




Article

Compounding in Ukraine: Assessment of the Risks for the Ointment's Quality by the FMECA Method

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Abstract: The level of compounded medicines (CM) quality has always been questioned in different countries. This problem has been resolved by the introduction of quality assurance system (QAS) standards. One of its main areas of significance is the risks assessment process, which is especially important for the compounding pharmacy according to the requirements of different international documents. Since ointments constitute a large part of CM, quantity assessment of risks for their quality by the FMECA method has been completed. During the first step of the research, 42 potential deviations of compounded ointments (CO) quality were identified. Via the questioning of compounding pharmacies specialists in different regions of Ukraine by a pre-developed ten-point scale, the severity of deviations consequence, their occurrence probability, and detecting possibility were determined followed by the calculation of the priority risk number (PRN) value. The Pareto analysis showed that nine possible CO quality defects represented 21% of their total number. Defects related to the composition or technology of ointments (29%) and their compliance with microbiological purity requirements (23%) had the largest percentage contribution to the total PRN value. It was also found that the deviations consequence had the most serious impact on the CO quality, due to their direct influence on patient health.

Keywords: risks management; FMECA; compounded ointments; priority risk number



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1. Introduction

Quality assurance system (QAS) is one of the main tools which guarantees quality, safety, and effectiveness of any medicines. The implementation of its recommendations is especially important in the compounded medicines (CM) preparation, as their state registration process is not required in any country in the world [1–4]. Mandatory implementation of QAS standards in compounding pharmacies is emphasized in a number of major international regulations governing this activity [5–10] and scientific publications [11–17]. The introduction of QAS in such pharmacies helps to improve functioning, quality, and competitiveness of CM [2,12,17].

The main element of the QAS is the risks for quality of medicines assessment, which prevents occurrence of any possible deviations during their preparation process [17–20]. Many

regulatory documents of European Union (EU), the United States of America, Australia, and other countries contain strict demands for risks assessment of CM preparation [5–10]. In foreign countries, the severity of such risks determines a level of the requirements for their quality. For example, Resolution CM/Res (2016)1 in EU distinguishes CM with high- and low-risks, which requires using different types of standards for their quality assurance [9,20–22]. GMP requirements should be used for the first group and Pharmaceutical Inspection Co-operation Scheme (PIC/S) recommendations for the second one [7]. By the Resolution requirements, risks assessment should be completed before any CM preparation [9]. Its appendices contain recommendations concerning general risks assessment and application of this process during a dossier for medicines drafting [9].

PIC/S guideline contains such requirements [7]. It emphasizes that the level of potential risk depends on the nature of medicine’s using and determined by the probability of deviation (defect) occurrence, its detection and consequences (by the ICH Q9 Guideline methodology [23], which is referenced in this document). All general monographs of the Compounding Compendium of the US Pharmacopoeia [8,17,18,24] contain recommendations for the CM preparation and quality control, which could prevent probable occurrence of any risk during the entire process of their preparation. Monograph “Pharmaceutical preparations” of the European Pharmacopoeia [5] and the State Pharmacopoeia of Ukraine [6] also recommend using risks assessment processes in compounding pharmacies. Risk assessment, according to its recommendations, should help to evaluate the critical impact of various parameters on the CM quality and the risk of impact on a particular group of patients. The most common is the description of risks assessment processes for compounded parenteral solutions with the different approaches by using FMECA method [25–30], due to the seriousness of consequences of possible deviations in their quality parameters.

Analysis of the range of a number of compounding pharmacies in Ukraine, located in different regions, showed that both single and multicomponent nonsterile ointments take second place in the total volume of CM. This dosage form has its own features in preparation process, quality control, and using, and as such risks for their quality assessment with critical points for every stage of their preparation process determination and recommendations for their prevention are also important. There is no information in the publications about quantitative assessment of the risks for the compounded ointments (CO) quality in particular by the FMECA method, so it was decided to do this in Ukrainian pharmacies.

