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Research Article

Analysis of non-compliances identified in GMP inspections between 2013 and 2022

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Abstract

Ensuring the quality and safety of medicinal products is of paramount importance to the pharmaceutical industry. Good manufacturing practice (GMP) regulations are part of a pharmaceutical manufacturer's quality management system and ensure that medicinal products are manufactured, imported and controlled consistently to quality standards appropriate to their intended use. The aim of the present study is to analyze the non-compliant operations identified during GMP inspections carried out by national competent authorities (NCA) in the EU/EEC between 2013 and 2022. A retrospective analysis of non-compliance reports published in the EudraGMDP database between 2013 and 2022 was performed. Overall, 99 reports by 21 national competent authorities were analyzed presenting the results of inspections in 19 countries. A total of 1458 deficiencies were identified, of which 544 (37%) were classified as major and 127 (9%) as critical. The most common non-compliant operations were the manufacturing of active substances (49 deficiencies) and the preparation of non-sterile products (47 deficiencies). In 41 cases, the NCA recommended suspension or voiding of the certificate of suitability (CEP) and in 36 cases revocation of the GMP certificates. The observed deficiencies highlight the importance and need for continuous monitoring and improvement of manufacturers' production processes and quality management systems.

Keywords

Pharmaceutical manufacturing, inspection, non-compliance, good manufacturing practice, GMP

Introduction

Good Manufacturing Practice (GMP) is a system of internationally recognized business rules that covers all aspects of production - personnel, premises, facilities, materials, documentation, quality control, and aims to ensure safety, efficiency and conformity to specification (Anon 2007). The concept of good manufacturing practice is based on the understanding that the quality of medicinal products cannot be guaranteed solely by control of the final product, but also depends on the manufacturing process (Petrova et al. 2019). However, to reach this conclusion, mankind has gone through many events related to the safety of medicinal products and as a result of which modern regulation has been established (Scheindlin 2011; Kostov et al. 2013; Quirke 2013; Ridings 2013; Woolf 2022). Marketing authorization holders must manufacture medicinal products ensuring their suitability for their intended use, comply with the requirements set out in the marketing authorization for clinical trials, and do not expose patients to risk due to insufficient safety, quality or efficacy. To achieve these objectives, it is necessary to implement a Quality System for pharmaceuticals, bringing together the requirements of the Good Manufacturing Practice Rules

and Quality Risk Management. This system should be fully documented and its effectiveness monitored on a regular basis. GMP applies to all stages of the product lifecycle, from the manufacture of medicines for clinical trials, through technology transfer and commercial production to product discontinuation (Stoimenova et al. 2020).

The entire process of manufacturing medicinal products, from the provision of raw materials to the release of the medicines for distribution, is subject to Good Manufacturing Practice (GMP) requirements (Talele et al. 2023). The GMP rules applicable within the European Union (EU) for medicinal products (MPs) for human use are laid down in Directive 2003/94/EU (Volume 4 Good Manufacturing Practice Guidelines) and in Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to the principles and guidelines of good manufacturing practice for active substances for medicinal products for human use, following the World Health Organization (WHO) recommendations on GMP (European Parliament and the Council 2003; Commission of European Union 2014) The principles and requirements of good manufacturing practice for medicinal products intended for clinical trials are regulated by Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by laying down principles and guidelines for good manufacturing practice for investigational medicinal products for human use and laying down provisions for the conduct of inspections.(European Commission 2017; Souto et al. 2020) The GMP rules are divided into several chapters defining specific requirements for the following main aspects of pharmaceutical manufacturing: personnel, premises and equipment, documentation, production, quality control, contract manufacturing and analysis, outsourcing, complaints and product recall, self-inspections, and labelling.(Gouveia et al. 2015)

A Certificate of Suitability (CEP) is a certificate stating that the active pharmaceutical ingredients (APIs) or pharmaceutical ingredients comply with the requirements of the relevant European Pharmacopoeia monograph. (Artiges 2002) These certificates are recognized in 37 countries, including EU members and Canada, Australia, Singapore, etc. A CEP is issued by EDQM following an inspection to determine compliance with the submitted dossier, the requirements of EU GMP Part II and the Annexes. Corrective action is taken in the event of identified non-compliant operations (critical or major).

