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Research paper

Developing a tool for the preparation of GMP audit of pharmaceutical contract manufacturer

Anu Linna [a,b,*], Mirka Korhonen [b], Jukka-Pekka Mannermaa [c], Marja Airaksinen [d], Anne Mari Juppo [a]

[a] *Division of Industrial Pharmacy, University of Helsinki, Helsinki, Finland*
[b] *Orion Corporation, Espoo, Finland*
[c] *Oy Verman AB, Järvenpää, Finland*
[d] *Division of Social Pharmacy, University of Helsinki, Helsinki, Finland*

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Abstract

Outsourcing is rapidly growing in the pharmaceutical industry. When the manufacturing activities are outsourced, control of the product's quality has to be maintained. One way to confirm contract manufacturer's GMP (Good Manufacturing Practice) compliance is auditing. Audits can be supported for instance by using GMP questionnaires. The objective of this study was to develop a tool for the audit preparation of pharmaceutical contract manufacturers and to validate its contents by using Delphi method. At this phase of the study the tool was developed for non-sterile finished product contract manufacturers. A modified Delphi method was used with expert panel consisting of 14 experts from pharmaceutical industry, authorities and university. The content validity of the developed tool was assessed by a Delphi questionnaire round. The response rate in Delphi questionnaire round was 86%. The tool consisted of 103 quality items, from which 90 (87%) achieved the pre-defined agreement rate level ($\geqslant$75%). Thirteen quality items which did not achieve the pre-defined agreement rate were excluded from the tool. The expert panel suggested only minor changes to the tool. The results show that the content validity of the developed audit preparation tool was good.

Keywords: Pharmaceutical industry; GMP; Outsourcing; Audits; Delphi method

1. Introduction

Pharmaceutical industry has struggled with many different challenges during the past few decades [1]. The biggest challenge is the pressure from health authorities to lower the price of medicines. At the same time the regulatory requirements are increasing and the development times of new products are getting longer [1]. Pharmaceutical industry is trying to respond to these challenges for example by consolidation, acquisitions and outsourcing.

The major challenge which pharmaceutical industry is confronting is how to produce safe and high quality medicines and in the same time reduce the costs dramatically [2]. Therefore, the companies have to focus on their core competencies and find solutions to handle the non-core competencies to be able to stay in the business [3]. As a result from that, outsourcing is a rapidly growing business in the pharmaceutical industry. Although a significant part of the outsourcing is and always will be *ad hoc* outsourcing, there is a trend towards strategic outsourcing in pharmaceutical industry [3,4]. The most commonly used outsourcing activity seems to be primary and secondary packaging, but also manufacturing and formulation activities are commonly outsourced [2]. It has been estimated that the total value of commercial pharmaceutical manufacturing of finished dosage forms is 83 billion US dollars, from which

* Corresponding author. Orion Corporation, Quality Assurance, Orionintie 1, P.O. Box 65, 02101 Espoo, Finland. Tel.: +358 10 426 4278; fax: +358 10 426 3131.
E-mail address: anu.linna-surakka@orion.fi (A. Linna).

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8–12 billion dollars is outsourced [5]. The tough competition in medicine prices is also moving the manufacturing operations to third countries, such as India [6].

Risks regarding pharmaceutical outsourcing are for example loss of control of quality and regulatory compliance [3]. Communication is a key issue in outsourcing, and consequently regular and honest communication is even more important than the quality agreement [7,8]. Pharmaceutical companies could have a lot of benefits by minimizing the amount of partners and by investing to build a strategic relationship with these partners [2]. Pharmaceutical industry does have a lot to learn about outsourcing from other technology-based industries, such as computer industry. Surprisingly large amount of pharmaceutical companies do not have defined processes for finding, choosing and managing contract manufacturers. As the final responsibility of the product remains with the marketing authorisation holder, it is crucial that the outsourced business is well controlled [9]. The importance of choosing the right contract acceptor can not be exaggerated, as some of the largest pharmaceutical recalls have been due to inadequate effort when selecting or monitoring the contractor [10].