A number of modern tools have been proposed now for risk assessments. Each of them allows to make a conclusion about medicine compliance to the requirements with a different level of confidence [23,31]. Of course, quantitative risk assessments methods are more reliable. The most popular among them is the failure modes, effects, and criticality analysis method (FMECA) [23,26,31]. As it is commonly used for the risks for the quality of CM [25–30,32] evaluation, it was also used in our work. Common research design is listed below (Figure 1).

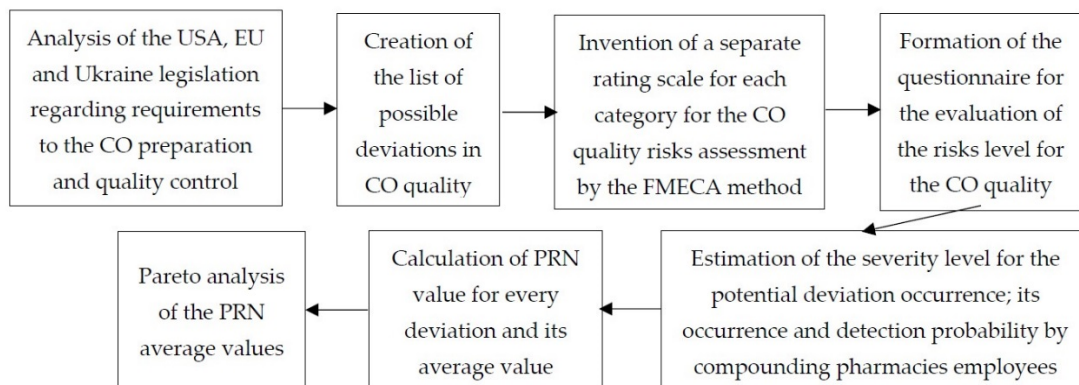


Figure 1. Research design.

2. Results

Modern QAS of compounding pharmacies affects all critical stages of medicines preparation (Figure 2), which can directly affect their quality and are determined by risks assessment.

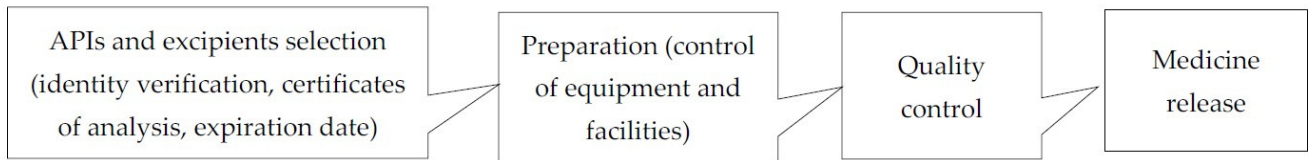


Figure 2. Main elements of the QAS in compounding pharmacies.

The process of risks assessment of any product can be carried out in two stages: identification and quantification. Preliminary identification of risks for the quality of CO allowed to identify and characterize possible factors influencing their quality by grouping them into main categories (personnel, API and auxiliary ingredients, facilities and equipment, preparation technology, stability, and quality control) [33]. However, a digital assessment of the significance of a certain defects impact on the CO quality can be estimated only by quantitative assessment.

At the first stage of quantitative risk assessment, a list of possible deviations in CO quality by analyzing the requirements and recommendations of the main regulations governing their quality was formed. A total of 42 possible defects in the quality of CO were identified. They were divided into six groups:

- ✓ defects associated with ointments appearance;
- ✓ defects associated with ointments composition/technology;
- ✓ defects associated with ointments microbiological purity;
- ✓ defects associated with ointments packaging;
- ✓ defects associated with ointments labeling;
- ✓ defects associated with ointments usage.

The largest number of defects is related to the composition and technology of ointments, the smallest—with the process of ointments application (the number of defects indicated in parentheses, Figure 3).

