



Good Manufacturing Practice for Medicinal Products in Bulgaria: an Analysis of Regulatory Inspection Findings

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Received: 15 Apr 2019 ♦ **Accepted:** 18 July 2019 ♦ **Published:** 31 March 2020

Citation: Stoimenova AH, Kirilov BJ, Gueorguiev SR, Petkova-Gueorguieva ES, Ognianov SG. Good manufacturing practice for medicinal products in Bulgaria: an analysis of regulatory inspection findings. *Folia Med (Plovdiv)* 2020;62(1):165-71. doi: 10.3897/folmed.62.e49802.

Abstract

Background: The manufacture of medicinal products for human use in the European Economic Area is governed by European Directives and Regulations stipulating the relevant principles and guidelines of Good Manufacturing Practice, describing the minimum standard to be fulfilled in the production processes.

Aim: To present analysis of the deficiencies reported following Good Manufacturing Practice inspections in Bulgaria in two consecutive years (2016, 2017) and to compare them with results from similar inspections reported by other EU member states.

Materials and methods: A retrospective study was carried out by reviewing the complete Good Manufacturing Practice inspection reports of all manufacturers conducted by the Bulgarian Drug Agency in 2016 and 2017, according to relevant requirements and applicable local legislation. The items reviewed were scope of inspection, type of companies, classification of deficiencies – ‘critical’, ‘major’ and ‘other significant deficiencies’, their nature and reference to EU Good Manufacturing Practice.

Results: The analyzed data included 55 inspections, revealing 460 various deficiencies, of which 2 were critical and 102 – major. Twenty inspections were performed in 2016 vs. 35 inspections in 2017.

The pattern of deficiencies was similar to the findings of other EU regulatory agencies, showing that equivalent requirements were applied. Our analysis showed that Bulgarian Drug Agency inspectors rarely raised deficiencies related to Computer Systems, Qualification/Validation, Personnel and Qualification of Suppliers unlike other EU regulators agents.

Conclusions: Our analysis of Good Manufacturing Practice inspection findings in 2016 and 2017 showed that the Bulgarian Drug Agency demonstrated its ability to detect non-compliances and take necessary regulatory actions. Quality related issues constitute the main reasons for non-compliances with the requirements.

Publishing the results from the inspections performed by the national competent authorities enhances the regulatory transparency that can be useful for industry to improve its Good Manufacturing Practice compliance.

Keywords

medicinal products, human medicine, good manufacturing practice, compliance, deficiencies

BACKGROUND

The manufacture of medicinal products for human use in the European Economic Area (EEA) is governed by European directives and is subject to the holding of relevant authorisations in accordance with Article 40 of Directive 2001/83/EC.¹ To obtain and retain a licence, a company is obliged to comply with the relevant principles and guidelines of Good Manufacturing Practice (GMP) as laid down in EU rules.² GMP includes ensuring that all manufacturing operations are performed in accordance with the relevant marketing authorization (Article 5 of Directive 2003/94/EC)³ and it describes the minimum standard that medicines manufacturers must meet in their production processes.

GMP requires that medicines:

- are of consistent high quality;
- are appropriate for their intended use;
- meet the requirements of the marketing authorisation or clinical trial authorisation.⁴

The national competent authority of each Member State is obliged to conduct repeated inspections to ensure that GMP requirements are met. This agency is responsible for inspecting manufacturing sites located within their own territories.

Manufacturing sites outside the EU are inspected by the national competent authority of the Member State where the EU importer is located, unless a mutual recognition agreement (MRA) is in place between the EU and the country concerned. If an MRA applies, the authorities mutually rely on each other's inspections.⁵

Different types of inspections (e.g. general GMP inspection, routine re-inspection, product related inspection, for-cause inspection) may be carried out according to the activities of the manufacturers. The conduct of GMP inspections may vary according to the objectives and may focus on the general level of GMP (e.g. first inspection in a third country), or on manufacture of a specific medicinal product or process (e.g. product-related inspection).

The goals of routine GMP inspections are to determine compliance with current GMP requirements and provide evidence for action as necessary; to support application approval decisions and to provide feedback to manufacturers to improve their compliance with the requirements.

For-cause inspection covers whatever causes the need for inspection. Product-related inspections are carried out with regard to the approval of the product and often focuses on process validation, supplier qualification and stability.

