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Experiences of using the GMP audit preparation tool in pharmaceutical contract manufacturer audits

Anu Linna[1,2], Mirka Korhonen[2], Marja Airaksinen[3] and Anne Mari Juppo[1]

[1]Division of Industrial Pharmacy, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland, [2]Orion Corporation, Espoo, Finland and [3]Division of Social Pharmacy, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland.

Abstract

Background: Use of external contractors is nowadays inevitable in the pharmaceutical industry. Therefore the amount of current good manufacturing practice audits has been increasing. During the audit, a large amount of items should be covered in a limited amount of time. Consequently, pharmaceutical companies should have systematic and effective ways to manage and prepare for the audits. This study is a continuation to the earlier study, where a tool for the preparation of cGMP audit was developed and its content was validated. The objective of this study was to evaluate the usefulness of the developed tool in audit preparation and during the actual cGMP audit. *Method*: Three qualitative research methods were used in this study (observation, interviews, and opinion survey). First, the validity of the information given through the tool was examined by comparing the responses to the actual conditions observed during the contract manufacturer audits (n = 15). Additionally the opinions of the contract manufacturers of the tool were gathered (n = 10) and the auditors were interviewed (n = 2). *Results*: The developed tool was proven to be useful in audit preparation phase from both the auditor's and the contract manufacturers' point of view. Furthermore, using the tool can also save some time when performing the audit. *Conclusion*: The results show that using the tool can give significant support in audit preparation phase and also during the actual audit.

Key words: *Audit; GMP; outsourcing; pharmaceutical industry; quality management*

Introduction

Outsourcing is a rapidly growing business in the pharmaceutical industry. The most commonly used outsourcing activity is primary and secondary packaging, but also manufacturing and formulation activities are commonly outsourced[1]. The tough competition in medicine prices is moving the manufacturing operations to third countries, and more than 50% of pharmaceutical companies have some outsourcing activities in India and/or China[2]. Especially India is growing in outsourcing business because, in addition to cost savings, Indian pharmaceutical companies can bring value with good experience and knowledge in current good manufacturing practice (cGMP) and availability of English-speaking scientific talent[3].

Risks regarding pharmaceutical outsourcing are, for example, loss of control of quality and regulatory compliance[1]. Recent examples show how these risks may suddenly come real. In the beginning of 2008 contaminated heparin product was suspected to cause several deaths and numerous adverse effects around the world[4,5]. According to US Food and Drug Administration (FDA's) investigations, the contamination was tracked down to the manufacturer of heparin active pharmaceutical ingredient (API) in China. In September 2008, FDA issued warning letters to two Ranbaxy Laboratories' manufacturing facilities in India because of cGMP deficiencies[6]. Additionally, FDA issued an import alert to all products manufactured in these two facilities, meaning that these products may not be imported to the United States before the company has corrected the deficiencies.

These incidents must be seen as warnings for pharmaceutical industry that when companies work with suppliers/contractors, they never know what might

Address for correspondence: Anu Linna, Orion Corporation, P.O. Box 65, 02101 ESPOO, Finland. Tel: +358 10 426 4278, Fax: +358 10 426 3131. E-mail: anu.linna@orion.fi

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happen[4]. It is therefore crucial that companies have efficient systems for supplier qualification and quality management of outsourced activities. This issue has also been highlighted by the authorities, as the new ICH Q10 Guideline 'Pharmaceutical Quality System' has a specific chapter for outsourced activities and purchased materials[7]. In 2004, the EU legislation was updated to include the requirement of cGMP for APIs, and in practice this led to requirement for pharmaceutical companies to audit all API manufacturers[8]. As the supply chain of products is getting more complex, the role of the qualified person responsible for batch release has also been changing[9]. A Qualified person should have more focus on the quality system of all parts of the supply chain instead of releasing the batches on the basis of documentation and checks. One key element for the quality management is the quality agreement, which should be in place with all the contractors.

Quality can be built into the outsourced product, for example, by training, auditing, and monitoring the contractor. Therefore the continuous evaluation of the contractor is essential[10]. Once a contractor has been chosen, there should be ongoing evaluation to secure the continuous quality of the product, and this is ideally done by regular audits[11]. The objective of the audit should not be focused on finding deficiencies but to give objective assessment of the company's operations and find ways to improve them[12]. The audit can only be as good as the auditor who performs it, and there are many personal skills required from a good auditor. The auditor should have excellent technical knowledge of the operations he is auditing. Additionally some personal skills such as questioning, listening, and organizational skills are essential to carry out the audit successfully[12,13]. Above all, the auditor should be open-minded and should focus on the evaluation of the potential patient risk when auditing. During the audit, a large amount of items should be covered in a limited amount of time. Therefore, the auditor should obtain as much information as possible before the audit[14,15]. One good way to gather information is to send a cGMP questionnaire to the company to fill in[10]. It is also common to require the company's site master file (SMF) in the preparation phase of the audit. SMF is a document containing basic information about the company and its quality management system[16].