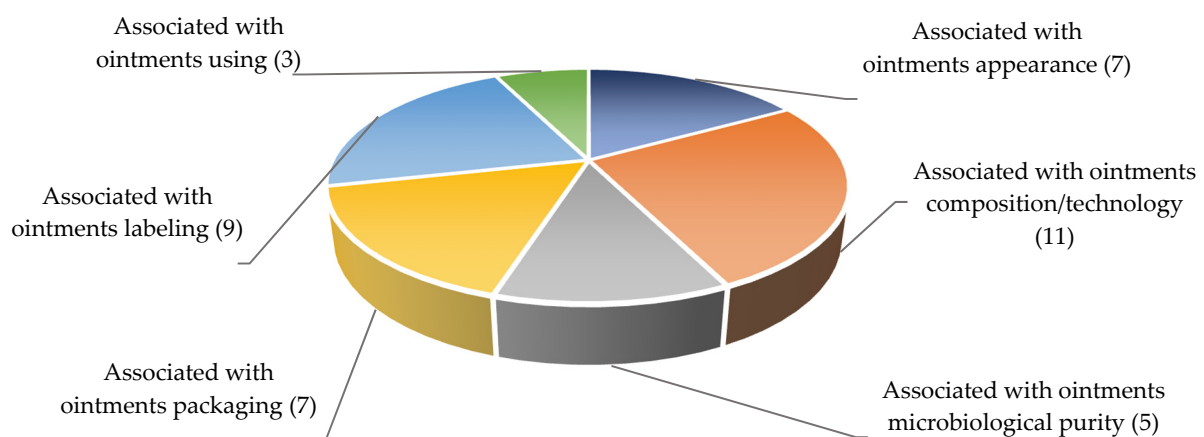


Figure 3. Possible deviations in compounded ointments quality.

All identified quality defects were the subject of evaluation in the created questionnaire, which according to the basic principle of the FMECA method, allowed to evaluate the consequence severity of the defect, the probability of its occurrence, and the possibility of its detection. The characteristics of the respondents who took part in the study are given below (Table 1). The evaluation of each criterion by specialists was based on practical

experience gained during the work in the compounding pharmacy. It should be noted that all pharmacies that participated in the study successfully implemented the QAS standards into their work.

Table 1. Characteristics of respondents who participated in the survey.

Respondent	Quantity	Specific Weight, %
Respondent position		
Head of the pharmacy	5	17.87
Deputy of the pharmacy head	2	7.14
Pharmacist	9	32.14
Pharmacist-analyst	9	32.14
Pharmacist assistant	3	10.71
Work experience		
Up to 10 years	11	40.74
10–20 years	7	25.93
20–30 years	6	22.22
30–40 years	2	7.41
40–50 years	1	3.70

The majority of respondents were pharmacists and pharmacists-analysts (64.28% in total quantity), which guarantees obtaining of the qualified answers to questions. A total of 89.29% of respondents had higher education. About 50% of respondents had work experience from 10 to 30.

We tried to cover different regions of Ukraine during the research. Pharmacies from 10 regions participated in it: Kirovohrad, Mykolaiv, Kharkiv, Khmelnytsky, Dnipropetrovsk, Sumy, Rivne, Luhansk, Odesa, and Zhytomyr. The percentage of participation of each of them is shown in Figure 4.