Before choosing any contract organisation, there should be an evaluation of the contractor, and most efficiently the evaluation is done by auditing the contractor for good manufacturing practise [9,11,12]. It is important that the contractor has been audited before the work starts, but it is equally important that the activities of the contractor is continuously evaluated when the work is actually on-going [9,11,13]. Before conducting an audit, the company should do some initial research, using for example questionnaires [12]. The auditor should obtain as much background information as possible and use this information when preparing the agenda or the checklist of the audit [14]. The use of checklist during the audit can be useful but the focus should not be too much on things mentioned on this list, or the main purpose of the audit will be lost [14–16]. During the audit, the focus should not be only on regulatory compliance, but the potential business risks and leadership issues should be covered as well [16,17].

The aim of this study was to develop a tool for the preparation of pharmaceutical contract manufacturer audit. The tool was a questionnaire, which contained mainly questions relating to GMP (Good Manufacturing Practise). The purpose of the questionnaire was to gain preliminary information about the contract manufacturer and help to prepare for the audit. The content validity of the preparation tool was assured by Delphi questionnaire round.

2. Methods

2.1. Design

A modified Delphi method was used in this study. The Delphi method is a method for achieving a group judgment for a subject matter in which accurate research-based information is absent or inconclusive [18,19]. In the conventional Delphi method a small group of experts develops a questionnaire, which is then sent to larger group of experts [20]. The questionnaire should be modified on basis of the first results, and then the questionnaire rounds should be repeated until the consensus has been achieved.

2.2. Step I: Development of the audit preparation tool

The audit preparation tool was developed together with experts ($n = 5 +$ researcher) of the case company (Fig. 1). The case company is a medium-sized pharmaceutical company, which has numerous finished product contract manufacturers. The tool was developed for a non-sterile product contract manufacturer of finished products. The experts have long experience in auditing of pharmaceutical finished product manufacturers. Development took place in brainstorming session, and thereafter the first draft of the tool was created by the researcher. The structure of the tool/questionnaire was based on the EU GMP guideline. The draft tool was commented by the experts and the tool was modified according to the comments.

2.3. Step II: Delphi questionnaire round

The content validity of the audit preparation tool was assessed by a Delphi questionnaire round. An expert panel was recruited to evaluate the contents of the tool. This expert panel consisted of 14 people who had long experi-

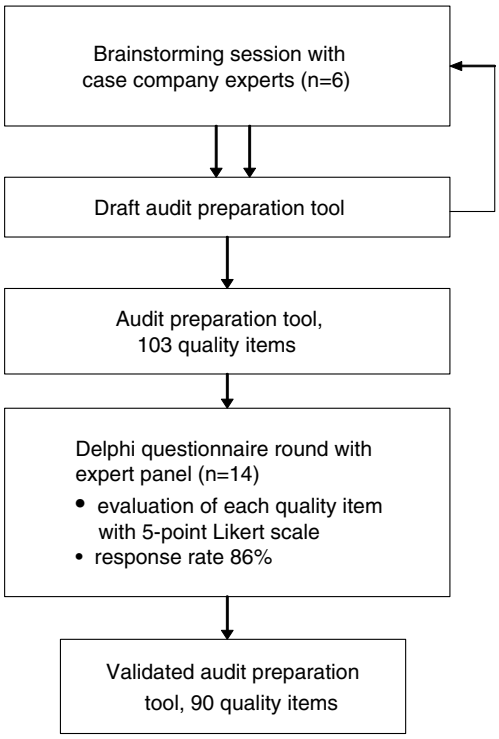

Fig. 1. Development of the audit preparation tool.

ence from pharmaceutical industry and GMP issues. The panel had members from the case company, from other pharmaceutical companies, from authorities and from the university. The original expert panel ($n = 5$) was included in this Delphi questionnaire round.

Due to sensitivity and interpretation issues relating to GMP and pharmaceutical industry, anonymity was considered essential in this Delphi questionnaire. Therefore, the questionnaires were sent by mail and the responses were handled anonymously. The face validity of the questionnaire was assured by including clear instructions how the respondents should fill in the Delphi questionnaire. Additionally each respondent was personally contacted before sending the questionnaire, and the purpose of the Delphi questionnaire was explained to them.