Frequency of inspections depends on the type of the inspection; inspectorate resources (number of inspectors, workload etc.); new facilities; the annual inspection plan (the regular inspections) and types of companies and the validity of the GMP certificate. Duration of inspections depends on type of inspection, inspectorate resources, size of the company, purpose of the visit and the numbers of inspectors.

At the end of each inspection of a manufacturer deficiencies or failures to comply with GMP are presented formally to the representatives of the company and should be discussed. The discussion involves the importance of the raised deficiencies as well as the deadlines for remedial actions. Subsequently these deficiencies are confirmed to the manufacturer in the draft inspection report. Any response from the manufacturer is considered in the final report and the process is completed with the issuing of the report by the relevant competent authority. If the outcome of the inspection is that the manufacturer is non-compliant, the competent authority may take any necessary regulatory action, which may involve suspension or revocation of the Marketing Authorization.

After inspecting a manufacturing site, EU competent authorities issue a GMP certificate or a non-compliance statement, which is entered in the EudraGMDP database. EudraGMDP is a publicly accessible database which contains manufacturing and import authorizations, registration of active substance manufacturers, GMP certificates and non-compliance statements.⁶

AIM

The aim of this paper was to present analysis of the deficiencies reported following GMP inspections in Bulgaria for two consecutive years (2016-2017) and to compare them with results from the GMP 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 as part of their program for continuous improvement.

MATERIALS AND METHODS

A retrospective study was carried out, by reviewing the full GMP inspection reports of all manufacturers inspected by the Bulgarian Drug Agency in 2016 and 2017. The inspections were performed according to the GMP requirements¹⁻³ and the applicable local legislation^{7,8}. The reports were reviewed for scope of inspection, type of companies, classification of deficiencies, their nature and reference to EU GMP and the conclusion.

Deficiencies are classified as 'critical', 'major' and 'other significant deficiencies'. A critical GMP failure occurs when a practice could give rise to a product which could or would be harmful to the patient or animal, or which has produced a harmful product. A combination of major deficiencies, which indicates a serious system failure, may also be classified as a critical deficiency.⁹ All deficiencies found during GMP inspections in Bulgaria are recorded in the database and classified as listed in the inspection report in accordance with the critical, major and other classification.

The deficiencies found by the Bulgarian authority were compared to deficiencies documented in other European Union member-states. Data for GMP inspections related to centralized procedures were retrieved from European Medicines Agency,^{5,9} supplemented by data from the official website of European Qualified Persons (QP) Association¹¹, official report of UK regulatory agency (MHRA)¹⁰ and published results from a survey amongst PIC/S participating authorities¹².

RESULTS AND DISCUSSION

GMP deficiencies documented by the Bulgarian Drug Agency 2016-2017

Data from 55 inspections carried out in 2016 and 2017 has been analyzed. The types of inspected sites are presented in **Fig. 1**. The vast majority of them are manufacturers of non-sterile finished products, performing primary and secondary packaging, quality control testing and batch certification. In 2017, unlike 2016, there were 4 sites manufacturing biologicals that have been inspected.

A total of 460 deficiencies, comprising critical, major and other deficiencies were recorded during the analyzed period of which 2 were critical deficiencies and 102 – major deficiencies (**Fig. 2**). Twenty GMP inspections were performed in 2016 vs. 35 inspections in 2017. The increased number of recorded deficiencies in 2017 corresponds to the

significantly higher number of inspections performed (75% increase).

During the inspections performed in 2016, GMP deficiencies were found at 16 sites. Out of the total number of 137 deficiencies (n=137), 37 were classified as ‘major’ and the rest – as ‘other’ (no critical deficiencies were detected). Fifteen GMP certificates were issued to manufacturers of medicinal products and active substances for conformity of production activities with the GMP requirements.

The inspections in 2017 revealed 323 deficiencies, 2 of which were ‘critical’, 65 – ‘major’ and the rest were ‘other’. One critical deficiency was documented in 2017 in relation to missing substantial of QMS and one was referred to the Quality control of the finished product. Five manufacturers showed no deficiencies and only recommendations were given by the inspectors.