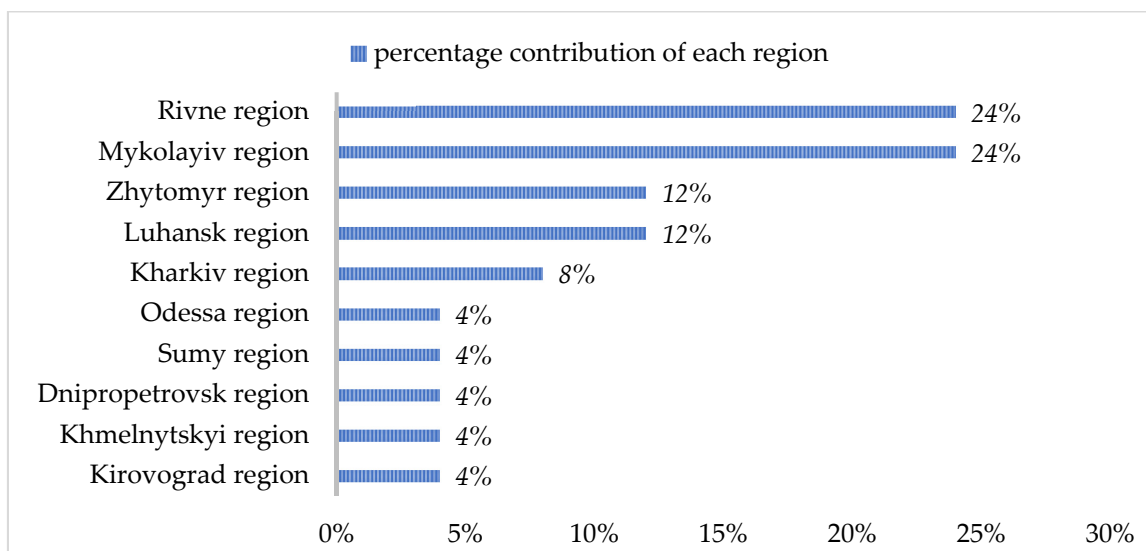


Figure 4. Percentage of each region’s participation in the survey (by the pharmacies quantity).

For the estimation of functioning and the effectiveness of QAS implementation in pharmacies, the average mark of the risks assessment values for each compounding pharmacy that participated in the study was calculated (Figure 5).

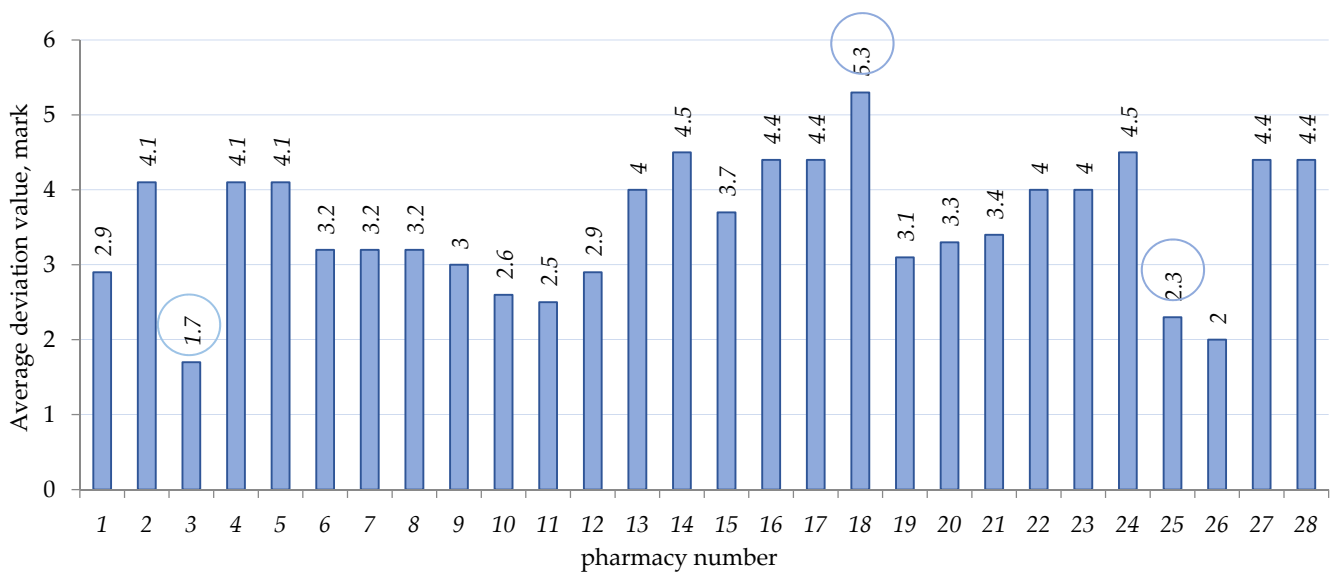


Figure 5. The value of the average score of defects in pharmacies. Notes: 1—Kirovograd region; 2—Khmelnytskyi region; 3—Dnipropetrovsk region; 4—Sumy region; 5—Odesa region; 6–12—Mykolaiv region; 13–15—Kharkiv region; 16–18—Luhansk region; 19–21—Zhytomyr region; 22–28—Rivne region.