The developed audit preparation tool was sent to the panel members in April 2005. The expert panel was asked to evaluate the importance of each quality item of the tool on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (totally agree). The expert panel was also asked whether there were some quality items missing from the audit preparation tool and if they had any other comments or ideas relating to the content of the tool. The consensus criteria were set as follows: if $\geqslant 75\%$ of the panel members scored the item 4 or 5, the quality item was interpreted to be essential and was kept in the tool. Otherwise, the quality item could be interpreted not essential and was excluded from the tool. Similar definitions of consensus have been presented in the literature [22–24].

3. Results

3.1. Step I

The final version of the audit preparation tool was achieved in February 2005. The questionnaire consisted of altogether 103 quality items from 13 different topics. The first part of the tool contained general information, such as manufacturing site and contact person information. The 12 other topics and their contents are presented in Table A.1 (Appendix A). Most of the quality items in the tool were questions which required answering by ticking either yes or no. This kind of structure was decided within the case company experts because it was considered easier and quicker to answer. If the tool would have consisted from many open questions, it would possibly have become too laborious to answer.

3.2. Step II

The Delphi questionnaire was sent to 14 experts, from which 12 returned the filled questionnaire (response rate 86%). The level of agreement of the quality items varied from 50% to 100% (Table A.1, Appendix A). There were 90 out of 103 quality items (87%) which did meet the pre-defined criteria for agreement rate ($\geqslant 75\%$).

The respondents had only two following comments relating to the missing questions from the questionnaire. It was commented that the questionnaire should include a question about the GMP system for which the company's quality system has been founded on (EU GMP, FDA cGMP). Also it was suggested that the questionnaire should include questions about the organisation charts and job descriptions.

4. Discussion

During a pharmaceutical contract manufacturer audit, a large amount of issues should be covered in a limited amount of time. Auditing is always a sampling activity, and therefore it is important that the auditor gets a good overview about the company's quality management system by going through selected issues thoroughly [11,17]. That is why the auditor should gain as much information as possible before the audit [14]. A GMP questionnaire has been discussed to be a useful tool in audit preparation [12]. Many pharmaceutical companies are using this kind of questionnaires, however, no published studies were found about the contents, validity and use of GMP questionnaire. A systematic search for the literature yielded one study on GMP questionnaire dealing with pharmaceutical raw material and packaging material suppliers [25].

The results of our study show that the content validity of the developed audit preparation tool was fairly good. Almost one half of the quality items (48 items out of the total 103) were considered essential by every expert panel member who responded (agreement rate 100%). Only 13 out of 103 quality items did not achieve the pre-defined criteria for agreement level. On the basis of the results, these 13 quality items were considered irrelevant, and were removed from the tool. In traditional Delphi method, a new Delphi questionnaire round would be recommended for further evaluation of the consensus within the panel members [20]. However, in this study the agreement level criteria was set as if the agreement level was below 75%, the quality item should be excluded from the tool. Therefore, no additional Delphi questionnaire round was conducted in this study. The tool reflects the current GMP norms and their interpretations, and thus, it is necessary to update it regularly according to changes over time. From time to time the tool should also be modified on the basis of experience gained of its usage [15]. Consequently, the contents of the audit preparation tool can never be finalized, but its development is a dynamic process.

According to the expert panel feedback, the suggested tool can be a valuable in audit preparation and give basic information about the contract manufacturer and their quality management systems. Since development of the tool in 2005, it has already been used by the case company and has proved to be useful in audit preparation. The expert panel gave also some criticism about the audit preparation tool. Two respondents commented that the ques-

tions are too detailed and for some questions it is not informative to give the answer in yes/no format. Open questions were therefore recommended. Nevertheless, 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.

As a limitation of the study can be considered the fact, that the development of the audit preparation tool was done in brainstorming sessions by a small expert group. However, all the experts were skilful and experienced auditors who could therefore point out the most important factors to be questioned from the contract manufacturer. Extensive knowledge is essential when developing GMP related questionnaires [15]. Also the size of the expert panel used in the Delphi round was quite small ($n = 14$). Nevertheless, all these experts were very experienced in pharmaceutical industry and GMP issues, and therefore had a good view on the study context. The diversity of the expert panel was assured by including members from authorities and the university in addition to the pharmaceutical industry. Also an excellent response rate for the Delphi questionnaire (86%) was achieved.. The size of expert group used in Delphi questionnaire has varied from 4 to 3000 experts [18]. There are a number of other studies with Delphi method in which the expert panel has been quite small [19,22,23].

