

Analysis of good distribution practice inspection deficiency data of pharmaceutical wholesalers in Bulgaria

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Abstract

The current study analyses the regulatory inspection findings of the wholesalers in Bulgaria in 2017 and compares the results with the findings from some other EU member-states. In total, 48 GDP inspections were performed in 2017. 50% of the inspections were performed in relation with issuing an authorization for wholesale of medicines, the rest half were related to changes in already granted authorizations.

During the inspections, 17 non-conformities (NCs) have been documented. The NCs were identified in 3 wholesalers and 6 deficiencies were classified as major. No critical deficiencies were found. NCs were found in 6.25% of the inspected companies. No critical NCs were identified and only 6 NCs were classified as major which demonstrated high level of compliance of distributions sites in Bulgaria with the requirements of GDP.

Keywords

Good Distribution Practice (GDP), medicinal products, non-conformities, deficiencies, supply chain, compliance, Bulgarian Drug Agency

Introduction

The wholesale distribution of medicinal products is an important activity in integrated supply chain management. Today's distribution network for medicines is increasingly complex and demanding. The wholesalers are obliged to preserve the quality of the distributed medicines unchanged throughout the whole legal supply chain as any departure from the requirements may deteriorate the quality of the medicines and therefore their efficacy and even safety. According to the European Commission Guidelines of on Good Distribution Practice of medicinal products for human use (2013), Good Distribution Practice (GDP) is that

part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorised or entitled to supply medicinal products to the public.

The EU Good Distribution Practice guidelines apply to manufacturers, wholesalers and other actors involved in the distribution of medicinal products. The revised GDP guidelines of the European Union were published on 8 March 2013 and became effective 6 months later, 19 years after the previous publication of 1 March 1994. The re-

vised guidelines brought about the much-needed changes in requirements to better reflect the complex distribution networks in supply chains and to be in line with Directive 2011/62/EU to prevent falsified medicinal products from entering the legal supply chain. These guidelines were later replaced by the 2013/C 343/01 guidelines of 5 November 2013 in order to correct two factual mistakes. They lay down appropriate tools to assist wholesale distributors in conducting their activities related to preserving the quality of the medicinal products and to prevent falsified medicines from entering the legal supply chain.

Compliance with GDP will ensure control of the distribution chain and consequently maintain the quality and the integrity of medicinal products. This compliance is checked on a regular basis by the regulatory agencies. Directive 2011/62/EU which amends Directive 2001/83/EC, states that ‘manufacturers, located in the Union or in third countries, and wholesale distributors of medicinal products shall be subject to repeated inspections’¹ by the competent authority of the Member State concerned. In Bulgaria, Bulgarian Drug Agency (BDA) carries out these inspections to check if wholesalers comply with the Directive 2001/83/EC as amended; the EU GDP guidelines 2013/C 343/01 and the Law on medicines in human health (2007) with the related regulation - Regulation 39/13.09.2007 on the principles and requirements of Good Distribution Practice. Any departure from GDP compliance could risk the quality of the medicines and potentially their effectiveness and safety. Any deviation to the requirements of GDP is recorded as a non-conformance for e.g. temperature excursion out of required range in warehouse. Non-conformities (NCs) must be documented and investigated and adequate corrective actions must be implemented by the wholesalers.

The current study analyses the regulatory GDP inspection findings of the wholesalers in Bulgaria in 2017 and compares them with results from the inspections from other EU-member states. The purpose of sharing these results is to allow the pharmaceutical industry to perform its own assessment against the findings/recommendations as part of their program for continuous improvement.

Methods

A retrospective study was carried out, by reviewing the full GDP inspection reports of all pharmaceutical wholesalers inspected during 2017. The inspections were performed according to the GDP requirements and the applicable local legislation. The inspection methods used were interviews, review of documentation and conduction of site visits. The reports from all inspections performed in 2017 (carried out across the whole year) were reviewed for the scope of the inspection, classification of findings, the content of findings (non-conformities and recommendations) and the conclusion. Non-conformities found were classified as critical, major and other. Critical non-conformities are those that indicate a significant risk that the medicinal product could or would be harmful for a patient, or the non-conformity that has produced a harmful product. Examples of critical non-conformities can include purchase or sale of medicines from/to unauthorized suppliers/clients; storage of medicines that require 2–8 °C at room temperature; recalled/returned products found in sale etc. A combination of major non-conformities that indicates a critical systems failure may also be classified as critical. Data was presented graphically followed by description of some examples of non-conformities against GDP and Law on medicines in human medicine. All non-conformities were included in the data.