The criticalness of every deviation impact on the ointments quality was assessed by calculating the PRN value for each pharmacy and found its average value based on the results for all pharmacies. The obtained results were processed by the Pareto method (Figure 6).

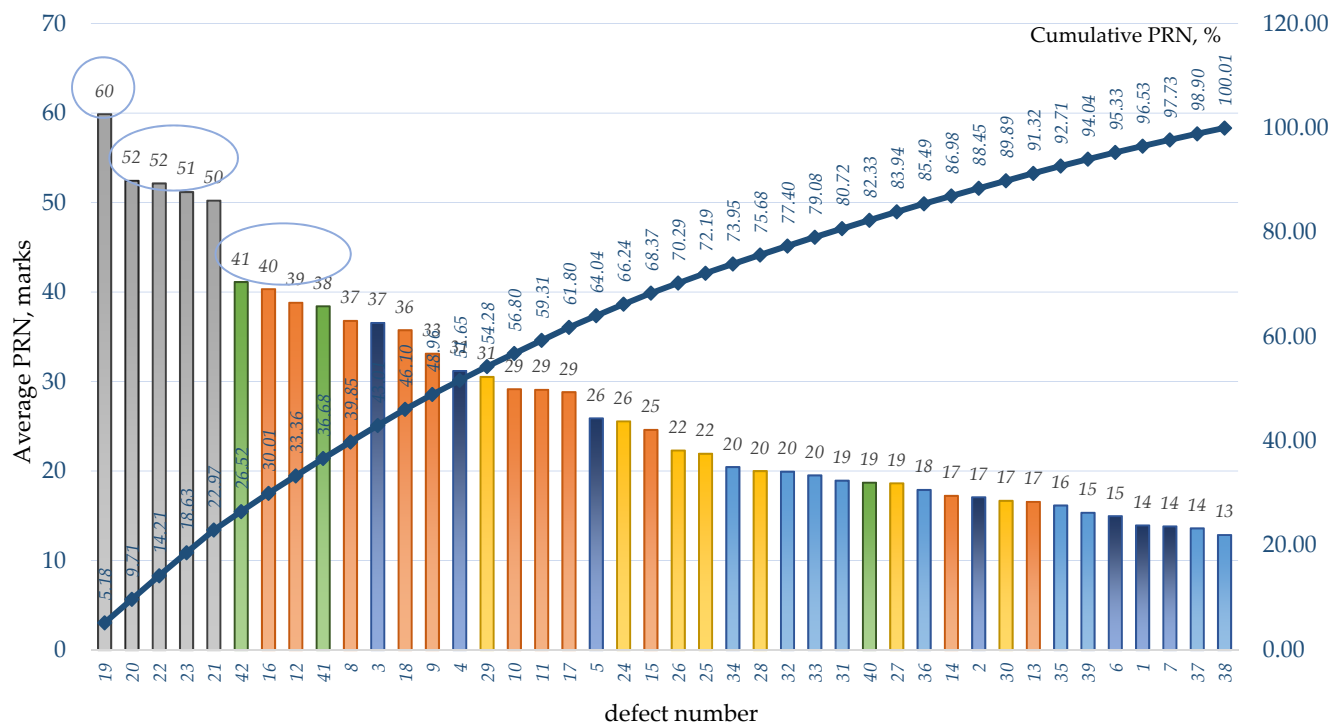


Figure 6. PRN average value analysis by the Pareto method.

