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Audit of the Production of Sterile Medicines for Compliance with the Requirements of the Draft EU GMP Annex 1 with Risk Analysis

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***Abstract*—The role of the PIC/S organization in the pharmaceutical industry was noted, the main aspects and place of inspection activities in the production of medicines were determined, the general classification of incompliances, as well as the main methods and tools for risk assessment were considered.**

An object of research is the operating production of sterile medicines and internal documentation of the site. In the course of the experimental part of the work, an audit of the operating manufacturing of sterile medicines was carried out included the following main steps:

1. Preparation for the audit of the production site [Comparison of the current version of Appendix No. 1 of the Rules of Good Manufacturing Practice of the Russian Federation (Order of the Ministry of Industry and Trade of the Russian Federation of June 14, 2013 No. 916 of the Ed. December 18, 2015 "On Approval of Rules of Good Manufacturing Practice") and draft Appendix No. 1 EU GMP (EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products)], developing an audit plan and protocol, assessment system;

2. Audit of the site and filling in the audit report;

3. Evaluation of the audit protocol, taking into account risk analysis. Risk analysis was performed using FMEA method;

4. Development of recommendations to eliminate incompliance and the formation of a report based on risk analysis.

Keywords—annex 1; aseptic production; PIC/S; risk analysis; inspection

I. INTRODUCTION

Aseptic production is one of the most difficult production methods in the pharmaceutical industry, since it is necessary to maintain sterility and apyrogenity throughout the production process, due to the lack of a final sterilization stage. More and more drugs are produced under aseptic conditions. In the territory of the Russian Federation, the main document in the field of requirements for the production of sterile medicines, including those manufactured under aseptic conditions, is Appendix 1 of the Rules of Good Manufacturing Practice, which complies with the EU GMP Rules and GMP PIC\S.

On August 28, 2017, the Ministry of Industry and Trade of the Russian Federation submitted a preliminary application for Russia's entry into PIC/S, which implies the adoption and consent of Russia to the requirements of GMP PIC/S. Currently, the EU and PIC\S are actively discussing a draft update of Appendix 1 to the GMP PIC\S rules, which was published on December 20, 2017 for public discussion [1-5].

II. EXPERIMENTAL

Changes in Appendix 1 are aimed at detailing the current statements, eliminating ambiguities and introducing new requirements. Thus, the changes will become an occasion for revising the current quality system at each enterprise engaged in the production of sterile medicines. That is why it is important to take preventive actions to identify inconsistencies of current practices and the organization of production with the requirements set forth in the draft Appendix 1.

Joining PIC\S requires a lot of actions on the part of the institutions regulating the production and circulation of medicines in the territory of the Russian Federation, among which, first of all, the harmonization of local regulatory requirements with international ones. Harmonization of the requirements of EU GMP Appendix No. 1 and Order No. 916 Appendix No. 1 is a priority, since the differences between the current version of Order No. 916 Appendix No. 1 and the draft Appendix No. 1 are significant and may affect the organization of production of sterile dosage forms.

Thus, a preventive analysis of the current conformity of production to the draft Appendix No. 1 will allow, by the time the updated version of Appendix No. 1 comes into force in Russia, to reduce the number of nonconformities, completely eliminate nonconformities, or develop a detailed plan for eliminating nonconformities depending on their priority.

The purpose of the study is to audit the operating production of sterile medicines for compliance with the requirements of the draft EU GMP Appendix 1 using a risk analysis. To develop a universal plan and audit protocol for the production of sterile medicines for compliance with the requirements of the draft GMP EU Annex 1.

