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Audit and Impact

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The pharmaceutical industry is a strictly regulated environment, with the object of ensuring that manufactured products are of a high quality and fit for their intended purpose. The main focus of the regulatory authorities is to ensure patient safety; in essence they are health and safety regulations. The current good manufacturing practice (cGMP) guidelines as set out in the EU Guidance and US Codes of Federal Regulations have been devised to control the drug manufacturing process, with the principal objective of ensuring products are demonstrated to be consistently manufactured to a high standard (1,2). Any changes to this manufacturing process must be managed in a controlled process of risk assessment in order to identify and evaluate the impact of those changes and to ensure that the safety of patients is not compromised.

BACKGROUND

Current GMP regulations require that pharmaceutical companies must ensure that all work conducted both on-site and outsourced off-site is compliant with the principles of cGMP, and that all starting materials supplied for product manufacture must themselves be manufactured according to cGMP.

Therefore, the expectation from the regulatory authorities for work performed off-site, including suppliers of starting materials, is that these processes must be formally evaluated as part of a quality management system to ensure compliance with the regulations. This is accomplished by an audit inspection procedure, which is a gap type analysis. This analysis compares the operations and systems of an outsourcing provider to a predefined set of criteria, and evaluates the level of compliance in order to provide a justification for either approving or rejecting the service offered. Dependent upon the quality management system and the perceived criticality of the service provided, the audit may consist of a simple written questionnaire or, as is usually required, an actual inspection and assessment of the facilities and proffered services. An example could be the supplier of simple consumables and reagents that may well only require a written postal audit, although the supplier of contract materials testing or manufacturing is a critical service, which would require an on-site inspection.

In conducting an audit, the choice of service will inevitably determine the questions which have to be answered. A contract manufacturer will require a different focus to that of a contracted analytical service, and it is often useful to have a number of questionnaires available to cover different service providers. These are useful as aidememoires, but it is essential not to follow such lists of questions slavishly and lose sight of the actual inspection process itself. There is no substitute for the power of observation. The Pharmaceutical Inspection Co-operation Scheme publishes some useful checklists in its publications website which are available for free and in common use as helpful starting points (3).

AUDIT PROCESS

In general, the following considerations are common to most inspection processes.

Selection of a Outsourcing Provider

This is dependent on the service required, and the initial stages may involve a proposed provider recommended by other users, or several which have been sourced from available literature, journals, websites and so on. The MHRA publish a list of inspected stand alone contract laboratories, which is a useful resource. In addition, guidance is available on the use of such laboratories by licence holders (4,5).

The process of selection should be described in a standard operating procedure; this may include considerations on how many should be assessed and against what selection criteria, such as accreditation

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to a quality standard, reputation in the industry, past experience, or even location.

Quality Status of the Service Provider

Considerations here include what accreditation or compliance the provider claims for the service, such as the UK Accreditation Service (UKAS), the International Organization for Standardization (ISO), Good Laboratory Practice (GLP), or cGMP. Outsourcing providers who claim to comply with cGMP should be in possession of the relevant licences and, if applicable, a letter of inspection from the MHRA supporting the contract provider as suitable to be named on licences. When selecting a provider, the first stage is often to establish the existence of a quality system and any third party inspection bodies, such as UKAS, which is useful for a calibration service.

Having established the existence of a quality system or accreditation, it is necessary to consider its relevance with the required standard. It is obvious in selecting a manufacturing outsourcing provider that those chosen must operate in compliance with cGMP requirements. This will contribute to the decision on whether a postal or physical inspection is required. It is an important consideration whether or not a provider will allow an audit inspection to take place, and in the case where an inspection is not welcomed, the selection process will be simplified by the exclusion of the provider from the approval process. A confidentiality agreement is also an important element to have in place. This may be signed on the agreed date of the inspection, or well in advance. In any event, it is the sign of a provider used to dealing within a regulatory environment that they request a confidentiality agreement be signed in advance of the audit. This will enable free discussion of any issues which may arise during the course of an audit.

Audit Conduct

Having agreed on an audit date, the actual conduct of the audit is fairly straightforward. The inspection itself is a formal process, which should follow a written procedure as part of your quality management system. The basic object is to confirm the presence of the provider, facilities and quality systems that are claimed to be in place. Having done this, it is then necessary to measure these against the required standards and establish the extent of compliance with these regulatory requirements. The process should be seen as a risk assessment. It is at this point that the questionnaires or aidememoires come in useful to aid the planning of the audit and to help ensure that all the relevant areas are covered and assessed. Questionnaires may also lend themselves to the risk assessment process as each question may be assigned a numerical score on a sliding scale of risk category. By such means it may be possible to score assessment outcomes, which can be useful in the justification of provider approval.

The audit process could be performed as follows. First there should be an introductory meeting to identify the parties involved and establish the scope of the audit. Audit inspections may cover total compliance of the entire facility to cGMP requirements or be limited to a specific area such as a single outsourced analytical test. The audit could therefore be narrow or more general in scope, depending on the service(s) provided.

