Strict guidelines have been put in place to ensure the level of drug development quality, from the outset to finished product. Studies have to adhere to good clinical practice and drug substance production must comply with good manufacturing practice.

Drug development is a highly regulated process in which each step, from the first valid preclinical drug candidate up to the fully developed drug, is shaped by stringent quality assurance measures. Preclinical studies in toxicology and pharmacokinetics must comply with good laboratory practice (GLP), while production of drug substance must follow good manufacturing practice (GMP).

Clinical studies are performed in compliance with good clinical practice (GCP). Although GCP has explicit requirements for the conduct of clinical studies, until recent years there has been no stringent requirement for the conduct of clinical laboratory analyses during clinical studies.

This was in striking contrast to the regulatory demands for manufacturing active pharmaceutical ingredients and investigational medicinal products, which must meet GMP guidelines, as well as preclinical toxicological or pharmacokinetic studies, in accordance with GLP. However, this gap has now been filled by the EMA, which has adopted the Medicines and Healthcare products Regulatory Agency guideline Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples, issued in 2009, followed by a draft reflection paper in 2010. The draft has been discussed intensively by interested parties (1). Several aspects have been softened in the final version of the guideline adopted by the GCP Inspectors Working Group in February 2012 (2).

One example of a revised requirement resulting from this guideline is that of informed consent. The draft reflection paper requested that laboratories review informed consent and ensure that study subjects sign the necessary form before starting the analyses. In the final version of the paper it is merely stated that the laboratory must be informed in a timely manner if a study subject has withdrawn its informed consent, while the obligation to obtain the consent remains with the sponsor. Despite these simplifications, the new EMA guideline contains several requirements which are clearly beyond the level of quality that can be delivered by a standard reference or hospital laboratory, and which can be summarised under the combined qualities of GLP and GCP: good clinical laboratory practice (GCLP).

Core Requirements

The EMA reflection paper is applicable to all laboratories contributing to studies submitted to authorities within the EU/EAA. This paper does not discriminate between different kinds of laboratory analyses: all data used to assess safety and efficacy must be determined in laboratories compliant with the requirements of the reflection paper – irrespective of their geographical location.

The laboratories involved in clinical trials need to comply with organisational requirements similar to GLP laboratories: the roles and responsibilities need to be defined and general training plans must be implemented, including annual...
training in GCP. Personnel must be covered by appropriate job descriptions and appropriately educated, experienced and trained. Each clinical trial should be overseen by a named individual who takes responsibility for the proper conduct of every aspect of the work. The laboratory management needs to implement a quality assurance programme, and all of the activities necessary for the conduct of the clinical trial work need to be covered by standard operating procedures. In-process quality controls and independent quality assurance audits of the facility, procedures and analytical phases are requested. Analytical data needs to be checked by quality control prior to release, and laboratories must participate in proficiency testing.

Contractual agreements between the sponsor, or its representative, and the laboratory need to be in place before any work on the clinical trial is initiated. These agreements should raise no conflict with the requirements outlined in the clinical trial protocol. The laboratory should have standard operating procedures in place for drafting, agreement and revision of agreements. The EMA guideline suggests establishing master service agreements in case a laboratory conducts multiple studies for a sponsor. These agreements need to be periodically reviewed.

Compliance
The compliance with the clinical study protocol is of utmost importance for the reflection paper and the laboratory must make sure that the analytical plan for any given study complies fully. There must be mechanisms in place to inform the laboratory about any amendments to the study procedure, and only specified analyses should be conducted. Any additional work must be covered by an amendment to the study protocol. Exceptions are only allowed for such analyses that should continue to be carried out because the safety of the patient is at risk. A typical example is the assessment of troponin T: elevated creatine kinase values (CK and CK-MB) may suggest the occurrence of an acute myocardial infarction, which should be ruled out by assessment of troponin T. Deviations from the clinical study protocol or standard operating procedures must be documented and assessed. Any serious deviation must be reported in a timely manner to the sponsor, to ensure that its impact on the integrity of trial data, patient confidentiality, consent and safety can be assessed. Samples must be labelled in such a way as to allow unequivocal identification, without disclosing the full identity of the study subject. In addition, samples must be handled and stored in a way that fully maintains sample integrity. Sample integrity must be checked at sample receipt, and if samples have been frozen or refrigerated during transport, this should be verified by appropriate measures, such as temperature loggers.

If a study subject withdraws their informed consent, the laboratory must be informed. The action to be taken is not specified in the reflection paper, however it may be inferred from the response of the EMA to the comments on the draft guideline that all samples drawn before the consent was retrieved should still be analysed (1). This procedure falls in line with regulations from the FDA, and also guarantees that samples which might provide insight into any safety issues will be subjected to analysis. Safety of study subjects and patients is more important than any other aspect of the trial. There must be mechanisms in place to guarantee a swift reporting of any significant deviations from the normal ranges to the sponsor or the sponsor representative.

Laboratory instrumentation must be subject to routine qualification, regular calibration and preventive maintenance. Analytical methods and computer hardware and software must be validated according to current standards. The reflection paper is relatively specific and provides details of the requirements that must be fulfilled in the computer validation package. Validation of methods, as well as the qualification and maintenance of instruments and computers, should be documented and archived. All study-related documents need to be archived under appropriate conditions, as long as they are requested by GCP and national legislation.

More than a year has passed since the new guideline has been adopted by the EMA. The reflection paper is very helpful in defining the quality standards that must be met by laboratories involved in clinical trials. Even the draft version had been used as a template by external auditors in the recent past, and the approved version is the blueprint for current vendor qualification checklists. The implementation of GCLP as a new standard between GLP and GCP is welcomed by many sponsors, CROs and central and specialty labs focused on clinical trials. It has strongly reinforced the trend towards central laboratories and enhances the value of clinical laboratory analyses in clinical trials.

References
1. Overview of the comments received on ‘Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical samples – draft’ (INS/GCP/532137/2010); EMA/INS/GCP/219642/2011
2. Reflection paper for laboratories that perform the analysis or evaluation of clinical samples; EMA/INS/GCP/532137/2010

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