The deficiencies found during the inspections in 2017 were significantly more (**Table 1**). For example, the increase of major deficiencies from 2016 to 2017 was 75.68% and the increase in other deficiencies – 156%. This, of course, corresponded to the higher number of inspections, but still – the ‘average’ number of deficiencies per inspection was 6.85 in 2016 and 9.23 in 2017. The significant increase of the deficiencies found in 2017 was not only due to the increased number of inspected sites in Bulgaria but also to more inspections performed in third countries. One facility in a third country has shown 53 deficiencies of which 9 were major.

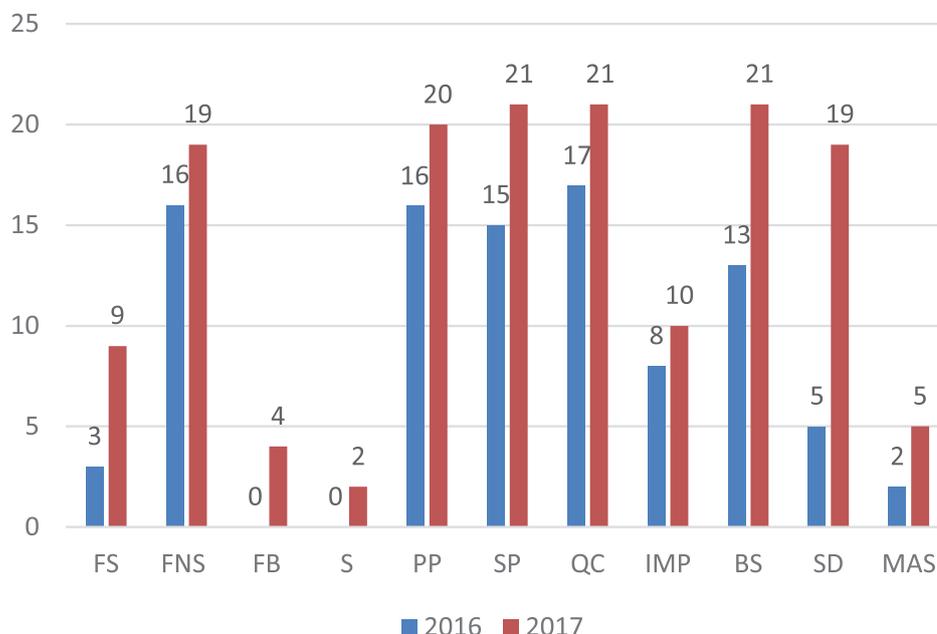


Figure 1. Types of inspected sites 2016-2017.

FS: manufacturing of finished product sterile; FNS: manufacturing of finished product non-sterile; FB: manufacturing of finished product biologicals; S: sterilization of excipient, active substance or medicinal product; PP: primary packaging; SP: secondary packaging; QC: quality control testing; IMP: importing; BC: batch certification; SD: storage and distribution; MAS: manufacture of active substance.

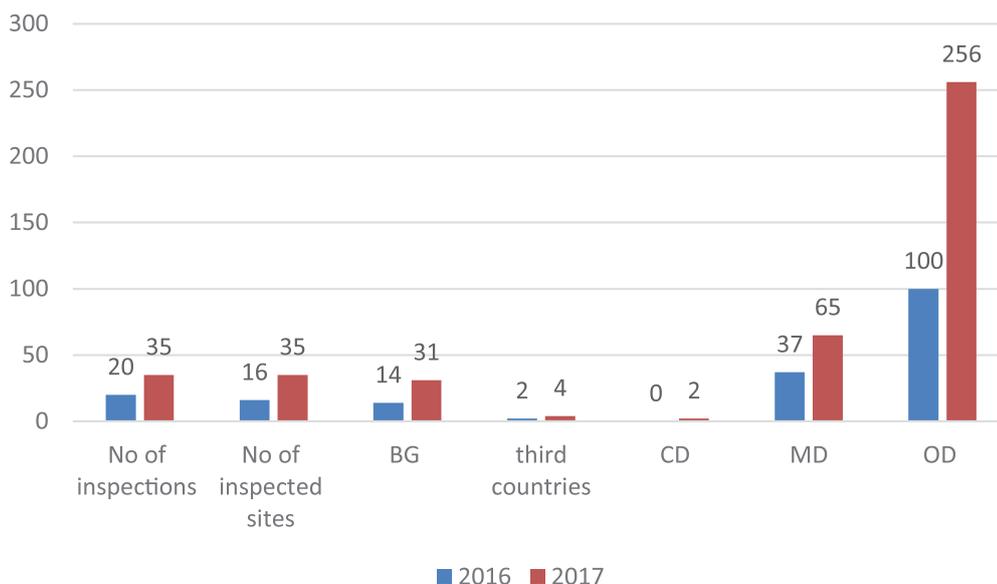


Figure 2. Number of GMP inspections 2016-2017.

