (in full or partially). Although some minor deviations from the principles of GLP were observed in most of the 29 GLP-compliant studies, the integrity of study data was not jeopardised. Eventually, 27 studies were recommended to be used for the respective safety evaluation.

Some major findings in this context were as follows: i) TFs should pay particular attention to the difference between amendments and deviations, how and when each should be documented and how and when their impact on the study should be evaluated by the Study Director (SD); ii) the SD should ensure that the GLP principles are adhered to when amendments and deviations to study reports are needed; iii) in the case of multisite studies, the accordance of the use and supervision of sub-contractors with the GLP principles should be carefully checked; iv) QA and the way the QA audits of studies should be fully documented to record the types of inspections performed and the critical phases inspected; v) complete information regarding the determination of the homogeneity, concentration and stability of the test item should be available prior to the commencement of the study.

Table 1 | *Summary of information on inspection requests to EMEA*

Year	Request type
1995-2003	2 GLP inspection requests by CHMP
2004-2007	6 GLP inspection requests by CHMP (study audits)
2008	4 GLP inspection requests by CHMP (study audits)

GLP: good laboratory practice; CHMP: Committee for Medicinal Products for Human Use.

Findings of non-compliance with the principles of GLP should be used by the assessor as one piece of information to decide whether or not a study can be used in the application and in turn whether the exclusion of a study affects the final decision for the application. In addition to this, it should be noted that a post-authorisation inspection may be requested by a rapporteur/co-rapporteur to clarify any GLP issues that may arise after the authorisation has been granted.

CONCLUSIONS

SOPs have provided a comprehensive framework for CHMP to request GLP audits. SOPs have also made available a comprehensive set of standard documents for reference when preparing inspections, communicating outcome of inspections and preparing inspection report. In this way, administrative aspects of inspections are easily dealt with. It is also worth mentioning that all Inspectorates approached have assigned resources to the inspections and that inspections have been performed within the timeframe indicated in the inspection request and contract. Performing and reporting the inspection by Inspectorates has been done in accordance with the procedure, thus further fostering international harmonisation of GLP issues.

Submitted on invitation.
Accepted on 22 September 2008.

Reference

1. Commission Regulation (EC) No. 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council. *Official Journal of the European Union* L 92/6: 30 March 2006.