

ANNEX 21

Importation of medicinal products

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Introduction

The initial version of the Annex 21 Importation of medicinal products was published in 2015; and in 2020 gets the first draft version. This draft version has undergone several changes in the previous two years, to reach its final version at the beginning of this year.

Annex 21 summarizes all Good Manufacturing Practice (GMP) requirements relating to the holder of marketing authorization (MA) and import authorization when the import is carried out in the territory of the European Union (EU) by a third country. This Annex summarizes all GMP requirements applicable to Manufacturing Import Authorization (MIA) holders when importing drugs outside the EU into the EU.

The guidelines in the main chapters and other annexes to the GMP guide should continue to apply, and the information in this annex should be used to supplement questions not covered by the other guides.

For the purpose of this Annex, the term importation refers to the action of physically bringing a medicinal product, from outside the territory of EEA/EU, whereas the fiscal transactions are not part of this annex.

If until now the question was raised whether the certification of the batch can start before the batch is physically imported into the territory of EU, Annex 21 emphasizes that the certification can only start at the moment when the batch is physically located in the territory of the EU.

The site where the physical importation takes place and the site where the Qualified person (QP) carries out the batch certification or confirmation for bulk and intermediate products, which may undergo further

manufacturing operations, considered to have specific importation responsibilities.

The above-mentioned importation responsibilities must be carried out by entities appropriately authorized under a MIA (Annex 21, 2022).

Annex 21 complements and confirms the requirements of Annex 16 about testing carried out in the territory of the EU and which should contain all analyzes proving that the medicinal product complies with the requirements of MA and specification limits, in addition to chapter 7 itself requires, agreements between all stakeholders need to be signed and updated accordingly (Annex 16, 2016; Chapter 6: Quality control, 2014).

The aim of this paper was to highlight the importance of Annex 21 Importation of medicinal products, its benefits and increase awareness of the growing number of requirements, which aim to ensure the quality, safety and efficiency of medicines.

New requirements

Regarding the Pharmaceutical Quality System, the site that imports the drugs should have a complete and detailed quality system in accordance with activities performed on the site and with the requirements listed in Chapter 1 of this GMP guideline (Directive 2003/94 EC, 2003).

Great attention is paid to preparing the product quality reviews (PQRs), which should be made by the site that performs the certification of the batches. The PQRs themselves should include the deviations that occurred during the transport of the drugs (Chapter 6: Quality control, 2014).

Also, new is the need to compare the results of the certificate of analysis generated by the third country with those obtained from the laboratory on EU territory.

For any deviations and out-of-trend (OOT) results, it is necessary to make an appropriate investigation and to find the root causes.

The site that performs the batch certification should ensure that the stability program performed in the third country's territory is in accordance with Chapter 6, and all protocols, results and reports from it should be available to the QP (Chapter 6: Quality control, 2014).

Most of the innovations are in the documentation and what imposes the need for the electronic batch record is the requirement of this annex, all documentation, including batch certificates, to be available to QP at the time of batch certification.

In contrast, the frequency by which the qualified person will review all documentation should be determined based on a risk assessment (Annex 21, 2022).

Electronic batch records

Electronic batch records are tools that digitally record all elements associated with the production process and analysis of finished products.

Replacing paper records with electronic records improves data integrity and ensures GMP compliance. The introduction of a paperless system provides the improvement of data integrity and accuracy and the advancement of process efficiency.

An additional challenge regarding what needs to be done and completed is to provide all the documentation available in a language understandable to QP.

This requirement arises from Annex 16, QP to certify batches of a medicinal product only upon complete verification of the documentation and compliance of the medicinal product with the marketing authorization (Annex 16, 2016).

Conclusion

This annex will strengthen the requirements regarding the certification of the batch, reducing the opportunities for errors, unintentionally/deliberately neglected deviations that occurred during transport, will provide a double check of the obtained results and will impose the need of appropriate investigations if detect discrepancies.

Annex 1 is only a confirmation of the requirements that are becoming more strict, in order to ensure the best quality of the finished products, by defining all the responsibilities that all stakeholders bear.

References

- Directive 2003/94 EC, for. *Principles of Good Manufacturing Practice for Medicinal Products for Human Use and Research for Medicinal Products for Human Use*, effective from: 14.10.2003. Available at: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:262:0022:0026:en:PDF>
- The rules governing medicinal products in the European community European Union, Volume 4, *Annex 16: Certification by a qualified person and placing on the market of a medicinal product*, effective from 15 April 2016. Available at: https://health.ec.europa.eu/system/files/2016-11/v4_an16_201510_en_0.pdf
- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use *Annex 21: Importation of medicinal products*, effective from: 16.02.2022. Available at: https://health.ec.europa.eu/system/files/2022-03/vol4_annex21_en.pdf
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