An audit agenda is an essential tool to allow the most efficient planning and conduct of the audit. It is often not practical to look at every aspect of a facility or process, and it becomes necessary to establish the critical points which have the greatest risk of failure or impact on the safety of the product, ensuring that these are inspected and assessed. It is often helpful to divide the inspection time into an examination of the existing system, including process specific documents, and to follow this up with the on-site inspection of the facility to confirm the existence and level of operational compliance of these systems and processes. This should include the quality manual, standard operating procedures, training records, facility equipment records including qualification, validation, maintenance and calibration histories, manufacturing specifications and any record identified as relevant, such as out of specification results and subsequent investigations. It is often during the review of quality documents that the selection of what is to be inspected can be made. A basic understanding of the processes followed will lead to a much more focused audit. If possible, it is useful to request copies of relevant documents several days in advance of an audit inspection, and many suppliers will agree to this.

The audit inspection will then progress in the presence of representatives of the provider. It is important to ensure that all necessary safety precautions are observed. There may be a safety

policy document, which should be acknowledged. As the inspection progresses, it is beneficial to make any observations known as and when they are encountered. This will allow feedback from the provider's representatives and ensure that no misunderstandings or errors are made either by the auditor or the audited.

Communication is a vital element of the audit process and, as with all audits, inspection attitude and approach have a huge impact on the success of the audit. A successfully audited provider who is likely to be approved for use becomes part of a larger process, which will eventually establish a working relationship between the outsource provider and their client. Clear lines of communication are essential in such a relationship to ensure the smooth and problem free provision of services. The audit process should be seen as the start of a potential working relationship and part of the role of the auditor is to facilitate good communications.

At the end of the audit day or days, depending on the scale of the outsourcing requirement, there must be a close out meeting between the auditor and facility management at which any observations made can be reported back and discussed. This is an opportunity to summarise the audit inspection process. There should be no surprises at this point, as all the issues will have been raised throughout the audit and clarified between the auditor and audited. The auditor should state the outcome of the audit. An opportunity for the utsourcing management to respond at this stage should be given but this should be limited to clarification and agreement on any observations, which might be raised, and which may require corrective action.

Audit Report and Approval

Following the completion of the audit, a written report should be produced summarising the process, listing any observations and stating the outcome of the inspection: approved, not approved or approved subject to a satisfactory response to any observations made. The report should accurately reflect the audit carried out, and it is common to issue a draft report to the provider to identify any potential inaccuracies. The report should be issued within a defined time scale to the designated outsourcing contact and to the auditors own facility management, with a clear date to have the response to all findings communicated back and a tracking system to follow up any consequent action plan. Once each item has been resolved, the audit will be formally closed at this stage. The final approval of an outsourcing provider should be dependent on both the written approval of the facility management and the quality assurance (QA) dept. It is not sufficient to approve a provider by management alone without the additional approval of QA, and similarly, QA cannot solely approve a provider. It is usual to manage this process under the remit of a department concerned with the management and approval of providers. The provider should then be formally listed on an approved register.

It is a mandatory regulatory requirement that prior to the commencement of any service provision, a technical or quality agreement must be put in place covering the services provided. This agreement must identify the contract giver and acceptor, detail the service provided, quality requirements and the responsibilities attributed to the contract giver and the contract acceptor. The agreement should then be reviewed at a defined interval. This may be done following routine reassessment of the provider or may be required if any changes take place to either the giver or acceptor, such as a change to the company name.

Reassessment

All approved service providers are required to be reviewed and re-approved at regular intervals. It is advantageous to develop a formal programme of re-approval, which includes all providers from the minor to the critical. As a part of this routine process, all approved outsourcing providers can be reassessed at a predefined interval to ensure continued compliance with regulatory requirements and the agreements that are in place. Annual auditing is the usual practice, although a longer interval may be acceptable if justified. Reassessments will usually entail a re-audit following the standard process outlined above and a reapproval to confirm the approval status or, if necessary, to remove the providers from the approved list. An important consideration here is the change control process mandated by cGMP regulations. If a provider cannot be approved then a formal change control risk assessment must be conducted to assess the impact on any manufactured product from the last audit and ultimately the safety of the product and patient.

It is important to continuously monitor the performance of providers, and to reappraise the approval status in the event of failing performance. An example could be failure to supply a starting

material to a pre-defined specification or delivery to established deadlines. A well-maintained history of performance will allow trend analysis and the potential to nip problems in the bud before they become critical. It may be necessary to re-audit in the event of a failure to maintain standards and, depending on the service provided, remedial action may be required.

CONCLUSION

This article is not intended to provide a definitive method of conducting audits of outsourcing providers, but instead to be a useful summary of the process, highlighting the main points and demonstrating the many issues to be considered as a part of the supplier approval process. The regulatory requirements are unavoidable and demand that outsourcing providers be part of a system that approves them as fit for purpose and that this should be demonstrable and open to inspection. The whole process of provider selection and approval must be part of the formal quality management system and captured in a standard operating procedure. Furthermore, having audited and approved an outsourcing provider, it is absolutely necessary to maintain the approved status and to ensure that this is accomplished and recorded in full.

References

1. *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007*, MHRA, 2007

2. 21 CFR Parts 210 & 211, *Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs; General and Current Good Manufacturing Practice For Finished Pharmaceuticals*, FDA, 2006

3. Pharmaceutical Inspection Convention, Pharmaceutical Inspection Cooperation Scheme, Publications, Recommendations, various, http://www.picscheme.org/index

4. *Department of Health and MHRA Stand Alone Contract Laboratories that have been inspected against EU GMPs between April 2006 and March 2008*, MHRA, http://www.mhra.gov.uk/, May 2008

5. *Guidance for UK Manufacturer's Licence and Manufacturer's Authorisation Holders on the use of stand alone contract laboratories*, MHRA, http://www.mhra.gov.uk/, Jan 2008