QUALITY MANAGEMENT IN PHARMACEUTICAL PROCUREMENT: MOST FREQUENT NON-CONFORMITIES IN PHARMACEUTICAL WHOLESALERS IN BULGARIA

Assena Stoimenova, Alexandra Savova, Manoela Manova, Guenka Petrova
Medical University of Sofia, Faculty of Pharmacy, Sofia, Bulgaria
Correspondence to: Assena Stoimenova
E-mail: assena_stoimenova@mail.bg

ABSTRACT

The goal of the study was to analyze the results of 31 quality audits of seven pharmaceutical wholesalers performed in 2002–2012 and to discuss the most frequent non-conformities. The findings raised during the audits were systematized according their grade, nature of cause and consequences for the quality of the products and services provided. In total, 41 deficiencies were recorded: 26 (63.41%) of them concerned the storage of pharmaceutical products, especially the cold-chain pharmaceuticals, and 10 concerned the documentation of different processes such as cleaning, trainings, transfer of responsibilities etc. We recommend that the Bulgarian Drug Agency prepare guidelines for distributors as other regulatory institutions in the EU have done, summarizing the best practices in pharmaceutical wholesaling as well as the deficiencies found during inspections. Such guidelines will benefit not only the wholesalers’ quality management system, but also the society in general.

Keywords: quality management, quality audits, ISO 9001, pharmaceutical wholesalers, medicinal products

Introduction

Today’s global pharmaceutical market has created a critical need for efficient international supply systems in the healthcare sector. For leading pharmaceutical manufacturers, wholesalers and retailers, the supply chain is now regarded as a strategic weapon in the battle to maintain competitive advantage (10).

The supply chain includes different partners: some are pharmaceutical (pre-wholesale providers, wholesalers), and others are not (carriers, forwarders) (7). The concept of quality management is fundamental to the pharmaceutical sector. Each participant in the supply chain has their vital role in providing the public with quality, efficient and safe medicines and shares the responsibility for the outcome of therapy together with the others (5, 6, 15). Protecting and securing the pharmaceutical supply channel requires constant vigilance in cooperation with all partners in the channel: the manufacturer, the distributor, and the pharmacy as well as with state and regulatory agencies (16).

The quality of medicinal products can be affected by lack of adequate control over numerous activities which occur during the distribution process. In order to maintain the original quality of medicinal products, every activity involved in their distribution should be carried out according to the principles of Good Manufacturing Practice (GMP), Good Storage Practice (GSP) and Good Distribution Practice (GDP) (15). GDP is applied to ensure that the high level of product quality achieved by observing the GMP is maintained through the distribution network (8, 15).

The quality system is an appropriate infrastructure encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or a service, e.g., distribution) and documentation will satisfy given requirements for quality. Within every organization, quality assurance serves as a management tool (15). This infrastructure is the sum of all that is necessary to implement an organisation’s quality policy and meet quality objectives. It includes organisation structure, responsibilities, procedures, systems, processes and resources. Typically, these features are addressed in different kinds of documents such as the quality manual and documented procedures, modus operandi etc. (14).

The quality management system of pharmaceutical wholesalers should comply with the main principles of GMP. It is recommended that the quality systems are inspected or certified for compliance (15).

Auditing is an independent, objective assurance and consulting activity designed to add value and improve an organizations’ operations. It helps an organization to accomplish its objectives by bringing a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and the governance process (15).

The purpose of a quality audit is to verify the compliance with the selected standards and regulations, and certainly not to seek any faults. Usually, such audits are performed once a year or more frequently if necessary.

The goal of the present study was to analyze the results of quality audits of seven pharmaceutical wholesalers performed in 2002–2012. The non-conformities were classified as critical, major or minor.

Materials and Methods

Thirty-one audits of the quality management systems of seven pharmaceutical wholesalers in Bulgaria were performed...
in 2002–2012. The audits were performed against the requirements of ISO 9001:2000, respectively ISO 9001:2008, the wholesalers’ own quality systems, the requirements of the Good Distribution Practice and the local regulations on medicine distribution. The findings raised during the audits were systematized according their grade (major and minor non-conformities, recommendation, and opportunities for improvement), the nature of their cause and the consequences for the quality of the provided products and services. The audits presented here were done by certification organizations and the results were incorporated into the affected quality systems and presented in special reports to the distributor’s management.

The audits were organized as two-stage audits and were process-based audits, focusing on the significant objectives. The first stage was document review and during the second stage the processes at sites were audited. Each audit had the following phases: i. an introductory meeting; ii. a detailed audit; iii. a closing meeting.