In preparation for the audit, an audit plan and protocol was developed, as well as an algorithm for working with the audit protocol (fig.1 and 2). In terms of audit, the most important steps are the preparatory phase and the immediate conduct of the audit. The audit protocol contains standard elements, such as the name of the document, version information and place in the enterprise documentation system. The basis of the protocol is an assessment table, which presents the clauses of the draft Annex No. 1, similar paragraphs of Annex No. 1 of the Rules of Good Manufacturing Practice of the Russian Federation and the

	Record	1 of 25
	AUDIT PROTOCOL	Code: PR-XXX Version: YYY № ZZZ

ДАТА ПРОВЕДЕНИЯ:

Participants	Position	Full name
Responsible for conducting audut		
Work group members		

No. of clause	Draft Annex 1 GMP EU	Annex No. 1 of the Rules of Good Manufacturing Practice of the Russian Federation	Com-pliance	SOP availability (if applicable)	Comment
4 Personnel					
4.1	Enough qualified personnel	*Absent in a current version*			
4.2 (43)	Minimum personnel in the clean area, control from the outside of the clean area as much as possible (viewing windows, cameras)	Exact copy			
4.3 (44)	Regular staff training at all levels	Paragraph 44 content a brief summary of the information in paragraphs 4.3–4.6 of the draft Annex 1			
4.4	Only trained personnel who have successfully completed the procedure for evaluating the correctness of dressing for classes A, and B and participating in the simulation of the aseptic process are allowed to work. Evaluation of the correct behavior when performing aseptic production operations.	*Absent in a current version*			
4.5	…	…	…	…	…

Fig. 1. Audit protocol template.

fields for assessing compliance [4]. When working with the audit protocol, it was decided to divide all types of incompliance into incompliance that require modernization of manufacturing site for their elimination (including equipment purchase, redevelopment of premises, purchase and installation of sensors) and incompliances, to eliminate which it is necessary to work with the company's internal documentation. In accordance with this division of nonconformities, their criticality for production, for product quality and, as a result, patient health was evaluated.

Incompliances were assessed by FMEA risk analysis [6]. The FMEA method is designed to assess potential process failures, as well as their possible consequences on process

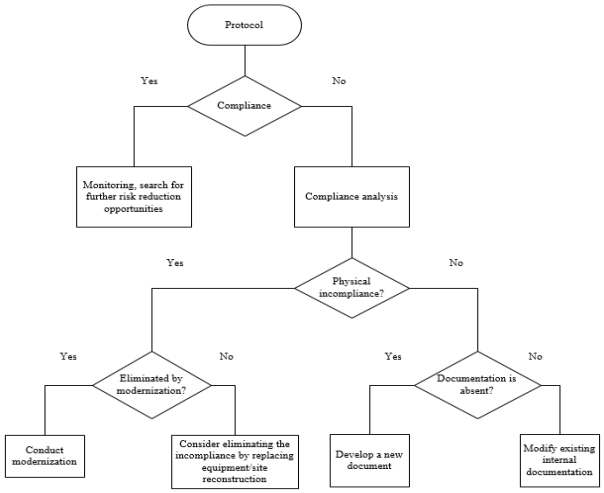

Fig. 2. The algorithm for working with the audit protocol.

results and / or product properties. The method is based on an understanding of the process and products. In FMEA, processes are divided into separate stages (stages, flowcharts). FMEA principles can be applied outside of project development at all stages of the product life cycle.

III. RESULTS AND DISCUSSION

FMEA method allowed to perform quantitative risk analysis of discovered during inspection incompliances. Definitions of Severity, Probability and Detectability are:

S (Severity) - the severity of the consequences of the error;

P (Probability) – error probability of occurrence;

D (Detectability) – error probability of detection.

The table I determines numeric connection between Severity, Probability and Detectability of discovered incompliances and a risk, linked with them.

TABLE I. FMEA METHOD TABLE FOR RISK EVALUATION

Criticality	Severity(S)	Probability (P)	Detectability (D)	Score
Very high	Deviations can lead to production shutdown	Very often	The error is not detected	5
High	The consequences of an error can cause regulatory authorities remarks	Often	Limited monitoring	4
Medium	A mistake can cause criticism in a regulatory authorities review	From time to time	Partial monitoring, error is easily recognized	3
Low	A mistake can cause non-critical comments as part of a regulatory authorities review.	Rare	Constant monitoring, which makes it possible to detect an error with high probability	2
Very low	The consequences of the error are not deviations from the internal requirements.	Very rare	Continuous monitoring to detect errors	1

Next important step was to estimate connection between total risk score and actions, which allow eliminating or at least mitigating discovered risk.