In the EU, national competent authorities are responsible for inspecting production sites located on their territory. Manufacturing sites outside the EU are inspected by the national competent authority of the Member State where the EU importer is located unless there is a mutual recognition agreement between the EU and the country concerned. If a mutual recognition agreement applies, the authorities rely on each other's inspections. Where products are imported directly into more than one Member State from a manufacturing site outside the EU, there may be more than one national competent authority responsible for verification. The EMA facilitates cooperation between the relevant competent authorities in the supervision of the establishment.

The EMA maintains a compilation of procedures and forms related to GMP inspections approved by all Member States. This facilitates cooperation between individual members and promotes harmonization and exchange of inspection information between national competent authorities. Inspections of manufacturers and importers of medicinal products shall be carried out in accordance with Articles 42 and 111 of Directive 2001/83/EC and Articles 90 and 123 of Regulation 2019/6, and Article 3 of Directive 91/412/EEC, and of manufacturers and importers of medicinal products for clinical trials, in accordance with Article 63(4) of Regulation (EU) No 536/2014.(EU 2001) In addition, Article 111 of Directive 2001/83/EC and Article 123 of Regulation 2019/6 contain provisions for inspections of manufacturers and importers of active substances used as starting materials (European Parliament and the Council 2003; Council of the European Union 2017).

EU competent authorities plan routine inspections following a risk-based approach or when non-compliance is suspected (European Commission 2023).

The foundation of GMP is self-monitoring and preventive control (Tsvetanova 2014). There are two types of audits in a quality system:

- Internal - self-inspections, organized according to standard operating procedures and programs, are performed to assess the effectiveness and suitability of the quality system. They are divided into planned, unplanned and unannounced.
- External - conducted to assess compliance with GMP requirements by competent authorities (IAA, EMA, FDA, etc.).

The main aims and objectives of an external inspection are:

- To ascertain whether the manufacturer is complying with GMP requirements and the authorizations for the manufacture and use of medicinal products, including authorizations for the manufacture of medicinal products for clinical trials.
- To assess the efficacy and suitability of the elements of the quality management system in accordance with the principles of GMP.
- To thoroughly assess the manufacturer's compliance with GMP standards.

The findings of the inspections are documented in a report according to the EMA template, corrective and preventive action programs are prepared, and follow-up on the implementation of planned activities to address non-conformities is carried out (European Commission 2023).

Types of deficiencies identified during inspections (Stoimenova et al. 2020):

- Critical deficiency - a failure that has resulted in, or results in, a significant risk of producing a product that is harmful to humans or veterinary patients, or a product that may result in harmful residues in a food-producing animal.
- Major deficiency - a non-critical non-conformity which has resulted in, or may result in, the manufacture of a product that does not comply with its authorization for use; or indicates a significant deviation from EU Good Manufacturing Practice; or (within the EU) indicates a significant deviation from the terms of the manufacturing authorization; or indicates a failure to comply with batch release procedures or (within the EU) a failure by the Qualified Person to comply with legal obligations; or a combination of several 'other' deficiencies.
- Other deficiencies - those that cannot be classified as critical or major but indicate a deviation from the requirements of Good Manufacturing Practice. Nonconformities for which there is insufficient information, and which cannot be classified as major or critical are also classified in this group.

Aim

The aim of the present study is to analyze the non-compliant operations identified during GMP inspections carried out by national competent authorities in the EU/EEC between 2013 and 2022.

Materials and methods

A retrospective analysis of the EudraGMDP database was performed. EudraGMDP is a database established under Article 111(6) of Directive 2001/83/EC and Article 80(6) of Directive 2001/82/EC (publicly available at http://eudragmp.ema.europa.eu/). It contains information on manufacturing and import authorizations, GMP certificates, identified GMP non-conformities and planned GMP inspections in third countries. The data in the database is provided by the national competent authorities in the EU/EEC. Since 2013, information on wholesale authorizations, Good Distribution Practice (GDP) certificates, identified non-compliances with GDP requirements and registration data of manufacturers, importers and distributors of active substances for human use in the EEC are also uploaded to the database. The data in EudraGMDP are public.

We have analyzed:

- The number of non-compliances identified during GMP inspections for the period 2013–2022.
- Type of non-compliance and actions taken.