Results and discussion

Regulatory inspection findings in 2017

The distribution of medicinal products in Bulgaria is regulated by the Law on Medicines in Human Medicine (2007) and Regulation 39/13.09.2007 on the principles and requirements of Good Distribution Practice. Relevant EU documents are also applicable. According to the official registry of Bulgarian Drug Agency, there are 263 valid authorizations issued for wholesaling activities for companies with facilities within the territory of the country (Figure 1). Previous publications, Stoimenova et al. (2013),

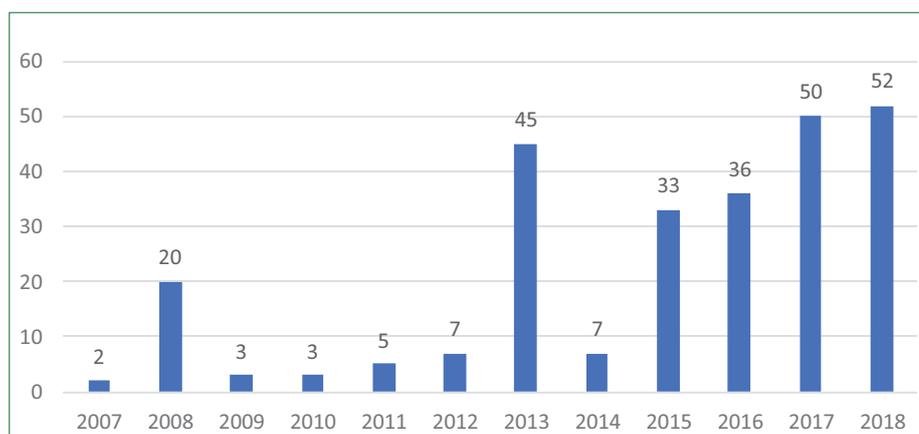


Figure 1. Number of authorizations issued 2007–2018.

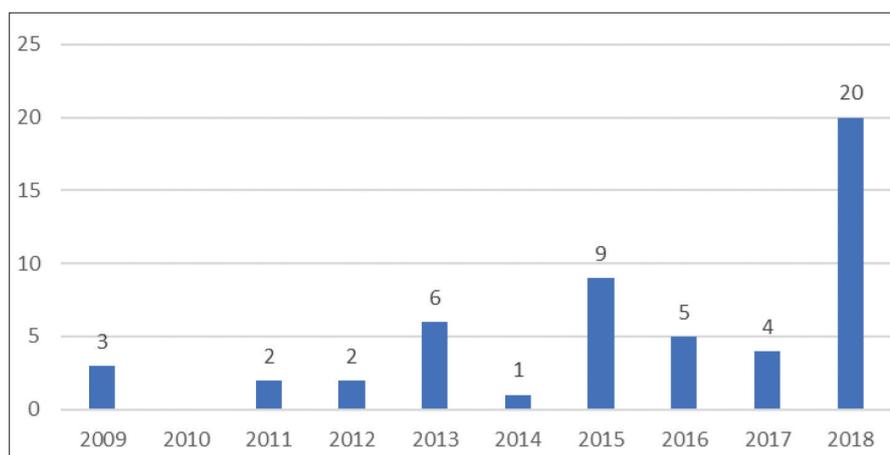


Figure 2. No of suspended wholesale authorizations 2009–2018.

Table 1. Wholesalers in Bulgaria.

Total No of wholesalers	No of wholesalers distributing narcotics	No of wholesalers distributing radiopharmaceuticals	No of wholesalers distributing immunology/plasma-derived products
263	31	9	80

Table 2. Observed deficiencies during inspections in 2017.