Risk Priority Number is calculated by the formula: RPN = S * P * D (table II)

The audit revealed 30 inconsistencies, 19 moderate and 11 significant, the criticality of which was further assessed using risk analysis using the FMEA method. The risk caused by each of the deviations was quantified and recommendations for addressing incompliance were developed. For example, the inconsistency with paragraph 4.12, consisting in the lack of completeness of the clothes of an operator working in an aseptic zone, can be eliminated by reviewing the completeness of workwear and updating the SOP at the entrance to clean rooms (table III and IV).

For every discovered in compliance recommendations were developed. During a repeated risk assessment, it was found that, taking into account the implementation of recommendations, most of the risks can be reduced to the level at which their adoption is possible, and critical risks can be reduced to a moderate level.

TABLE II. RISK SCORE AND ACTIONS TO TAKE INTERCONNECTION

Score	Risk	Actions
61-125	Critical	Risk mitigation, urgent solutions required
31-60	Significant	Risk mitigation required (CAPA)
11-30	Moderate	Risk taking, evaluate appropriateness CAPA
Ниже 10	Negligible	Risk taking

TABLE III. RESULTS OF REEVALUATION OF THE RISKS

Annex 1 clause	Recommendation	S	P	D	RPN
4.5	Introduced paragraph on the disqualification of personnel in SOPs, control of personnel	2	2	2	8
4.12	Supplementing the completeness of clothing, updating SOP for changing clothes	4	2	3	24
4.15	Development of SOP for the preparation of clothing	1	2	3	6
5.10	Installation of an alarm system in the air lock	2	2	3	12
5.29	Re-qualification of all cleanrooms, development of a re-qualification schedule	2	2	3	12
5.31	Control of microbial contamination of disinfectants	2	1	3	6
6.3	Re-validation of cleaning	2	2	2	8
7.16	Consider installing a TOC sensor	2	1	3	6
8.9	Assess the appropriateness of using isolating technologies	1	4	2	8

TABLE IV. RESULTS OF REEVALUATION OF THE RISKS

Annex 1 clause	Incompliance description	S	P	D	RPN	Recommendation
4.5	There is no procedure for the disqualification of workers	2	4	3	24	Introduced paragraph on the disqualification of personnel in SOPs, control of personnel
4.12	Gowning does not correspond to the cleanroom class (open areas of the operator's skin in zone A)	5	5	3	75	Supplementing the completeness of clothing, updating SOP for changing clothes
4.15	There is no SOP for the preparation of technological clothing	3	3	3	27	Development of SOP for the preparation of clothing
5.10	The absence of any system to prevent the simultaneous opening of two doors of the air lock	4	5	3	60	Installation of an alarm system in the air lock
5.29	Qualification of clean rooms was carried out more than a year ago	5	5	5	125	Re-qualification of all cleanrooms, development of a re-qualification schedule
5.31	Disinfectants used are not monitored for microbial contamination	2	4	3	24	Control of microbial contamination of disinfectants
6.3	No validation protocol for technological equipment cleaning	4	4	4	48	Re-validation of cleaning
7.16	TOC sensor for water for injections continuous monitoring is not installed	2	4	3	24	Consider installing a TOC sensor
8.9	Isolation technologies are not implemented	1	4	2	8	Assess the appropriateness of using isolating technologies

IV. CONCLUSION

The criticality of identified inconsistencies is assessed based on a risk analysis. 8 deviations represent a critical risk, 9 - high and 13 – moderate.

Practical recommendations for elimination incompliances have been developed. As a result of a repeated risk assessment, it was found that the implementation of the recommendations will reduce the RPN of risks associated with the identified deviations to an acceptable level.

It is relevant to use developed audit plan and audit protocol when evaluating the operating manufacturing of sterile medicines.

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