Table 1. Deficiencies during GMP inspections in 2016-2017

Groups	Critical		Major		Others	
	2016	2017	2016	2017	2016	2017
Quality System	-	1	16	22	41	84
Sterility assurance	-	-	1	-	1	-
Production	-	-	2	8	4	33
Complaints and recalls	-	-	-	-	1	1
Qualification/validation	-	-	1	-	2	1
Premises and equipment	-	-	5	11	30	70
Computerized systems	-	-	1	-	1	-
Personnel	-	-	1	2	1	11
Documentation	-	-	6	10	3	37
Quality control	-	1	1	12	15	19
Qualification of suppliers	-	-	3	-	1	-

Comparison of our results with GMP findings from regulatory authorities in other EU member-states

Most of the respective findings in chapter 1 of the EU-GMP Guidelines (Pharmaceutical Quality System) referred to 1.4 describing the pre-requisites for an appropriate Pharmaceutical Quality System which corresponded to the findings from Medicines and Healthcare Products Regulatory

Agency (MHRA) in United Kingdom.¹⁰ Deficiencies related to the written procedures, job descriptions and various programs (self-inspection, trainings etc.), unregular product quality reviews and audits of suppliers were identified by the inspectors in 2016. The focus on the major findings referred to the Quality System in 2017 was put more on contractors, corrective and preventive action plan (CAPA) issues, audits of suppliers, change control etc.

Examples of deficiencies related to the Quality system included the items listed below and other issues as well:

- In some cases there were no formal CAPA raised and in others the CAPA were not adequate. There was no review of repeated deviations;
- No effective control system to monitor product quality (product quality reviews);
- At the time of inspection overdue CAPAs were observed;
- Failures to identify opportunities for continual improvement of the Quality system;
- Product quality reviews not done in timely manner;
- No review of the effectiveness of the change control activities.

Critical and major deficiencies of Quality management system have been involved in issuing of GMP Non-Compliance Reports for several companies in EU during the last years. A manufacturer in Spain was found not to have established a quality management system including adequate controls to ensure the accuracy and completeness of the critical records data. Another one in Romania has been reported with 34 deficiencies, of which 4 were critical and 10 majors. Critical deficiencies were related to the Quality Management System, qualification/validation activities, manufacturing and material management documents and quality control laboratories activity. Lack of effective Quality Management System was critical deficiency at a manufacturer in Spain.¹¹ The same approach has been observed in Bulgaria where one manufacturer has failed to prove GMP compliance and Non-compliance report was issued.

Most of the other findings referred to Quality system and to Premises and equipment – gaps in temperature mapping exercise and related documentation, pipes not marked for the transported liquid, calibration certificates not dated etc. Fail to prove regular auditing of the suppliers was also observed. Quality control issues were both related to starting materials and finished products. Documentation issues were mainly raised with regard to missing dates or signatures.

GMP inspection is, by its nature, a sampling exercise, as an inspector cannot examine everything so normally, he/she concentrates on those operations where, in his/her judgment, any failure to comply with GMP is likely to give rise to the greatest risk to the patient. Thus, the incidence of deficiencies reported reflected both their real incidence and the extent to which, based on risk analysis, the inspector has been looking for them.

However, there are some trends in GMP deficiencies raised during the inspections performed by the Bulgarian Drug Agency and other EU regulators. Our study confirmed that deficiencies related to the Quality system, Premises and Equipment, Documentation, Production and Quality Control are amongst the most frequently found during GMP inspections in Bulgaria, which is also a trend observed during GMP inspections in other EU countries. This trend is confirmed by the latest findings reported as

well as by previous studies and indicates that the industry is weak in these areas across the EU.¹² There were no significant differences among EU countries in terms of the way GMP deficiencies were inspected and cited. The pattern of deficiencies was like the findings of other EU regulatory agencies, showing that equivalent requirements were applied. At the same time our analysis showed that Bulgarian Drug Agency inspectors rarely raised deficiencies related to Computerized systems, Qualification/validation, Personnel and Qualification of suppliers unlike their colleagues from other EU regulators. This finding requires more detailed investigation to establish the nature of this trend.