	Computerized systems	Temperature mapping & monitoring		
Major NCs	2	4		
	DDD	Incoming control	Storage	Picking
Other NCs	5	3	2	1

reported 202 authorizations in 2012 which is substantial increase. In addition, there 10 registrations of wholesalers authorized by another competent authority in EU (Cyprus, Czech Republic, Hungary, Netherlands, Romania and United Kingdom) and operating in Bulgaria with no local facilities. 31 out of 263 distributors are dealing with medicinal products containing narcotic substances and only 9 are selling radiopharmaceuticals (Table 1). 49 authorizations for wholesaling of medicinal products have been suspended in Bulgaria for the period 2009–2018 and were not included in the Table 1 (Figure 2).

During 2017, inspections were performed in 48 distributors. A wide range of business models are represented, e.g. full line, short line, third party logistics, marketing authorisation holders, and exporters. One inspection was follow-up inspection related to previously found major deficiencies. During the inspections, 17 non-conformities (NCs) have been documented (Table 2). The NCs were identified in 3 wholesalers and 6 deficiencies were classified as major. No critical deficiencies were found. Recommendations were given to 5 companies related to quality management system as these were lacking Quality manuals and some documents related to the management of the system, ensuring setting quality goals and continuous improvement & preventive culture.

Some examples of *major non-conformities* documented in 2017 are:

- Temperature mapping exercises had not been adequately conducted, to establish the suitability of the storage areas or to determine the placement of the thermometers in the areas that experience the extremes of temperature fluctuations;
- Unproper monitoring of temperature and humidity for the ambient storage;
- Software for stock management not available and failure to prove existence of reliable system for recall of medicinal products;

According to the World Health Organization GDP for pharmaceutical products (2010), new temperature-controlled storage areas must be temperature-mapped as part of a fully documented verification process, before the installation is commissioned and handed over by the installer. This is also reflected in GDP requirements under p. 3.2.1 *Temperature and environment control* which requires initial temperature mapping exercise to be carried out on the storage area before use, under representative conditions. The temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring devices are positioned in the areas that experience the extremes of fluctuations. Until this has been done, it is not safe to store temperature-sensitive medicinal products in such areas. 4 of the companies failed to prove that the mapping exercise was done accordingly.

Computerized systems are required by p. 3.3.1 of the Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01). Moreover, these systems before brought into use, it should be demonstrated, through appropriate validation or verification studies, that they can achieve the desired results accurately, consistently and reproducibly.

Some examples of *other non-conformities* documented in 2017 are:

- Documentation not compliant with GDP – lack of standard operation procedures (SOPs) for some activities such as incoming control of medicinal products, storage and picking of goods or substantial part of process not described well;
- Lack of Disinfection, disinsection and deratization (DDD) program – reference to GDP: Premises and Equipment.

Comparison of findings with results from previously performed audits of wholesalers in Bulgaria

Previous publication of Stoimenova et al. (2013) shared results from audits against ISO 9001 requirements of wholesalers in Bulgaria. ISO 9001 certification is not obligatory but in 2004 it was set as a requirement for distributors supplying hospitals. Unlike the inspections which seeks to confirm the compliance with the legislation, 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. This different approach ensures the different nature of the inspections vs. audits which based on the sample approach might lead to different deficiencies found. The number of NCs found by the certification companies as per Bruinink and Bishara (2018) correspond to the number we observed in the inspection reports. The major NCs found during the audits in period 2002–2012 concerned the storage and transpor-

tation of temperature-sensitive medicinal products. Lack of temperature mapping was also an issue during the period 2002–2005 as well as deficiencies related to the monitoring of temperature and humidity in the ambient storage areas. No deficiencies regarding the computerized systems were documented according to the publication, which could be related to the fact that the new EU requirements for GDP were not in force when the audits reviewed have been performed. No new similar data is available in order to ensure adequate comparison of findings. The type of other NCs found during the inspections in 2017 were not detected as deficiencies during the audits in the period 2002–2012.

Comparison of findings with results from GDP inspections from other EU member-states

There is a limited number of publications concerning deficiencies raised during GDP inspections across the EU countries. We found results from inspections performed in Malta, Netherlands and United Kingdom (UK) and reported by Brown (2017a); Bruinink and Bishara (2018a) and Farrugia et al. (2018a) (Table 3).