This study is in continuation of the earlier study where a tool for the preparation of cGMP audit was developed and its content was validated[17]. The tool was developed for a nonsterile product contract manufacturer of finished products. The aim of this study was to assess the usefulness of the cGMP audit preparation tool in audit preparation phase and also investigate how the information given through the audit preparation tool correlated with the actual conditions when the audit took place. Additionally, the aim was to gather information about contract manufacturer's experiences of the audit preparation tool.

Methods

Several qualitative research methods were used in this study (Figure 1). First, correlation between the information given through the audit preparation tool and conditions detected during the audit was examined. The developed cGMP audit preparation tool has been routinely used by the case company in contract manufacturer audits since its development in 2005. The case company is a medium-sized pharmaceutical company, which has numerous finished product contract manufacturers. The aim of this part of the study was to investigate how accurately and honestly the contract manufacturers fill up the tool and answer to its questions. The research method in this part of the study was observation, which has been widely used in studies in pharmacy practice area[18].

The tool was sent to the contract manufacturer before the audit to be filled and returned, and the filled tool was thereafter reviewed by the auditor before

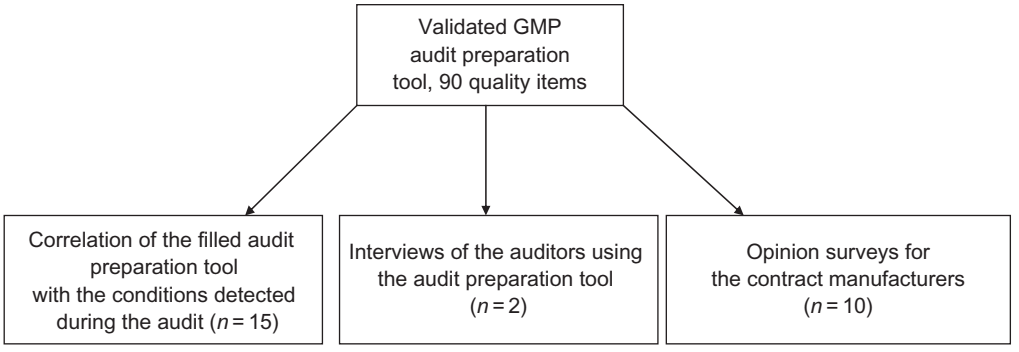

Figure 1. Methods used in the evaluation of the GMP audit preparation tool.

conducting the audit. During the audit, the validity of the information given through the tool was examined by comparing the responses to the actual conditions observed during the audit. The results were measured as number of deviations between the responses in the tool compared to the conditions observed during the audit. The deviations were marked into the filled tool during the audit and informed to the author. This evaluation was carried out for 15 out of the total 80 contract manufacturers of the case company. These sites were randomly selected to the study, and the contract manufacturers were not informed about this observation method before or during the audit.

Additionally, the auditors using the developed cGMP audit preparation tool were interviewed to assess the usefulness of the tool. Theme interviews were used in this part of the study. The theme interview method focuses on certain themes chosen by the researcher before interviews[18]. All the contract manufacturer auditors of the case company (n = 2) were interviewed. The interviewed auditors had not participated in the audit preparation tool development phase. The aim of the six themes discussed in the interviews was to gain information about the usefulness of the tool in audit preparation and also during the audit. There were also questions concerning the contents of the tool and possible problems noticed during the usage of the tool. The one-in-one theme interviews were carried out, recorded, and thereafter transcribed verbatim by the researcher (A. Linna). The analysis of the data was conducted by using content analysis.

Finally, the opinions of the contract manufacturers about the audit preparation tool were collected. A short opinion survey was sent to all contract manufacturers who had filled up the audit preparation tool before the audit (n = 10). The opinion survey instrument consisted of six structured questions relating to the contents and the usefulness of the tool from contract manufacturers' point of view (Figure 2). The contract manufacturers were asked to answer to each question with a five-point Likert scale ranging from 1 (strongly disagree) to 5 (totally agree). The opinion survey had additionally two open questions for possible general comments of the tool contents and usefulness.