List of possible defects in the ointments quality: 1—color changing; 2—the appearance of a nonspecific odor; 3—stratification; 4—crystallization of solids in the finished ointment; 5—the presence of visible solid particles; 6—fogging ointment bottle inside; 7—formation of gas bubbles in the finished ointment; 8—exceeding the API maximum therapeutic dose in the finished ointment; 9—the quantitative content of API in the finished ointment is

lower than prescribed in the recipe; **10**—excess of the amount of excipients in the ointment; **11**—understatement of the excipients amount in the ointment; **12**—the presence of incompatible ingredients in the finished ointment; **13**—exceeding the deviation of the total mass of the finished ointment; **14**—exceeding the deviation of the total volume of the finished ointment; **15**—unequal distribution of solids in the ointment (inconsistency of homogeneity of API dosing in the finished ointment); **16**—using of not registered in Ukraine or not approved for use by the Ministry of Health of Ukraine substance for the ointment preparation; **17**—inconsistency of the CO composition, specified in the passport of written control to the recipe; **18**—inconsistency of the ointment base with the nature of ointment action; **19**—exceeding the total number of aerobic microorganisms; **20**—exceeding the total number of yeasts and molds; **21**—presence of *St. aureus* in the ointment; **22**—presence of *Ps. aeruginosa* in the ointment; **23**—presence of *C. albicans* in the ointment for vaginal use; **24**—using of the translucent container for packaging ointments containing light-sensitive ingredients; **25**—leaky packaging; **26**—using of an unsealed container for the packaging of sterile ointment; **27**—lack of “running-in” packaging for packaging ointments containing toxic, narcotic, psychotropic substances; **28**—using of primary packing materials which do not correspond to the requirements defined in SPhU, technological instructions or other regulatory documents for packaging of finished ointment; **29**—incompatibility of primary packaging materials (adsorption of the finished ointment or its ingredients, leaching of packaging components into the medicine, chemical interaction) with the medicine or its individual ingredients; **30**—regarding transport packaging (in terms of deformation prevention, breakage and other damage to the medicine, etc. during its storage and transportation); **31**—incorrect indication or absence of ointment storage conditions on the label; **32**—absence “keep in a cool place” superscription on the ointment label which requires these storage conditions; **33**—absence “keep in a dark place” superscription on the ointment label which require these storage conditions; **34**—missing or incorrect indication on the ointment label date of preparation or expiration date; **35**—absence “sterile” or “aseptically made” superscription on the sterile ointments label; **36**—absence “be careful” superscription on the label of ointments containing toxic substances; **37**—discrepancy between the number on the recipe and the number on the label of the finished ointment; **38**—inconsistency of the patient’s surname on the recipe with the surname indicated on the label, prescription or its copy; **39**—absence of the application method on the ointment label; **40**—using of the container without control of the first opening for the sterile ointment packaging; **41**—irritating effect of the ointment due to incorrectly chosen technology of its preparation (eg, the introduction of zinc sulfate or resorcinol to the CO in the form of solution); **42**—lack of therapeutic effect of the ointment due to non-compliance with the rules of substances introduction into the ointment base (e.g., the introduction of protargol, collargol, tannin in the ointment by type of suspension).

For the significance assessment of each defects group, the sum of the average PRN values of each its components were calculated. As a consequence, their percentage contribution to the total PRN value (Table 2) and an average defects value was determined for each main group were calculated.

Average value for each assessed category was calculated to assess their degree of significance:

- ✓ severity of potential deviation occurrence—5.5 points;
- ✓ occurrence probability—2.0 points;
- ✓ detection probability—3.1 points.

Table 2. Calculated characteristics of defect groups (for all pharmacies).

Defect Group	Defects Average Value, Points	PRN Average Value	% PRN from Total PRN
Defects associated with ointments appearance	3,2	153	13
Defects associated with ointments composition/technology	3,6	330	29
Defects associated with ointments microbiological purity	4,9	266	23
Defects associated with ointments packaging	3,3	156	13
Defects associated with ointments labeling	3,0	155	13
Defects associated with ointments using	3,7	98	9

3. Discussion

QAS of compounding pharmacies applies to all stages of preparation and quality control of CM. Some of its elements have been used for a long time, however, the assessment of risks for each and determining the importance of their impact on the quality of CM will prevent possible defects in their quality. Most compounding pharmacies all over the world are guided by the basic principles of QAS in their work. The effectiveness of its operation can be assessed only by proving the compliance of the quality of CM with existing requirements.

