MEDICAL AND PHARMACEUTICAL SCIENCES

DOI: https://doi.org/10.36719/2707-1146/43/5-8

Rafael Abdullayev
Istanbul University
arafael9696@gmail.com
Mahbuba Valiyeva
Azerbaijan Medical University
Doctor of Science in Pharmacy
mahbubav_amu@rambler.ru
Tohfa Nasibova
Azerbaijan Medical University
PhD in Pharmacy
tnesibova@amu.edu.az

INTERNATIONAL PRACTICES ON GMP IN PHARMACEUTICALS

Abstract

Pharmaceutical science encompasses meticulous processes, from initial pharmacological testing to distribution and pharmacovigilance. Each stage demands unwavering precision and adherence to regulatory standards to ensure the quality and safety of medicinal products. This article delineates the multifaceted landscape of pharmaceutical regulations, focusing on Good Manufacturing Practice (GMP) standards as a cornerstone of quality assurance. GMP standards, encompassing GxP principles, mandate adherence to rigorous protocols throughout the drug lifecycle. Within the European Union (EU), GMP standards are codified in directives and regulations governing medicinal products for human and veterinary use. Volume 4 of Eudralex serves as a compendium of EU regulations, providing comprehensive guidelines for pharmaceutical manufacturing.

Mutual Recognition Agreements on GMP inspections between the EU and other jurisdictions aim to facilitate trade and regulatory cooperation, exemplifying international collaboration in pharmaceutical oversight. Recent agreements between the EU and the US FDA streamline inspection processes, reducing redundant inspections and expediting market access for pharmaceutical products.

Moreover, electronic systems such as EudraGMDP enhance transparency and regulatory compliance within the pharmaceutical industry. By evaluating international GMP practices, this article underscores the importance of harmonizing regulatory standards for Good Manufacturing Practices globally.

In conclusion, adherence to GMP standards not only ensures the quality of pharmaceutical products but also plays a pivotal role in the development of pharmacy practices worldwide.

Keywords: *Pharmacy, GMP, Eudralex, EMA, FDA, IRIS, Eudra GMDP*

Introduction

Pharmaceutical science is a very broad concept and requires strict responsibility and precision at every step. Here, each step refers to the stages from initial pharmacological testing of a potential medicinal product to mass production, documentation procedures for registration and sales authorization, presentation to the customer in a pharmacy, and even monitoring the side effects and adverse effects of the drug. Of course, these stages are divided into many steps, each of which is small and detailed, and proceeds in appropriate sequences. Each of these parts has special nuances that ultimately focus on the quality of the drug and are important to pay attention to. These nuances are complexed and grouped in the form of standards, rules, and regulations. The most important standards encountered and required to be followed in pharmaceutical activities include GxP

standards, which require strict adherence to relevant regulations at all stages of drug preparation and delivery from the manufacturer to the consumer. Standards such as GMP - Good Manufacturing Practice (1), which covers the production process, GDP - Good Distribution Practice, which is especially important for wholesale enterprises, GLP - Good Laboratory Practice (2), which regulates laboratory processes, GPvP - Good Pharmacovigilance Practice, which serves to collect and process information about the additional and side effects caused by the drug in the body after taking it (3), GCP - Good Clinical Practice, which controls the quality and accuracy of clinical practices (4), and GDocP - Good Documentation Practice, which ensures compliance of submitted documents with the rules (5), can be the most important examples of GxP (Ronninger, 2012: 3). It is important to comply with each of these regulations, and at the same time, when importing pharmaceuticals and biologically active food products to most countries, including Europe, Azerbaijan, it has been accepted as a strict requirement that manufacturing enterprises have only GMP certificates among those listed. For this reason, compliance with GMP requirements, and obtaining and periodically renewing the GMP certificate are at the top of the list of duties of every pharmaceutical manufacturing enterprise (Doneski, 2023: 2).

GMP standards are regulated by legal requirements, including Directive 2001/83/EC and Directive (EU - European Union) 2017/1572 relating to medicinal products for human use; Directive 2001/20/EC and Regulation (EU) 536/2014 for investigational medicinal products; Directive 91/412/EEC and Regulation (EU) 2019/6 for veterinary medicinal products; active substances used for humans include Regulation No. 1252/2014 (1, 8). Directive 2003/94/EC applies to both human and investigational medicinal products. The principles and guidelines of Good Manufacturing Practices defined in the Commission Directives 2003/94/EC and 91/412/EEC are reflected in Volume 4 of Eudralex, otherwise known as "The rules governing medicinal products in the European Union". This volume consists of an introduction and 4 parts, and these parts are composed of different chapters and appendices (8). Part I contains "Basic requirements for medicinal products" and consists of 9 chapters approved between 2013 and 2015.