Data was analyzed using descriptive statistics. Initial data processing, entry and subsequent analysis were performed using Microsoft Excel 2019. For the summary of quantitative parameters, the number of responses, mean, median, standard deviation, minimum and maximum values were presented.

Results and discussion

The analysis of the 99 reports published in EudraGMDP by national competent authorities on non-compliant operations identified during inspections carried out between January 2013 and December 2022 shows that non-conformities with GMP rules were identified in manufacturers in 19 countries on 5 continents (Fig. 1). The largest number of manufacturers were from China (25) and India (39).

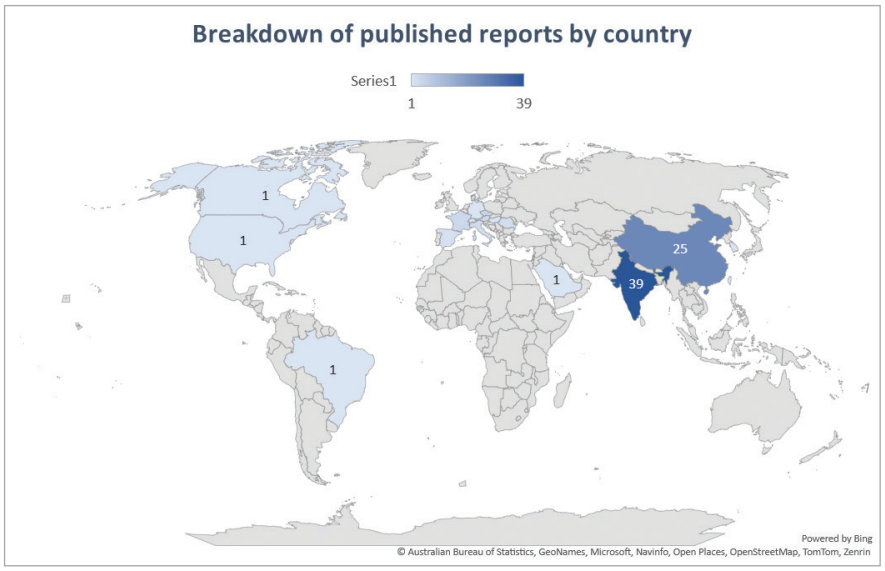

Figure 1. Breakdown of published reports by country.

There is also a downward trend in the annual number of non-compliance reports. The highest number was in 2013 - 18 reports (Fig. 2). For the last 3 years of the analysis horizon (2020–2022), 5 non-conformity reports have been published, the decrease probably being due not only to increased compliance with the GMP requirements, but also due to the COVID-19 pandemic, the extended validity of already issued GMP and GDP certificates until the end of 2023, and the lower number of inspections overall. However, Covid-19 can be seen as a catalyst to consider the benefits of remote inspections. While in well-developed countries such as the USA, the feasibility of conducting remote collaborative and interactive GMP audits has already been evaluated and recommended (Huysentruyt et al. 2021; Baker et al. 2023), the implementation of risk-based monitoring of sites, mainly through on-site inspections, is generally recommended by the EMA. Although remote inspections are recognized by both the EMA and the FDA with the publication of the EMA "Guidance on Remote GCP Inspections during the Pandemic COVID19 in May 2020 and the US FDA document „Conducting Remote Regulatory Assessments Questions and Answers Draft Guidance for Industry" in July 2022, the supervisory vigilance approach is still an obligation of the national competent authorities. In case of non-compliance, the national competent authorities have the authority to take the appropriate regulatory action against manufacturers, importers and distributors who do not comply with the GMP standards. In addition, the precise set of methodologies and technical means to conduct a remote audit or inspection should be further investigated and optimized to ensure a thorough examination of all relevant criteria defined by the GMP regulations.

Another point to consider is that the pharmaceutical supply chain was extremely strained as a result of the global COVID-19 pandemic. Drug shortages that had already been observed were exacerbated, and the difficulty in obtaining active substances from Asia due to travel restrictions and inadequate manufacturing due to fluctuating COVID-19 guidelines increased the risk of distribution of non-quality assured products (Izutsu et al. 2023). It can be speculated that one of the main reasons is the lack of mutual recognition agreements or other facilitating agreements between resource-poor, low-income countries and better-resourced countries that can guarantee product manufacturing and quality control (Nebot Giralt et al. 2020; Tirivangani et al. 2021).