Results

Correlation of the filled tool with conditions detected during the audit

In the first part of this study, the correlation between filled tool and the conditions detected during the audit was examined with 15 contract manufacturers. The result was that the contract manufacturers fill up the tool fairly accurately and honestly. In these 15 audits conducted in the contract manufacturer's premises, only two deviations were noted when comparing the filled tool to the actual conditions. For example, one of the contract manufacturers had answered to the tool that the pressure differences in the manufacturing area are checked and documented during operation, and during the audit it was noticed that this was not done. Additionally, it was noted that to some questions in the tool it was in some cases difficult to answer with the scale 'yes/no'. For instance, when the validation process for computerized systems was on-going, it was difficult for the contract manufacturers to answer the

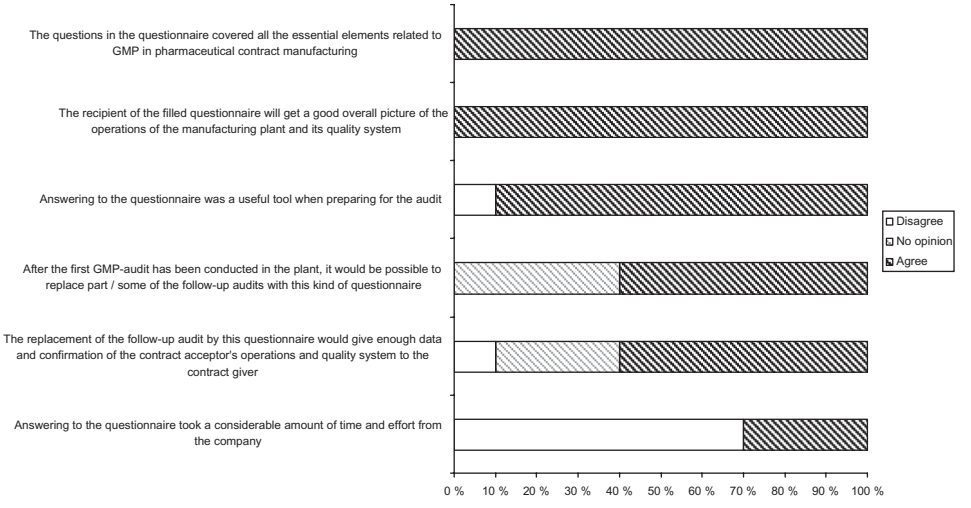

Figure 2. Results of the opinion questionnaire sent to the contract manufacturers (n = 10). The answers were given in a five-point Likert scale ranging from 1 (strongly disagree) to 5 (totally agree), responses 1 + 2 (disagree) and 4 + 5 (agree) are combined in this chart.

question 'Have you validated your GxP-critical computer systems?' with the scale 'yes/no'. There were also few cases where some of the questions in the tool had not been answered by the contract manufacturer, presumably because the question was difficult to be answered with the scale 'yes/no'.

Interviews

Both of the interviewees considered the tool to be useful in audit preparation and also during the actual audit. It was mentioned that auditor can get a good basic impression of the contract manufacturer and its quality system on the basis of the filled tool. According to the interviewees, the auditor can save some time and also focus on some specific issues during the audit with the help of the filled tool. The tool was found especially useful when no SMF was available from the contract manufacturer in the audit preparation phase or when the SMF was in some language other than English. According to the case company's policy, SMF is routinely required from the contract manufacturers and it is reviewed by the auditor before the audit. According to the interviewees, the only problem with the tool was that it is difficult to answer with the scale 'yes/no' to certain questions. Both of the interviewees mentioned that the contents of the tool are covering all the essential elements relating to current GMP requirements. However, it was also mentioned that the contents of the audit preparation tool should be updated whenever new requirements are implemented in the cGMP legislation or guidance.

Opinion survey

It was also essential for this study to gather opinions and feedback from the contract manufacturers on the audit preparation tool. A short opinion survey was sent to the contract manufacturers (n = 10) after they had filled up the tool. The results show that filling up the tool was considered useful also from the contract manufacturers' point of view (Figure 2).

All the contract manufacturers agreed that the contents of the audit preparation tool/questionnaire were covering the essential elements relating to cGMP. Contract manufacturers were also asked whether the follow-up audits could be partly replaced by using only the tool/questionnaire. Major part of the respondents (60%) agreed about this, which is not surprising when taking into account the numerous amounts of audits to be hosted by the contract manufacturers nowadays. One general comment was given by a contract manufacturer concerning the audit preparation tool, and this comment was that the tool is well planned and reflects the current GMP requirements.