CONCLUSION

Our analysis of the GMP inspection findings for 2016 and 2017 has shown that Bulgarian Drug Agency has demonstrated its ability to detect non-compliances and undertake necessary regulatory actions. Quality related issues constituted the main reasons for non-compliances with GMP requirements.

During the regulatory inspections of pharmaceutical manufacturers in 2016, GMP non-conformities were found in 84.21% of the inspected companies. No critical NCs were identified. The most frequent were deficiencies related to Quality Management System, personnel trainings, premises and equipment etc. which corresponded to the findings from other regulators in EU.

Although the number of sites where deficiencies were raised remained relatively the same in 2017 (85.71%), the deficiencies found during the inspections in 2017 were significantly more. The increase of major deficiencies from 2016 to 2017 was 75.68% and the increase in other deficiencies – 156%.

Publishing the results from GMP inspections performed by the national competent authorities is a step forward on regulatory transparency, which can be useful for industry to improve its GMP compliance.

ACKNOWLEDGEMENTS

This study received no specific grant from public funding agencies in the commercial or non-for-profit sectors.

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Надлежащая производственная практика для лекарственных средств в Болгарии: анализ данных регулирующих инспекций

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Дата получения: 15 апреля 2019 ♦ **Дата приемки:** 18 июля 2019 ♦ **Дата публикации:** 31 марта 2020

Образец цитирования: Stoimenova AH, Kirilov BJ, Gueorguiev SR, Petkova-Gueorguieva ES, Ognianov SG. Good manufacturing practice for medicinal products in Bulgaria: an analysis of regulatory inspection findings. *Folia Med (Plovdiv)* 2020;62(1):165-71. doi: 10.3897/folmed.62.e49802.

Абстракт

Введение: Производство лекарственных препаратов для использования человеком в Европейском экономическом сообществе регулируется европейскими директивами и правилами, устанавливающими соответствующие принципы и направления для надлежащей производственной практики, которые определяют минимальный стандарт, которому необходимо следовать в производственных процессах.

Цель: Предоставить анализ недостатков, выявленных после проверок надлежащей производственной практики в Болгарии в течение двух последовательных лет (2016, 2017), и сравнить с результатами аналогичных проверок, о которых сообщается другими государствами-членами ЕС.

Материалы и методы: Ретроспективное исследование было проведено путём анализа отчётов о проверках надлежащей производственной практики производителей, проведённых Болгарским агентством по лекарственным средствам в 2016 и 2017 годах, в соответствии с применимыми требованиями и действующим местным законодательством.

Были рассмотрены следующие элементы: объём проверки, тип компании, классификация дефектов - «критические», «существенные» и «другие существенные недостатки», их характер и ссылки / ссылки на надлежащую производственную практику Европейского Союза.

Результаты: Проанализированные данные включали 55 проверок, которые выявили 460 различных недостатков, из которых 2 были критическими и 102 были основными. В 2016 году было проведено двадцать проверок и 35 в 2017 году.

Схема недостатков была аналогична той, которая была обнаружена в других регулирующих органах ЕС, что свидетельствует о применении эквивалентных требований. Наш анализ показал, что инспекторы Болгарского агентства по лекарственным средствам редко отмечали такие недостатки, как компьютерные системы, квалификация / валидация, кадровое обеспечение и квалификация поставщиков, в отличие от других регулирующих органов ЕС.

Выводы: Наш анализ данных инспекций надлежащей производственной практики в 2016 и 2017 годах показал, что Болгарское агентство по лекарственным средствам продемонстрировало свою способность выявлять несоответствия и принимать необходимые меры регулирования. Проблемы с качеством являются основными причинами несоблюдения.

Публикация результатов инспекций национальными компетентными органами повышает прозрачность регулирования, что может помочь промышленности придерживаться надлежащих производственных практик.

Ключевые слова

Лекарственные средства, лекарственные препараты для человека, надлежащая производственная практика, соответствие, недостатки
