GOOD MANUFACTURING PRACTICE COMPLIANCE REPORT & INTERIM UPDATE GUIDELINES FOR COMPLETION AND SUBMISSION

Background

The latest form (new version 2.0 April 10) can be used for reporting both the Compliance Report and subsequent Interim Updates by selecting the applicable option on page 1.

The Compliance Report/Interim Update forms part of the MHRA risk based inspection system and is required to be completed by each site holding or named on a UK manufacturing license, sites holding a Blood Establishment Authorisation or non UK sites that are named on a UK Product License.

The Compliance Report will be completed in preparation for a Good Manufacturing Practice inspection of the site while an Interim Update should be submitted by sites between inspections. The purpose of the Compliance Report/Interim Update is to report to the appropriate MHRA inspector the changes on site in the following categories since the last inspection:

- Shift in performance
- Key Personnel or staff numbers
- Company ownership/ structure or status
- Processes/ Products
- Facilities/Equipment
- Other

Compliance Report
Change is regarded as either an indicator of an increase or decrease in risk or as a risk itself. As such the inspector will consider the changes in planning for the inspection and reaching a conclusion as to the current risk rating of the site. It should be noted that risk rating is not concluded until after the inspection.

Interim Update
This is supplied using the same form as the Compliance Report but provides a report to the inspector of actual changes that occur between inspection cycles. Inspectors assess the significance of changes reported and may move the planned inspection period based on the risk presented by the changes. The risk rating will only be changed after a subsequent inspection.

Introduction

The following information is provided for general guidance for completion of the Compliance Report and Interim Update. *It is the responsibility of the site to judge what information/data indicates significant change (increase or decrease) in site risk to GMP Compliance, product quality and patient safety. As individual sites are best placed to know what changes could have an impact on the above attributes the decision on what to report is with the site*. This will be reviewed with the inspector during the inspection, it is expected that there may be 'grey areas' where sites believe changes are not significant but inspectors believe they are or may be significant. Such cases will be discussed during inspection when sites may be requested to justify their position. It is the intention of the MHRA to ensure that the Risk Based Inspection system is applied in an objective manner to allow balanced risk assessments across all applicable sites. Risk rating will be utilised to define future inspection frequency and duration.

Specific Guidance

MHRA are seeking to identify significant changes in a site that would potentially alter, or indicate a change to, the inherent risk to product quality and patient safety for site activities.

GOOD MANUFACTURING PRACTICE COMPLIANCE REPORT & INTERIM UPDATE GUIDELINES FOR COMPLETION AND SUBMISSION

In order to complete this report sites should consider but not limit to the areas recorded below. Sites may wish to consider what is reported through change control, management review meetings or other strategic business meetings and considered significant by the site. Sites may also wish to consider how they will manage reporting of such changes to MHRA and whether this should be formally incorporate in site systems such as Change Control, Management Review, and Product Quality Review etc:

Shift in performance

- Outstanding or overdue Corrective and Preventive Action (CAPA) – major trend changes in CAPA to be reported rather than individual CAPA i.e. where the ability of the site to close CAPA within own targets is compromised by continual and repeated examples of failure to hit due dates or repeated rescheduling of due dates of significant CAPA items.
- Significant changes in numbers of complaints, recalls or non conformance identified that indicates a step change in performance of the site or a particular unit or product within the site.
- Slippage or amendment to actions agreed with an Inspector to correct deficiencies from a previous inspection.

Key Personnel or Staff Numbers

- Any key organisational changes that would not be picked up through the manufacturing licensing process e.g. change of site manager (senior person on site) where this individual is not named on the license. Non UK sites should also report changes in key QA or Production staff.
- Announced staff redundancies or termination of long term or embedded contract staff (i.e. indicating downsizing of the operation).
- Significant addition of staff to meet an upturn in demand should be reported particularly where this equates to around a 10% increase or more and particularly where temporary staff will be used to fill the shortfall.

Company Ownership/ Structure or Status

- Change of ownership of the site or change of position or role of the site in the wider organisation e.g. site sale or company merger or takeover, organisation restructured and site or QA lead reporting through different group or person.
- Site/company entered into administration or experiencing a financial difficulty that has/will result in budget cuts affecting good manufacturing practice compliance.

Processes/ Products

- Changes in the types or numbers of products manufactured/ handled and changes in the number of batches manufactured or handled. Although changes to types of products would be picked up through the licensing process it may be that a site has re-introduced a product type after a lengthy period without manufacture. Increase in demand for products may have resulted in increased volumes – this is particularly significant where shift patterns are changed to accommodate or staff are recruited, transferred or made redundant.
- Outsourcing activities or bringing back in house previously outsourced activities directly related to production or Quality Controls.

- GMP compliance issues identified with any API sources that would lead to the conclusion that the source was not or may not be GMP compliant e.g. critical or numerous major findings in an audit of the API site, recurring failures on incoming goods testing of the API.
- Sterility test failures
- Media fill failures resulting in re-validation in accordance with guidelines in annex 1of the EU GMP Guide.

Facilities/Equipment

- Changes to facilities e.g. addition or change of use of buildings, major refurbishments to buildings or utilities or problems with any of the aforementioned that may affect product quality or ability to manufacture/supply.
- New or modified equipment or IT systems used for storage, control, processing e.g. Addition of equipment that introduces new technology to the site, new LIMS or manufacturing execution systems or major modifications to such systems.
- Addition or replacement of largely similar equipment to that already in use would not be considered a risk by the inspectorate e.g. new HPLC system similar to those already in use.

Other

- Any other changes or issues that the site believe may indicate a step change in the sites risk to product quality or of being non GMP compliant, producing defective batches or affecting patient safety.

Mitigating Action
It is the intention to take into account mitigating action taken by sites in relation to change. As such relevant mitigating action already taken against changes reported should be recorded in a succinct manner. Evidence of this may be reviewed during the inspection.

Interim Update - Changes Made Post Inspection

Significant changes confirmed between inspection visits must be reported to MHRA **but only for sites that have been inspected post 01 April 09**. These changes must be submitted on the same form as the Compliance Report but page 4 will not be required.
The guidance given above for content of the Compliance Report should also be applied to the Interim Update.
The completed form should be sent by e mail to the inspector that last inspected your site with a copy to gmpinspectorate@mhra.gsi.gov.uk.
For planned changes these should be advised at implementation of the change or if appropriate e.g. staff redundancies, once the change is confirmed and prior to actual implementation.

These will be assessed by the relevant inspector and impact on the next planned inspection period assessed. It is intended that risk rating will only be amended following subsequent inspection; sites will not be formally advised of any change in their next inspection date although this may be informally communicated by the inspector.

Failure to submit a required Interim Update notification of change may be assessed by the inspector as an increased risk factor.