Part II, "Basic requirements for active substances used as starting materials", came into force in August 2014. Part III includes documents related to GMP about quality management, risk assessment, batch control, export, shipping, and marketing of pharmaceutical and medicinal products. In addition to the documents mentioned, Part II of Volume 4 of "The Rules Governing Medicinal Products in the European Union" includes various appendices. Annex 1 of sterile medicinal products, Annex 2 of biologically active substances and medicinal products for human use, Annex 3 of radiopharmaceuticals, Annex 4 of all veterinary medicinal products except immunological veterinary medicinal products, Annex 5 of immunological veterinary medicinal products, Annex 6 of gaseous medicinal products, Annex 7 of plants origin medicinal products, Appendix 9 liquids, creams and ointments, Appendix 10 pressurized and metered dose aerosols for inhalation, Appendix 13 medicinal products for investigational purposes, and Appendix 14 are designed to control the production of products obtained from human blood or plasma.

Also, Annex 8 Sampling of Starting and Packaging Materials, Annex 11 Computerized Systems, Annex 12 Use of Ionizing Radiation in the Manufacture of Medicinal Products, Annex 15 Qualification and Validation Processes, Annex 16 Qualified Person Certification and Batch Release, Annex 17 Parametric Release, Annex 19 retention and reference samples, and Appendix 21 sets out the requirements for the import of medicinal products.

Part IV of the 4th volume of the "The rules governing medicinal products in the European Union" is composed of "Guidelines for Good Manufacturing Practice specific to Advanced Therapy Medicinal Products" (9).

To overcome trade barriers, the EU has signed Mutual Recognition Agreements on GMP inspections with regulatory authorities located outside its borders. These agreements aim to allow EU authorities and their counterparts to trust each other's GMP inspections, waive batch testing of products entering their territory, and share information on inspections and quality defects. Mutual Recognition Agreements on GMP have been signed between the EU and Australia, Canada, Israel,

Japan, New Zealand, Switzerland, and the USA, covering medicinal products intended for human and animal use.

On May 30, 2023, the US Food and Drug Administration (FDA) announced that Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, and Spain has confirmed that its national authorities are equivalent to the United States in terms of inspection capacity, capabilities and general procedures for Good Manufacturing Practices for veterinary products. At the same time, the EU has recognized the US FDA as the equivalent competent authority for Good Manufacturing Practices for veterinary products. Later, on September 26, 2023, the US FDA recognized the Swedish authority, and on November 28, 2023, the Latvian authority. This means that the EU and US FDA can rely on the results of pharmaceutical GMP inspections carried out in the parties' respective territories, and there is no longer a need to repeat inspections of manufacturing sites.

The EU also has Mutual Recognition Agreements equating Good Manufacturing Practices for medicinal products for human use with Croatia, Italy, Malta, Czech Republic, Romania, Lithuania, Cyprus, Germany, and Slovakia, including countries for veterinary products. The list of countries with agreements based on human and veterinary drugs is reflected in the Sectoral Annex to the EU-US Mutual Recognition Agreement together with the relevant dates. It is mentioned in the Sectoral Annex that the agreements valid for medicinal products intended for humans have entered into force since July 2019. For veterinary medicines, this document entered into force on May 11, 2023, when the EU and the US signed Joint Sectoral Committee Decision No. 2536/2023. The recognition of verifiability and comparable procedures makes bringing medicines to market faster and cheaper, reduces administrative burdens and costs from re-inspections, and allows manufacturers in other countries to focus more.

The mentioned agreements are based on audits of the Joint Audit Program in all EU Member States and close technical cooperation between the European Medicines Agency (EMA), the US FDA, and the Commission. Currently, the evaluation by the competent authorities of the EU continues according to the schedule agreed with the US. The US FDA has set a target date of July 2024 for the completion of the assessment of the inspection capacity of all EU authorities for veterinary medicines. The batch testing waiver will only come into effect when all EU veterinary authorities are recognized by the US. From that point on, veterinary products imported from the US will no longer need to be re-tested for quality control before being placed on sale in the EU. As a continuation of the technical cooperation between the EU and the USA, it is planned to expand the scope of the Sectoral Annex in the direction of vaccines for humans and even plasma-derived medicinal products at a later stage. These topics are currently on the agenda of the meetings of the EU-US Trade and Technology Council (Lopez-Navas, 2022: 8).