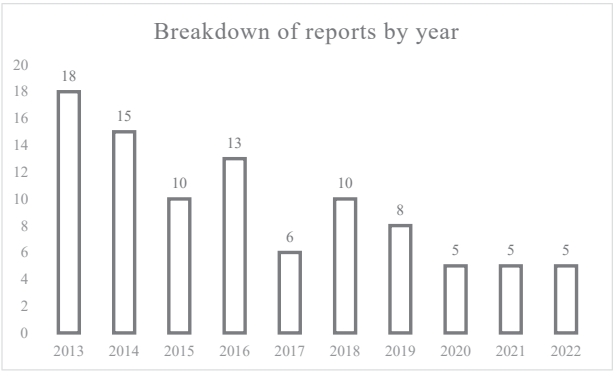

Figure 2. Breakdown of reports by year.

Reports have been published by a total of 21 competent authorities. The highest number of non-compliance reports was published by the French Health Products Safety Agency (21%), followed by the MHRA (United Kingdom) (15%). These numbers need to be interpreted in the context of the UK leaving the EU and the fact that the database only includes documents issued by UK authorities up to 31 December 2020. Of the manufacturers examined, 53 were active pharmaceutical ingredient (APIs) manufacturers. Of these, 24 were located in China, 20 in India and 8 in other countries. The number of APIs manufactured was more than 50 from diverse pharmacotherapeutic groups including homeopathic medicines.

Analysis of published reports shows that 1,458 deficiencies were identified, although some reports only mention the number of major and critical deficiencies without explicitly specifying the total number, leading to an underestimation of this indicator (Table 1). Major deficiencies accounted for 37% of all deficiencies identified, critical deficiencies accounted for 9%, all the rest were in the category "other". An average of 7.88 (±5.5) major deficiencies and an average of 2.23 (±1.8) critical nonconformities were observed per 1 manufacturer.

Table 1. Number of non-compliances identified.

Non-compliances	**1458**
Mean	24.3
SD	10.68
Median	24
Major non-compliances	544 (37%)
Mean	7.88
SD	5.5
Critical non-compliances	127 (9%)
Mean	2.23
SD	1.8

Non-compliances by operation are also examined. The highest number was found in the manufacture of other active substances (49 manufacturers), followed by the manufacture of non-sterile products (47), product packaging (33) and stability testing (32). Significantly fewer deficiencies were found in the manufacture of sterile products (20) and biological products (5).

The relationship between the type of product and the level of non-compliance should be discussed as part of the specification of the quality assurance measures and manufacturing process for specific products such as sterile preparations, biologics or nanoparticle products (Ramanan and Grampp 2014). Special requirements to minimize the risks of microbiological, particulate and pyrogenic contamination should be met in case of sterile production (Kolhe et al. 2013). What is more, all these criteria are highly dependent on the knowledge, training and attitudes of the personnel involved, the type of manufacturing facility, on-site control, documentation, etc.- all set in the bundle of the GMR guidelines. Sterile manufacturing must strictly adhere to carefully established and validated methods and processes, as quality

assurance is of particular importance (Halls 2004; Kolhe et al. 2013; Agalloco and Akers 2015; Eberle et al. 2016).

In addition, non-compliance with GMP requirements and the subsequent closure of manufacturing facilities play a significant role in drug shortages. Identified deficiencies often not only prevent batches of medicines from being released to the market, but also require the redesign of manufacturing algorithms or the implementation of corrective actions, which can cost patients months and result in unmet medical needs. The link between GMP non-compliance and drug shortages is well illustrated by the quality control of sterile injectable drugs, due to their sensitivity to contamination, and biologics, due to the risk of fill-finish contamination and their sensitivity to subtle changes in the manufacturing process and in the storage and handling of their finished dosage forms. As a result, ICH Guideline Q10 on Pharmaceutical Quality System recommends the establishment of a well-organized internal quality system that goes beyond the de facto minimum quality standard defined by GMP. It is the industry that should strive to change the paradigm and achieve an effective quality system that reduces the burden of shortages. It is already accepted that the adoption of quality risk management by manufacturers would better ensure the provision of safe and high-quality pharmaceutical products to the market, with regulators merely overseeing the process by applying a more risk-based approach to establishing regulatory oversight. For example, to properly manage the reduction of quality risk, self-inspection procedures should be expanded and optimized.