Delphi method has been previously proven to be useful when measuring opinions in pharmaceutical industry, as it gives total anonymity to the respondents [21]. Especially in pharmaceutical manufacturing sector this is important, because the discussion between manufacturers and authorities is often not very open [21]. However, in this study the anonymity made it possible to receive also the opinions of authorities about the audit preparation tool and this was very valuable for the study.

The developed audit preparation tool has proven to give significant support when performing contract manufacturer audits. This study will be continued by investigating how the filled audit preparation tool correlates with the reality when the audit takes place. This will be examined by checking the company's answer to each question and compare it to the conditions noted during the audit. Valuable information about the usefulness of the preparation tool will therefore be obtained in the further studies. It would also be important to receive contract manufacturer's comments about the filling of the preparation tool, and this information will also be gathered in future. Additionally, further studies will aim to develop a specific audit preparation tool for sterile products.

5. Conclusions

The content validity of the developed audit preparation tool was good and expert panel suggested only minor changes to the tool. The modified Delphi method was applicable in content validation of the preparation tool. The audit preparation tool received also some criticism, and further studies are required to examine the best usage of the tool. In the first part of the study a systematic development of audit preparation tool gave promising results and the study will be continued aiming at a in valid quality management evaluation system.

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Appendix A

A.1.

Agreement rates for the questions in the GMP-questionnaire (% of the expert panel members, $n = 14$)

Question	Agreement rate (%)
Plant information	
When has the company been established?	67[a]
When has the manufacturing site been established?	100
Do you have a Site Master File?	100
What types of products are manufactured or packed in the manufacturing site? (solid dosage forms, small volume parenterals, etc.)	100
Number of different products which are manufactured in the manufacturing site?	75
Are any of the following materials handled in the same facilities/equipment/utensils as products that are supplied to Contract Giver: penicillins, cephalosporins, cytotoxics, hormones	92
Approximately how many employees work at this manufacturing site?	92
Has any part of the manufacturing or packaging chain or the quality control of the product been outsourced to other company?	92
If yes, have you audited the contractor(s)?	100
If yes, do you have a written contract with the contractor(s)	92

(*continued on next page*)

Table A.1 (*continued*)

Question	Agreement rate (%)
Audits/inspections	
When did you have the latest inspection by National authorities?	100
How many critical, major or minor observations were given in this inspection?	50[a]
FDA (USA) inspection (if yes, when)	92
How many observations (483, warning letters) were given?	58[a]
Other authorities (if yes, when and which)	83
How many critical, major or minor observations were given?	50[a]
Facilities	
Is there a cleanliness classification in the production area?	92
Has the production area been qualified?	100
Do you have monitoring program for:	
Pressure difference	92
Temperature	83
Humidity	92
Microbes	92
Are there air-locks between differently graded facilities?	67[a]
Is the inter-lock system in use?	50[a]
Utilities	
Is your purified water system validated?	92
Do you have monitoring program for:	
Water	100
Steam	92
Compressed air	83
Nitrogen	92
Equipment	
Has qualification been carried out for all product related equipment?	100
Do you have a maintenance program for equipment?	100
Are calibration records maintained for product related equipment or instrument?	100
Warehouse	
Is the reception check documented?	83
Is the FIFO/FEFO system used in material logistics?	75
Is there a written pest control program?	100
Is there an area/system that restricts the use of materials/products due to their status (quarantine, approved)?	100
Do you have a segregated area for rejected materials?	83
Do you have cleaning instructions in the warehouse?	92
Do you keep cleaning records in the warehouse?	83
Do you have temperature and humidity monitoring in the warehouse?	100
What are the specifications for storage of room temperature (temperature and relative humidity)?	75
Have you performed temperature mapping in the warehouse?	92
Is there a temperature control of transport conditions for finished products?	83
Sampling	
Do you have a separate, controlled area for sampling of received materials?	100
Do you take wooden pallets into the sampling area?	67[a]
Do you have a written sampling plan for all materials?	100
Are reference samples of following materials retained?	
Raw materials	100
Primary packaging materials	92
Printed packaging materials	100
Do you carry out container based identification for all raw materials?	75
Manufacturing	
Is there a pressure difference between:	
The manufacturing area and the surrounding area	100
Manufacturing rooms and the inner corridor	100
Is the pressure difference checked and documented?	92
Are all the raw materials sieved before they are used in production?	58[a]
Are the metal checkers used routinely in tablet manufacturing?	100
Is there a double checking system in use to control critical manufacturing steps?	100
Is the yield checked against defined limits?	100
Is rework allowed in the manufacturing?	100
How long is the cleaning of equipment valid without re-cleaning?	92