According to Brown (2017b), in 2016 1428 distributors were inspected against the GDP requirements in the UK, and nearly 10% of them (148 companies) were sampled for the purpose of analysis of the inspection findings. Critical deficiencies were excluded from the published analysis as they generally cover broader sections of the GDP guidelines and are assessed individually due to the seriousness of the issues. Other deficiencies due to their high number were not included in the published results. Top cited major deficiencies against GDP requirements, found during inspections in United Kingdom in 2016 were those related to the quality system (22%); transportation (13%); responsible person (12%); supplier qualification (10%); equipment, documentation and temperature control (each 9%); storage and customer qualification (each 5%).

In Malta, as reported by Farrugia et al. (2018b), during a period of 6 years 78 companies were inspected against the GDP requirements. The number of deficiencies documented were quite a lot: 10 critical, 132 major and 633

Table 3. Results from GDP inspections Bulgaria, Malta, Netherlands and United Kingdom.

Country	Period	No of companies	NCs found	Nature
Bulgaria	2017	48	Critical-0; Major-6; Other -11.	Major: Computerized systems, Temperature mapping & monitoring. Other: Documentation, Premises and Equipment.
Malta	2013–2018	78	Critical-10; Major-132; Other -633.	Critical: Premises and Equipment, Storage, Documentation, Training and Falsified Medicine. Major: all sections of the EU GDP guidelines. Other: Quality System, Other personnel and Training.
Netherlands	2016	35	Critical-not discussed; Major-56; Other-not discussed.	Critical: Major: temperature management & mapping, quality management, risk management, transportation, Responsible Person, qualification of suppliers and customers. Other:
United Kingdom	2016	1428 inspected, 148 selected for the report.	Critical- not included into the report; Major (for the sample) -209; Other- not included into the report.	Critical: N.A. Major: Quality system, Transportation, Responsible person, Supplier qualification, Equipment, Documentation, Temperature control, Storage and customer qualification. Other: N.A.

other non-conformities. The nature of the deficiencies is shown on Table. Major deficiencies have been assigned to nearly all sections of the EU GDP guidelines. It was found that 44% (n = 34) of wholesale dealers were assigned one or more major findings in Malta.

The results of the 35 GDP inspections in 2016 in Netherlands according to Bruinink and Bishara (2018b) showed 56 major findings. These are in the areas of temperature management in storage areas: temperature mapping and control, quality management issues, transportation issues, Responsible and qualification of suppliers and customers.

The deficiencies found in the wholesalers, inspected in Bulgaria during 2017 are related to equipment, documentation and storage which are represented by 9%, respectively 5% in the findings raised by MHRA in United Kingdom. The nature of major findings in Bulgaria match with those one detected in 2016 during the GDP inspections in Netherlands.

No single NCs was raised by the Bulgarian Drug Agency against the responsible person requirements or transportation unlike the findings in UK/Malta. Bulgarian inspectors did not raise any critical deficiencies in 2017. The percentage of the wholesalers with major deficiencies recorded is significantly lower in Bulgaria in comparison with the other countries (i.e. 6.25% vs. 44% in Malta and 56 major NCs were recorded for 35 inspections in Netherlands vs. 6 major NCs recorded for 48 inspections in Bulgaria). Regarding the quality system, only recommendations were documented during the inspections in Bulgaria.

Conclusions

During the regulatory inspections of pharmaceutical distributors in 2017, non-conformities to the requirements of GDP were found in 6.25% of the inspected companies. The deficiencies found in the wholesalers, inspected in Bulgaria during 2017 are related to equipment, documentation and storage of medicinal products. No critical NCs were identified and only 6 NCs were classified as major which demonstrated high level of compliance of distributions sites in Bulgaria with the requirements of GDP. However, the number of major deficiencies raised by Bulgarian inspectors is significantly lower than ones documented by their colleagues in other EU member-states – an observation which requires deeper investigation focused on the methodology of the inspections performed in different countries although the EU GDP and related legislation should assure same approach by the inspectorates.

This data is presented in order to assist wholesalers, and those who intend to obtain an authorization for wholesaling of medicines to understand areas where significant GDP failures have been observed by the Bulgarian Drug Agency as well as to present the findings found by another EU national competent authorities. A preparation of guidelines sharing best practices, documented by the inspectors of Bulgarian Drug Agency during GDP inspections of pharmaceutical wholesalers might be also beneficial to ensure greater compliance with the requirements.

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