An advance notice of audit was normally given to a company at least a month before the audit date. The duration of each audit was approximately 8 hours.

The audit methods used were interviews and review of documentation and records. The non-conformities were classified as critical, major or minor. The non-conformities related to actions recorded in the documentation system but not done in practice were classified as major, while the non-conformities which were a deviation from the system were documented as minor. A detailed report of the non-conformities, recommendations and good practices identified as well as an overall estimation of the quality system was sent to the wholesaler within a month after the audit.

Results and Discussion

General information regarding the wholesale of medicinal products in Bulgaria

The distribution of medicinal products in Bulgaria is regulated by the Law on Medicines in Human Medicine and the related regulations. Relevant EU documents are also applicable and, in addition, wholesaling companies that import from non-EU countries should be in compliance with Good Distribution Practices (GDP) for pharmaceutical products, WHO Technical Report Series, No. 937, 2006, Annex 5 as requested by many overseas marketing authorization holders (Table 1). As already discussed in our previous publication, the legal concept for quality management and self-inspection obligations and the approach to GDP philosophy is somewhat fragmentary (13). This national particularity does not in reality mean that the wholesalers do not have quality management systems, as Bulgaria is part of EU and the distributors follow the EU relevant legislation which requires a quality management system. Besides, the Bulgarian wholesalers are regularly audited by the marketing authorization holders, which further contributes to the development of their quality system. ISO 9001 certification is not obligatory but in 2004 it was set as a requirement for distributors that supply hospitals, which led to a fast increase in ISO 9001 certifications in the pharmaceutical sector.

<table>
<thead>
<tr>
<th>Legislation</th>
<th>Relation to wholesale of medicinal products</th>
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<tbody>
<tr>
<td>Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03). (8)</td>
<td>Applicable for wholesalers in EU.</td>
</tr>
<tr>
<td>GDP for pharmaceutical products, WHO Technical Report Series, No. 957, 2010, Annex 5. (15)</td>
<td>Not binding document, but lots of overseas marketing authorization holders require that wholesalers follow it, because of the more detailed information available regarding different aspects of GDP.</td>
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<tr>
<td>Bulgarian Law on medicinal products for human medicine, Chapter 9. Wholesale. (3)</td>
<td>Contains the requirements of Directive 2001/83/EC.</td>
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<tr>
<td>Regulation No 39/2007 on principles and requirements of Good Distribution Practice. (11)</td>
<td>Contains the majority of the requirements of Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03) as well as some local requirements concerning the reports of wholesalers to Bulgarian Drug Agency and premises.</td>
</tr>
<tr>
<td>Regulation No 9/2008 on recall of medicinal products. (12)</td>
<td>Regulates recall of medicinal products which do not comply with standards for quality, efficacy and safety.</td>
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</table>

According to the official register of the Bulgarian Drug Agency (2) there are 259 registered sites (warehouses) in Bulgaria now. The number of wholesaler companies is 202. The wholesalers established by the marketing authorization holders and distributing only their products are 63. In fact, most wholesalers of this type of do not distribute the medicinal products directly to the pharmacies but sell to wholesalers that offer delivery to pharmacies. Unlike in other EU countries, no single marketing authorization holder has invested so far in direct distribution to pharmacies probably due to the big number of pharmacies in Bulgaria and significant investments needed (9).
One hundred fifty-seven sites are situated in the capital, Sofia. Most of the so-called full service wholesalers in fact outsource the transportation of medicinal products, as this is an activity related to significant investments.

Some of the wholesalers deliver medicinal products to the hospital market and, according to the official information from the Bulgarian Drug Agency, the sales to hospitals in 2009 were 47276800 packs (18.53% of the total market), which is equivalent to 287765805 BGN (18.40% of the total market) (2).

These distributors, as already mentioned, need to have ISO 9001 certification and seven of them were subject to the present study.

**Audits results**

The seven studied wholesalers had a quality management system established and maintained according to the current ISO 9001, GDP and other relevant local regulations. Thirty-one audits were performed in the studied distributors in 2002–2012: seven certification audits, five re-certification audits and 19 surveillance audits were held (Table 2). The audit reports provided a summary of the audit actions, observations made during the audit, deficiencies (non-conformities) noted during the audit, an audit team/auditor assessment on the quality system and conclusions. This publication focuses on the deficiencies only.