Table A.1 (*continued*)

Question	Agreement rate (%)
Packaging	
Are the packaging lines separated by wall from each other?	83
Is the primary packaging area (where open products are handled) controlled in the same way as the manufacturing area?	92
Is it allowed to take wooden pallets to the packaging area where open product is handled?	83
Have all the packaging lines been qualified?	92
Are there bar code readers or cameras in the packaging line for the check of printed packaging materials?	100
Is the functionality of the code readers/cameras controlled during packaging process?	100
Is there a written procedure for line clearance of packaging lines?	100
Are in-process controls undertaken during packaging activities?	100
Are there reconciliation procedures for printed packaging materials?	83
Is it possible to return to the packaging line packages or materials which the bar code reader or camera has rejected?	92
Is repacking allowed?	92
Are reference samples of the finished product maintained?	100
Does the reference sample consist of at least the quantity necessary to perform two full analysis?	100
Laboratory/quality control	
Is the specification linked to the test method?	100
Is the raw data checked by another person?	100
Are the chemical and microbiological testing methods validated?	92
Are there logbooks for each laboratory equipment?	92
Have you validated your equipment?	100
Is the shelf life of reagents and standards defined and marked onto the bottles?	100
Are microbiological tests carried out periodically from the finished product?	75
Do you have an OOS (Out of Specification) handling system?	100
Has there been any OOS case during last year concerning the product? If yes, how many?	83
Is there a written stability program?	100
Is there ongoing stability study regarding to the product?	83
Have you done temperature mapping regarding to the stability chambers?	100
Training	
Do you have a plan and schedule for the GMP-training of the personnel?	100
Do you have training records for the personnel?	100
Do you have job descriptions for key personnel?	100
Do you have a system for the qualification of a new employee?	92
Quality items	
Which organisation is responsible for releasing the raw materials and packaging materials?	100
Are all the raw materials and packaging materials released before they can be used in production?	92
Can you guarantee the identity and traceability of materials and products from purchase to final shipment of the finished product?	100
Is Qualified Person responsible for the release of finished product?	92
Do you have a deviation handling system?	100
Have there been any deviations during previous year concerning the product? If yes, how many?	92
Have there been any rejected batches during previous year concerning the product? If yes, how many?	92
Do you have written procedures describing the handling of complaints and recalls?	100
Has there been any customer complaint during previous year concerning the product? If yes, how many?	67[a]
What is your time limit for handling and answering customer complaints?	75
Has there been any recalls during previous year? If yes, how many?	92
Do you have Product Quality Review system in use?	92
Do you have change control system in use?	100
Do you evaluate the need to inform your partners before implementing any changes?	92
Do you have an annual self-inspection program?	100
Do you have an electronic or manual SOP system?	67[a]
Do you have a vendor certification system?	100
Are raw materials purchased only from approved vendors?	92
Do you have a system for reduced analyzing for approved vendors?	92
Validations	
Do you have a Validation Master Plan?	92
Is the manufacturing process of the product validated?	100
Was the process validation done	
Retrospective	67[a]
Concurrent	58[a]

(*continued on next page*)

Table A.1 (*continued*)

Question	Agreement rate (%)
Prospective	58[a]
Is revalidation of the manufacturing process carried out regularly?	75
Do you have a cleaning validation system in place?	100
Have you defined your GxP-critical computer systems?	83
Have you validated your GxP-critical computer systems?	83

[a] Agreement rate below the pre-defined criteria and the item excluded from the final audit preparation tool.

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