

Guidance for UK Manufacturer's Licence and Manufacturer's Authorisation (for Investigational Medicinal Products) Holders on the use of UK Stand Alone Contract Laboratories

Introduction

This document:

- Is applicable to all manufacturer licence holders, i.e. import, export, herbals and specials
- Provides an update and details changes to the June 2010 published guidance
- Outlines the MHRA's criteria for inspection of UK contract laboratories.
- Provides guidance* as to when a UK contract laboratory must be named on a manufacturer's licence for relevant medicinal products for human** use and/or a manufacturer's authorisation for investigational medicinal products.
- Provides guidance as to when a UK contract laboratory is not required to be named on a manufacturer's licence or authorisation.
- Outlines the MHRA's expectations of the Manufacturer's Licence and Manufacturer's Authorisation holders and UK Stand Alone Contract Laboratories
- Outlines the inspection process for UK contract laboratories

*This document is for guidance and it is acknowledged that there may be some specific situations where the actual requirements may vary. In the case of contract laboratories supporting manufacture of biological products, the requirement for inspection will be made on a case by case basis, taking into account the guidance on application of GMP described in Annex 2 of the GMP Guide.

**Responsibility for veterinary only licences lies with the Veterinary Medicines Directorate.

It is acknowledged that there are a number of manufacturer's licence and manufacturer's authorisation holders that can also offer contract quality control testing to GMP. The inspection of these QC testing activities is included within the scope of their routine GMP inspections. In this situation the licence holder who is performing the testing and acts as the contract acceptor should be named as a contract laboratory on the contract giver's licence.

Updates and Changes to the August 2014 published guidance

The process of publication of a list of inspected GMP QC laboratories by MHRA has been removed. The current GMP certificate status of all inspected facilities can be determined via the online Eudra GMDP database.

Criteria for inspection of contract laboratories by the MHRA

In accordance with the MHRA's risk based approach to inspections; fee bearing inspections of stand alone contract quality control testing laboratories will be conducted against EU GMP if the laboratory is undertaking the following testing of a medicinal product or an investigational medicinal product for human use:

- Microbiological, biological and chemical/physical testing of finished medicinal products. i.e. final testing prior to QP certification for the purposes of batch release.
- Stability testing of finished marketed medicinal products
- Environmental monitoring and/or process simulation (media fill) work for sterile product manufacturer
- Biological testing if it is required to be conducted in accordance with the GMP Guide as described in Annex 2.

When contract laboratories must be named on manufacturer's licences/authorisations

Contract Laboratories that meet the criteria for inspection must be named on manufacturer's licences or manufacturer's authorisations, irrespective of the quantity or frequency of testing. This also includes any UK stand alone contract laboratory subcontracted by another stand alone contract laboratory.

Stand alone contract laboratories that are testing finished products on import into the EU must be named on the manufacturer's licence and marketing authorisation.

When contract laboratories should not be named on manufacturer's licences/authorisations

Stand alone contract laboratories that conduct all other testing (e.g. raw material and API testing) or produce data for research where the products are not intended to be released onto the market or used in a clinical trial do not need to be named on a manufacturing licence or manufacturer's authorisations.

MHRA expectations of Manufacturer's Licence holders, Manufacturer's Authorisation holders and Stand Alone Contract Laboratories

Manufacturer's licence and or manufacturer's authorisation holders (contract givers) that wish to use a contract laboratory (contract acceptor) must:

- Have a system in place to assess the suitability, competency and GMP compliance of proposed contract laboratories prior to their use, whether the contract laboratory meets the criteria for a MHRA GMP inspection or not
- Ensure that the contract laboratories used, irrespective of their location or whether they meet the criteria for inspection, are visible within the manufacturer's quality management system and listed in their site master file
- Update their respective licences/authorisations to name the contract laboratory if the contract laboratory meets the criteria for a MHRA GMP inspection
- Ensure that a written Technical Agreement which describes the GMP responsibilities of each party, and also refers to the scope of testing and type of tests covered by the agreement has been put in place.
- Have a system of on-going supervision for contract laboratories, including arrangements to periodically formally re-assess compliance, based on risk
- Ensure that contract laboratories meeting the criteria for inspection have a valid GMP certificate in place prior to data generated by the laboratory being used by the contract giver for batch disposition decisions.