Non-compliances related to the manufacture of sterile products were most commonly associated with identified deficiencies in the product packaging process (65%) and stability testing (50%). Manufacturers with identified deficiencies in the production of organic products also had deficiencies in stability testing (60%) and secondary packaging (40%).

Non-compliance with the GMP requirements for packaging was most common for both primary and secondary packaging (49% of cases). Non-compliance in secondary packaging was observed most frequently for sterile products (6.50%). Besides, 32 deficiencies were identified concerning the assessment of the stability of medicinal products/active substances, with the most common being microbiological sterility, and chemical and physical stability testing.

The non-compliance detected during inspections led to the suspension of the manufacturing authorizations of 24 manufacturers. A total of 145 major and 36 critical deficiencies were identified. The total number of deficiencies mentioned in the inspection reports is 268, but it should be noted that the total number of nonconformities is often not specified, which leads to an underestimation of this indicator, as the non-compliances in the 'other' category are missing. On average, 23.8 deficiencies were observed per producer, of which 2.72 were critical and 11.6 were classified as major.

Fig. 3 provides a comparison of the major and critical deficiencies in the general sample and among the manufacturers with suspended manufacturing authorization. The average number of critical deficiencies in the two groups is almost the same, 2.23 versus 2.72, but there is a significant difference in the number of major deficiencies,

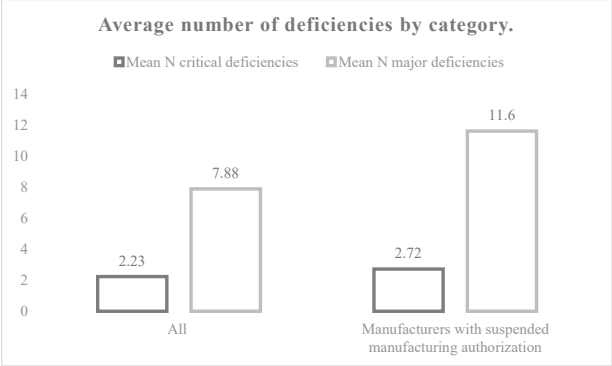

Figure 3. Average number of discrepancies by category.

7.88 in the total sample versus 11.6 for manufacturers with a revoked production approval. (+47%).

For 41 of the producers inspected, the inspecting agency ordered the suspension of the Good Manufacturing Practice certificate, for 36 of them the Certificates of Suitability were also revoked, and for some of the producers 16 CEPs were suspended. In 4 cases, partial suspension of GMP certificates was recommended - 2 cases from 2014 for a UK sterile dosage forms manufacturer, 1 case from 2015 in China and 1 case from 2018 in Austria. It is worth noting that compromising the effectiveness of GMP compliance monitoring would significantly jeopardize the efforts of all subsequent safety and quality surveillance systems for medicinal products, such as pharmacovigilance monitoring, anti-counterfeiting control, etc.

Other measures taken include variations to the marketing authorization (27 cases), withdrawal of batches of medicinal products/active substances (30 cases), prompt notifications (3 cases) and prohibition of supply by the manufacturer concerned (51 cases).

It should be noted that, in many cases, the inspecting agencies have left the decision to block and withdraw batches to the national agencies of the countries for which the medicinal products/active substances concerned were intended. In some cases, supply bans were recommended only after a preliminary assessment as to whether they were critical products or critical supply routes that would be adversely affected and could lead to a shortage of medicinal products.

Conclusion

The analysis of GMP inspection noncompliance reports over ten years provides valuable information on challenges and areas for improvement in the pharmaceutical industry. The most common recurring problems and potential gaps in GMP compliance are highlighted.

The deficiencies identified highlight the importance and need for continuous monitoring and improvement of manufacturers' manufacturing processes and quality management systems. Collaboration between sector stakeholders - regulators and manufacturers is critical to ensure the sustainable effectiveness of GMP inspections. As technology advances and global supply chains become more complex, the challenges associated with GMP compliance are increasing.

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