An agreement was signed between the EU and Japan on 18 July 2018 to expand the range of medicines for which they recognize the results of inspections at each other's manufacturing sites, which is considered a continuation of the first agreement signed on 29 May 2004. The full scope of the said agreement includes chemical pharmaceutical products, homeopathic medicines (as long as they are accepted as medicines in Japan and subject to GMP requirements), vitamins, minerals, and herbal medicines (if they are considered medicines on both sides); includes certain biological pharmaceuticals, including immunological agents and vaccines, active pharmaceutical ingredients (APIs) for any of the above categories, and sterile products belonging to any of the above categories. This agreement serves both parties to rely on Good Manufacturing Practice inspections in each other's territories, to waive batch testing of drugs entering Japan from EU countries and vice versa, and to share information on inspections and quality defects.

Directive 2011/62/EU amending Directive 2001/83/EC introduced EU-wide rules for the import of active pharmaceutical ingredients. Article 46b(2) established that APIs can only be imported if accompanied by written approval from the competent authority of the exporting third country stating the similarity to the GMP and control standards adopted by the EU (8).

As GMP procedures are strictly and precisely implemented in the EU, various electronic systems have been established to facilitate the work of manufacturers. For example, marketing authorization holders and applicants should use the EMA's IRIS system to communicate with the EMA regarding GMP inspections required by the EMA's scientific committees (11).

EudraGMDP is a publicly available EU database containing production and import permits, registration of active ingredient manufacturers, GMP certificates, and declarations of non-conformity. After inspecting the production site, the EU authorities enter the GMP certificate or statement of non-conformity into the EudraGMDP database (6, 12).

Conclusion

Thus, in this article, international practices on GMP were evaluated, and such information should be analyzed and correctly applied for the further development of Good Manufacturing Practices in our country. This characteristic will play a large role in the development of not only Good Manufacturing Practices but also general pharmacy in our country.

References

1. European Medicines Agency. Good Manufacturing Practice (Accessed March 17, 2024). https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice
2. European Union. Good Laboratory Practice (Accessed March 17, 2024). https://single-market-economy.ec.europa.eu/sectors/chemicals/good-laboratory-practice_en
3. European Medicines Agency. Good Pharmacovigilance Practices (Accessed March 17, 2024). https://www.ema.europa.eu/en/glossary/good-pharmacovigilance-practices
4. European Medicines Agency. Good Clinical Practice (Accessed March 17, 2024). https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice
5. University of Rochester. Good Documentation Practices (GDP) (Accessed March 17, 2024). https://www.rochester.edu/ohsp/resources/studydocumentation/gdp/#:~:text=Good%20Documentation%20Practices%20(GDP)%20is,both%20paper%20and%20electronic%20format
6. Ronninger, S., Schmitt, S., Rangavajhula, V., Hough, E., Lyda, J. (2012). Considerations on Auditing and GxP Requirements along the Product Lifecycle. PDA Journal of Pharmaceutical Science and Technology, 66(5), pp.396-402. DOI:10.5731/pdajpst.2012.00881
7. Doneski, L., Dong, M.W. (2023). Pharmaceutical Regulations: An Overview for the Analytical Chemist. LCGC North America, 41(6), pp.211-215. DOI:10.56530/lcgc.na.ua3181v7
8. European Union. Good Manufacturing and Distribution Practices (Accessed March 17, 2024). https://health.ec.europa.eu/medicinal-products/good-manufacturing-and-distribution-practices_en
9. European Union. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines (Accessed March 17, 2024). https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
10. Lopez-Navas, L., Torrents, S., Sánchez-Pernaute, R., Vives, J. (2022). Compliance in Non-Clinical Development of Cell-, Gene-, and Tissue-Based Medicines: Good Practice for Better Therapies. Stem Cells Translational Medicine, 11(8), pp.805-813. DOI:10.1093/stcltm/szac046
11. European Medicines Agency. IRIS (Accessed March 17, 2024). https://iris.ema.europa.eu/
12. European Medicines Agency. EUDRAGMP (Accessed March 17, 2024). https://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=l9aqYsTv6CTwYmws5GWlQd0iWlqT8glrZwLGeismUJ2W1ltWqn_G!1686084519

Received: 27.02.2024 Accepted: 02.04.2024