The presence of an EU GMP certificate may be used as information to support the use of a contract laboratory; however the scope of any certificate should be confirmed to be relevant to the work to be performed. The certificate may form part of the contract giver's wider assessment process, but should not be used exclusively as a substitute for a formal assessment by a prospective contract giver.

A laboratory used on an 'ad hoc' basis to perform specialist testing in support of investigations is not expected to be approved prospectively on the manufacturer's licence and or manufacturer's authorisation, in order to facilitate timely investigation of unplanned events. Contract Givers are encouraged to implement a process by which minimum expectations can be assessed in a timely manner, for instance by the use of a basic questionnaire, and/or by listing key compliance expectations as part of the written request for analysis that is then issued to the contract laboratory.

Contract laboratories involved in quality control testing of medicinal products or investigational products for human use must do so in accordance with the marketing authorisation, product specification file and EU GMP.

Inspection Process

Inspections of new laboratories are triggered by the submission of a variation to the manufacturing licence and or manufacturing authorisation to name the laboratory.

The scope of the inspection of a stand alone contract laboratory will be to assess their quality system for compliance with EU GMP, along with the specific activities they perform, i.e. Chemical/physical analysis, microbiological testing, biological testing.

Within the UK there is no requirement for a stand alone contract laboratory to hold their own manufacturer's licence or manufacturer's authorisation however a GMP certificate will be issued to the contract laboratory

following a satisfactory inspection outcome.

Confirmation of the compliance status of a stand alone contract laboratory will be communicated directly to the laboratory on completion of the inspection process. The contract laboratory must notify the contract giver in writing of any data generated prior to receipt of a GMP certificate and any data generated by the laboratory must not be used by the contract giver for batch disposition purposes until a certificate of GMP compliance has been issued.

GMP certificates issued to stand alone contract laboratories details can be accessed via the EudraGMDP database.

GMP non-compliance

GMP non-compliance may be managed via inspectorate Compliance Escalation or consideration of regulatory action by the Inspection Action Group.

Compliance Escalation is a non-statutory process to take action in response to poor compliance which does not yet meet the threshold for consideration of adverse regulatory action. The main aim of the Compliance Escalation process is to direct companies towards a state of compliance, thus avoiding the need for regulatory action and the potential adverse impact to patient health through lack of availability of medicines.

Actions may include close monitoring of compliance improvement work through inspection, meetings, and correspondence with company senior management, alerting them to the compliance concerns and clearly outlining the consequences of continued non-compliance. Upon satisfactory conclusion of the remediation work, the company will be returned to the routine risk based inspection (RBI) programme; however referral for consideration of regulatory action may still occur if the required improvements are not achieved in a timely manner.

In the event of serious non-compliance issues, a referral may be made to the Inspection Action Group (IAG). The final outcome of the IAG process may result in:

- The laboratory being removed from the licence and/or authorisation.
- The laboratory being issued with a statement of non-compliance with GMP.
- The laboratory having their GMP certificate either withdrawn or replaced by a conditioned GMP certificate that only allows specific testing to be performed.

These actions may prevent the use of the laboratory for GMP testing until a satisfactory re-inspection has taken place.

GLP and GMP

The term Good Laboratory Practice (GLP) is a generic term that causes confusion when used to describe the quality control testing of medicinal products. Compliance with the OECD Principles of GLP is a regulatory requirement when conducting non-clinical safety studies of new chemical or biological substances. There is no legal requirement for the quality control testing of medicinal product to be conducted in accordance with the OECD Principles of GLP and there is no requirement for laboratories involved in quality control testing of medicinal products to be members of the UK GLP Compliance Monitoring Programme.

References

Eudralex volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice.

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