Discussion

In light of recent events, such as heparin contamination and FDA's warning letter to certain Indian manufacturer, the importance of efficient auditing cannot be overstressed[4–6]. The number of audits has significantly increased recently because of changes in legislation and increased focus on product quality[7,8]. Therefore, pharmaceutical companies should have systematic and effective ways to handle and prepare for the audits. The results of the study show that the developed audit preparation tool was considered useful in the audit preparation phase and also during the audit. The use of the tool will save some time during the audit, as the auditor will have a basic impression of the company and its quality management system already before the actual audit. Additionally, it is possible for the auditors to pick up some specific issues from the filled tool which require further attention during the audit. These are very essential factors as audit is always a sampling exercise with a limited amount of time[12,19]. The better the audit can be prepared and planned, the more reliable is the result of audit[12].

The correlation between the filled audit preparation tool and the conditions detected during the audit was surprisingly good, as only two deviations were noticed in this comparison. This result shows that the contract manufacturers are filling up the tool fairly honestly and they are willing to have open communication with the auditor. A good measure of the correctness of contents of the audit preparation tool is that no major problems were detected in this comparison. During some audits it was noticed that to certain questions in the tool it had been difficult to answer with a scale 'yes/no'. The same issue relating to the structure of the questions in the tool was noticed already in the development phase of the audit preparation tool and that is why open questions also were recommended[17]. However, within the case company it was decided in the beginning of the study that the easiness of answering to the audit preparation tool is an important factor, and therefore the questions with yes/no alternatives were widely used in the tool. The further development of the tool should focus on this issue to improve the usefulness of the tool and to avoid similar problems in the future.

The results of the opinion survey sent to the contract manufacturers showed that filling up the tool was considered useful for audit preparation from contract manufacturers' point of view as well. The contract manufacturers also agreed about the contents of the audit preparation tool. This gives further confirmation for the content validity of the audit preparation tool which was achieved in the earlier study of the group[17].

The decision of what contract manufacturers to audit and how often should be based on a risk-based rating

system[20,21]. By using such system, it can be evaluated whether a mail survey would be enough for some contractors to postpone the next audit[21]. When asking contract manufacturers' opinion whether the follow-up audits could be partly replaced by using only the tool, the majority of the respondents (60%) agreed. This result was expected, because the number of audits to be hosted by contract manufacturers has been increasing. However, the goal of this study was not to find way to replace follow-up audits with the help of the tool; instead the filled tool was planned to be used as supportive instrument in the risk evaluation of the contract manufacturers between the audits. However, the current opinion in the pharmaceutical industry seems to be that actual audit should never be replaced by sending only questionnaire and reviewing some documentation of the company[22,23].

The methodology used in this study was qualitative, as it was considered more accurate approach for assessing the reliability and the usefulness of the audit tool than quantitative methodology. To receive as valid and reliable results as possible, three different qualitative research methods were applied. This kind of combination of methods is called triangulation, and it has proven to help in achieving more reliable results in qualitative research[24]. As the results of different parts of this study were convergent with each other, it can be concluded that the selected methodology was suitable for this study. A limitation of this study is the small number of interviewed auditors. The number of auditors in the case company using the audit preparation tool was only two. Consequently, no conclusions can be made on the basis of the interviews. However, the results of the interviews can be used as supportive information for this study as the interviewees were experienced auditors and had been using the audit preparation tool routinely.

The developed tool was proven to give significant support in audit preparation and also in actual audit of contract manufacturer. In further studies, it could be examined how this kind of tool could support the continuous risk evaluation of contract manufacturer's quality management system and compliance with cGMP. Pharmaceutical companies should have a valid compliance measurement system for the evaluation of contractors, and an example of this kind of system has been published by Schering AG[22]. It has been discussed that this kind of documentation-based system can never replace the actual audit, but it can give significant support for compliance evaluation in between the audits. As the contents of the current audit preparation tool are only appropriate for nonsterile product contract manufacturers, further development is needed to create specific tool for sterile product manufacturers and possibly also for API manufacturers.

Conclusions

The developed tool was considered valuable in audit preparation and it was proven to give authentic basic information about the contract manufacturer and its quality management system. Filling up the tool was considered useful for audit preparation also from contract manufacturers' point of view. Additionally using the tool can also save some time when performing the audit. In the further parts of this study the role of the developed audit preparation tool should be extended to be used in total quality management evaluation system of the contract manufacturers.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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