A quantitative assessment of the sum of the values of possible deviations in CO quality was completed for this purpose. It proved by a fairly high level of implemented QAS and its functioning in each pharmacy (Figure 4), as evidenced by the relatively low values of the average score of three defects categories.

In most pharmacies, the average score of three categories of defects was in the range between 1.7 to 4 points. The lowest value was characterized by pharmacy No 3 (Dnipropetrovsk region, 1.7 points), and the highest pharmacy No 18 (Luhansk region, 5.3 points). Pharmacy No 26 of Rivne region also had a rather low average score (only 2 points). The main part of pharmacies had an average value of possible deviations from 2.5 to 3.4 points. Only 12 pharmacies were characterized by higher than four points (4–4.5 points) (Figure 4).

The analysis of the obtained average PRN values by the Pareto method indicated the presence of nine of the most serious possible defects in the quality of ointments, which made up 21.43% of their total value. Thus, according to the Pareto principle, they had a determinative influence on the CO quality. It was established that the highest PRN value had a defect of the total number of aerobic microorganisms exceeding (60 points). All defects associated with possible microbiological ointment contamination (No 19–23) characterized by the high PRN value. The severity of these defects was not accidental. In the case of the ointment microbiological contamination, its stratification could be observed, but most importantly was the possibility of harm to the patient's health. Pharmacies rated the introduction to the ointment of a substance unregistered in Ukraine or not approved for use by the Ministry of Health of Ukraine at 40 points, and at 39 points—the presence of incompatible ingredients in the finished ointment. In 38 and 41 points, pharmacies assessed two defects related to the ointment's application. It should be mentioned that the PRN value for any defect did not exceed the critical value (100 points) (Figure 5).

The calculated value of the PRN percentage contribution confirms that defects related to the composition/technology of ointments and their compliance with the requirements for microbiological purity have the largest percentage contribution to the total PRN value (29% and 23%, respectively) (Table 2).

Among three evaluated categories, the highest average score was characterized by the first category (due to potential deviations in the quality of ointments), which was not surprising. Indeed, each defect had its own significance and the score of its consequences characterized it. Defect occurrence consequence characterized the level of impact on the patient's health or the quality of the medicine, so its score must have been the highest.

4. Materials and Methods

The legislation of USA, EU, and Ukraine, which regulates CO preparation and quality control, was analyzed to determine possible deviations in this dosage form quality. General risk assessments method B.1 "Method of brainstorming" was used for possible deviations (defects) list formation. Quantitative analysis of the risks for CO quality was completed by the FMECA method (B. 2.3., according to the IEC/ISO 31010:2019 guideline [31]). It provides the selection of critical stages of medicines preparation, identification of possible quality deviations, assessment of their consequences, probabilities and possibilities of their detection, determination of the severity of each potential defect, and the formation of recommendations for their reduction. Thus, the FMECA method allows the determination of the degree of possible defects impacting a products quality and directly assesses the risks associated with the process of preparation and quality control of CO in the pharmacies [9,11].

An appropriate questionnaire for the evaluation of risks level for the CO quality by the estimation of possible deviations in their quality was developed. It allowed the determination of the severity of each possible deviation in quality by the assessment of the potential defect consequences level, the probability of its occurrence, and the possibility of detection. For the increasing of the accuracy for each category estimation, a separate rating scale from 1 to 10 points was developed. These three categories are common for the FMECA method, however a rating scale for the estimation of potential defects for CO quality was developed for the first time.

Severity of potential deviation occurrence (S).

Very dangerous—10 points—the worst impact on the patient's health and the ointment quality, as well as overdose during ointment use with the definite occurrence of serious side effects.

Dangerous—9 points—negative effects on the patient's health and the ointment quality, complete lack of pharmacological effect, and/or isolated serious side effects during ointment using.

Very important—8 points—significant impact on the patient's health and the ointment quality, insufficient strength of pharmacological effect, and possible occurrence of minor side effects.

Important—7 points—potential defect has an important impact on the patient's health and the ointment quality, can lead to the isolated cases of insufficient strength of pharmacological effects, and possible occurrence of minor isolated side effects.