**TABLE 2**

<table>
<thead>
<tr>
<th>Year</th>
<th>Certification audits</th>
<th>Re-certification audits</th>
<th>Surveillance audits</th>
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<tr>
<td>2002</td>
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<td>2011</td>
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<td>2012</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>7</strong></td>
<td><strong>5</strong></td>
<td><strong>19</strong></td>
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</tbody>
</table>

In total, 41 deficiencies were recorded. Twenty-six (63.41%) of them concerned the storage of pharmaceutical products, especially the cold-chain pharmaceuticals; 10 concerned the documentation of different processes such as cleaning, training, transfer of responsibilities etc. (Fig. 1). The major non-conformities concerned the storage and transportation of cold-chain products. The rest were classified as minor.

Out of the 26 non-conformities concerning the storage of medicinal products (Fig. 2), 16 were related to the storage of cold-chain products (2 °C–8°C), and 10 concerned the ambient storage. In the wholesalers audited in the period 2002–2005 there were no evidences for performance of temperature distribution studies in the cool rooms (temperature mapping).

The non-conformities related to the ambient storage concerned a lack of evidence for monitoring the temperature and humidity in general storage areas (four non-conformities), no evidences of calibration of thermometers (four non-conformities) and not enough distance between the boxes of different batches (two non-conformities).

Other compliance issues concerned the cleaning documentation, training records, transportation of medicinal products, suppliers’ records and transfer of responsibilities (Fig. 2). Five non-conformities were raised with regard to the cleaning documentation due to a lack of records, incomplete documentation and no evidence for a performed review of the cleaning records by the designated employee. Recommendations were made with regard to increasing the frequency of cleaning.

Four deficiencies were documented for training records. In one distributor there was documentation for the trainings for the key personnel only. The other three distributors did not have proper documentation for trainings performed internally.
Deficiencies found in the transportation were raised due to lack of control of temperatures in the dedicated vehicles (two non-conformities) and non-validated vehicles (one deficiency raised due to lack of temperature mapping). The corrective actions were related to purchase and implementation of temperature recorders in the vehicles and performance of validation. Recommendations were given to all distributors to perform worst-case evaluations (temperatures maintained during the hottest summer day and coldest winter day).

In two of the audited distributors there were two deficiencies with regard to the suppliers’ records, namely lack of proofs for suppliers’ evaluation and re-evaluation in connection with complaints. In all cases except one, the delegation and transfer of responsibilities were performed and documented according to the requirements. The only non-conformity raised in this respect concerned the delegation of transportation service to a company whose personnel was not properly trained regarding the handling of medicinal products during transportation and associated risks.

Our study showed that the main non-conformities in the audited wholesalers were associated with the storage, transportation and documentation. These results correlate with published reports on inspection findings in pharmaceutical distributors in the United Kingdom, identifying that storage and transportation are one of the areas with most non-conformities documented (1). The performance of distributors in these activities improved during the studied period, as corrective actions were undertaken after detection of every deficiency, the adequacy of these corrective actions was verified by the auditors and the their efficiency was checked during the next audits. Appropriate trainings and case-study discussions as well as the feedback from the auditors contributed to the improved performance which, at the end, benefited the organizations’ management as well as the service provided to pharmacies. Last but not least, the corrective actions improved the guarantee for maintenance of quality, efficacy and safety of medicines provided to the society.

Conclusions
During the first five years of the observed period (2002–2010), there were no requirements for establishment of quality management systems in the pharmaceutical wholesalers. At that time, only the contracts between marketing authorization holders and wholesalers contained requirements for the most important elements of GDP. These requirements and the subsequent audits performed by the marketing authorization holders served as a preparatory phase for GDP and ISO 9001 implementation in Bulgarian pharmaceutical wholesalers. Since 2004, ISO 9001 certification started to gain popularity among the pharmaceutical wholesalers, mainly due to the fact that the certification was set as a prerequisite for participation in hospital tenders. Later, a significant part of Bulgarian pharmaceutical wholesalers passed successfully ISO certification and were audited regularly. The deficiencies found in most problematic areas – storage, transportation and documentation, and the corrective actions undertaken contributed to increasing the compliance with ISO 9001, GDP and the specific national requirements. We recommend that the Bulgarian Drug Agency prepare guidelines for distributors as other regulatory institutions in the EU have done, summarizing the best practices in pharmaceutical wholesaling as well as the deficiencies found during inspections with recommendations how to achieve compliance. Such guidelines will benefit not only the wholesaler’s quality management system, but also the society in general.

REFERENCES