Moderate—6 points—potential defect moderately affects the patient's health and the ointment quality, as well as an uneven manifestation of the pharmacological effect during the ointment application without possible occurrence of side effects.

Weak—5 points—the effect of the potential defect is weak; it has little influence on the patient's health and the ointment quality.

Very weak—4 points—the effect of the potential defect is very weak; it does not have a significant impact on the patient's health and the ointment quality.

Insignificant—3 points—the potential defect may slightly affect the patient's health and the ointment quality.

Very insignificant—2 points—the potential defect has almost no effect on the patient's health and the ointment quality.

Absent—1 point—the potential defect doesn't affect the patient's health and the ointment quality.

Occurrence probability (O).

Very high—10 or 9 points—the defect is extremely common (30–50% or more).

High—8 points (about 12% of CO defects) and 7 points (about 5% of CO defects)—such defects are quite common in practice.

Moderate—6 points (about 1% of CO defects), 5 points (about 0.25% of CO defects), or 4 points (about 0.05% of CO defects)—defect is accidental.

Low—3 points (about 0.001% of CO defects) or 2 points (about 0.0001% of CO defects)—there are very few such defects.

Small—1 point—the occurrence of the defect is unlikely (0.00001% or less of CO defects).

Detection probability (D).

Almost impossible—10 points—methods of a defect detection are absent; it is impossible to detect it.

Very badly—9 points —probability of a defect detection by existing control methods is very low.

Badly—8 points—there are non-specific methods of a defect detection, which will not allow to unambiguously detect it.

Very hard—7 points—it is necessary to conduct complex multifaceted research using specific equipment and reagents for the defect detection, it requires analysis conduction outside the pharmacy.

Hard—6 points—it is necessary to conduct research using specific equipment and reagents for the defect detection, it requires analysis conduction outside the pharmacy.

Moderate—5 points—the defect detection techniques are available, but they are quite long and require appropriate instrumentation, such as a spectrophotometer.

Very good—4 points—easy-to-perform and specific pharmacopoeial or validated techniques are available that can reliably detect a defect and require additional equipment.

Almost certainly—3 points—there are fairly easy and specific pharmacopoeial or validated techniques that will reliably detect the presence of a defect and do not require additional equipment.

Probably (easy)—2 points—developed procedures or approaches for a defect detection without additional research are available (e.g., survey or leave control).

Very easy—1 point—the presence of a defect can be detected visually without any research.

A total of 28 employees from 28 compounding pharmacies, which are directly related to the process of preparation and quality control of CO, participated in the study as specialists.

For the assessment of the severity of each possible quality defect, the PRN value by multiplying the scores of each category ($PRN = S \times O \times D$) was calculated. Its maximum value was 1000 points but a value of 100 points was established by us as a maximum allowable value. It was used to evaluate the criticality of each possible deviation for the CO quality.

To assess the effectiveness of the implementation of QAS requirements in the ointment's preparation process, the average mark of the risks assessment values for each compounding pharmacy that participated in the study was calculated. The average score of defects for each of three categories (severity, occurrence, and detecting of a potential defects) was determined. The average score of three obtained values was found as a result.

5. Conclusions

The conducted research allowed to prove the conformity of the CO quality to the modern requirements and the absence of significant risks for their quality. Due to the significant impact of their microbiological purity parameters on the CO quality, sanitary requirements during the preparation process should be carefully observed (appropriate training of personnel, checking of equipment and facilities for their preparation, and selection of optimal packaging) to minimize their impact. Adherence to these measures will minimize the likelihood of the defects.

There were no trends between the geographical location of the pharmacy and the quantity or severity of the defects of CO quality. The obtained scores of defects in different regions of Ukraine were quite similar and were not characterized by significant differences, due to the similar equipment of pharmacies and the appropriate level of staff qualification.

The research methodology can be used for the quantitative assessment of the risks for the CO quality in different countries. Research results indicated the effectiveness and necessity of the QAS requirements implementation in the compounding pharmacies.

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