Short Communication

Gautier Dozias*, Julie Thiec, Gwenola Le Den and Virginie Cogulet

Risks associated with the evolution in the compounding process of parenteral nutrition solutions: use of the “FMECA” method

<https://doi.org/10.1515/pthp-2020-0017>

Received October 2, 2020; accepted January 25, 2021;

published online February 10, 2021

Abstract

Objectives: An audit of the practices of our compounding unit was performed in 2016: areas of improvement were proposed, such as the automatization of our process. An automated compounder was acquired (MediMixmulti® MF4120R). The aim of the study was to anticipate the risks of the new process, in order to improve its security and to support the professionals during this evolution of our compounding process.

Methods: The Failure Modes, Effects and Criticality Analysis (FMECA) method was carried out in order to detect potential failures brought by the automatization of parenteral nutrition (PN) manufacturing in the new process. The FMECA method included four steps that were divided into five work sessions of one and a half hour each over a period of two months. A working group made up of professionals involved in the PN production process was set up (pharmacists, pharmacy resident, manager and pharmaceutical technician).

Results: Fifty failure modes were determined by this analysis, of which 96% could have an impact on the patient, 90% on the health staff and 74% on the product. The FMECA shows that 18 failure modes have a tolerable or unacceptable CI ($CI \geq 100$) for which it is necessary to implement preventive measures as a priority. This work also made it possible to review the barrier measures already in place for the current process.

Conclusions: The risk analysis allowed us to analyze the failures of both the actual and the future manufacturing processes. Once the most critical failure modes were identified, specific recommendations were proposed and an improvement plan was established. First, the compounder needs to be fully qualified. Then, the quality manual of the PN process will be reviewed and updated. Once these steps are completed, the pharmacy professionals (pharmacists, pharmacy technicians) will be trained and the PN production will be performed using the automated compounder on a daily basis.

Keywords: hazard analysis and critical control points; neonatology; parenteral nutrition; risk management.

Introduction

Over the last 50 years, parenteral nutritional support has allowed a better patient management for infants who could not receive enteral or oral nutrition. The French Authority in Health Management published guidelines in 2018 [1], advising the use of standardized industrial nutrient solutions, which reduce microbiological and physico-chemical risks.

When these solutions cannot match the patient's needs, hospital pharmacies can be required to prepare parenteral nutrition (PN). This is a high risk activity, under pharmaceutical responsibility. The pharmacist in charge of this process must control the asepsis of the production, compatibility between components, stability, the operator's formation and quality of final products.

Our unit produces about 1,500 PN infusions per year, mainly for infants hospitalized in neonatal intensive care unit and neonatal unit.

An audit of the practices of our compounding unit was performed in 2016: areas of improvement were proposed, such as the automatization of our process. An automated compounder was acquired (MediMix^{multi}® MF4120R). Before performing the qualification of this new equipment,

*Corresponding author: Gautier Dozias, Centre Hospitalier Régional et Universitaire de Brest, Brest, Bretagne, France,

E-mail: gautier.dozias@chu-brest.fr

Julie Thiec, Gwenola Le Den and Virginie Cogulet, Centre Hospitalier Régional et Universitaire de Brest, Brest, Bretagne, France

it was decided to analyze the new process and the new risks involved.

The aim of the study was to anticipate the risks of the new process, in order to improve its security and to support the professionals during this evolution of our compounding process.

Methods

The Failure Modes, Effects and Criticality Analysis (FMECA) method was carried out in order to detect potential failures brought by the automatization of PN manufacturing in the new process [2]. The goal of this proactive analysis was to anticipate as many potential adverse events as possible. Risk mapping obtained will allow the implementation of significant preventive measures for the future automated production process and should be completed with the monitoring of their effectiveness [3]. It also allows to describe and discuss the process and the security measures already in place.

FMECA process must answer the following questions: « How could the process not achieve its goals and what effects could result, what are the possible causes of the drift and how do we plan to detect it? » [4].

The FMECA method included four steps: delimitation and segmentation of the analyzed process, identification of potential failure modes, their causes and effects, rating of failure modes according to their criticality and implementation of preventive actions to minimize the risk of process failure. These steps were divided into five work sessions of one and a half hour each over a period of two months. A working group made up of professionals involved in the PN production process was set up (pharmacists, pharmacy resident, manager and pharmaceutical technician).

This method required the use of rating scales for severity, frequency and detectability. The rating scales used in this analysis are based on those used in a FMECA previously performed in the establishment on another production process [5] and a FMECA performed on the same production activity in another hospital center [6]. These rating scales were tested by the working group before starting the analysis.

Frequency, which is the probability of the failure's mode occurrence, was rated from 1 « it is almost impossible for this event to occur » to 10 « this event will occur multiple times with certainty (from every week to every day) ». Severity, which is the impact on the process and/or the patient, was rated from 1 « no impact on the process » to 9 « shutdown of a manufacturing step with no degraded mode, and worsening of a patient's health ». Detectability, which is the probability of non-detection and non-conformity was rated from 1 « detection is certain » to 9 « no detection possible ». The product of these three rating factors determined the criticality of the failure mode, i.e. their criticality index (CI). The value of this index made it possible to prioritize the risk of each sub-step on the basis of an acceptability scale: a CI inferior to 100 was considered acceptable, a CI between 100 and 300 was considered tolerable and a CI over 300 was considered unacceptable.

All of the data was listed in an Excel® spreadsheet.

Results

Delimitation and segmentation of the process to be analyzed

The scope of the analysis was limited from the “pharmaceutical validation of prescriptions” step to the “dispensation” step. Six steps were identified and then divided into 19 sub-steps.

Failure modes analysis: identification of potential failure modes, their causes and effects

Fifty failure modes were determined by this analysis, of which 96% could have an impact on the patient, 90% on the health staff and 74% on the product. We found the highest number (13) of failure modes in “Preparation of controlled atmosphere area” step. Conversely, we found the lowest number of failure in the “Dispense” step.

Rating of failure modes according to their criticality

The overall CI of our process was 5,723. The value of the CI varied from 4 to 630. Six failure modes had an unacceptable criticality, 12 had a tolerable criticality and 32 an acceptable criticality. All the failure modes and their respective criticality are shown in Figure 1. The « Preparation of controlled atmosphere area » step had the greatest number of failure modes. The « Preparation of raw materials and entry into controlled atmosphere area » step had the highest overall CI (2,499).

The most critical failure modes detected involved breaching of the asepsis rules of the process. This was due to the impossibility of detecting human failures and the choice of the team to indicate high ratings for this type of failure.

Establishment of preventive actions to minimize the risk of process failure

The FMECA showed that 18 failure modes had a tolerable or unacceptable CI ($CI \geq 100$) (Figure 2) for which it was

Figure 1: Failure modes by step and their criticalities.

necessary to implement preventive measures as a priority. During a last work session, proposals were combined to respond to the risks generated by these failure modes. The proposed measures were validated by the working group according to their feasibility and the resources necessary and available for their applications (Table 1). This work also made it possible to review the barrier measures already in place for the current process.

Discussion

The evolution of a pharmacotechnical activity process generates risks that must be anticipated. The pharmaceutical team who wishes to modify its production process must have a strict project approach, multidisciplinary and based on a rigorous methodology. These rules ensure control of the different phases of the implementation of this change.

Figure 2: Failure modes for which the criticality index is greater than 100.

Table 1: The measures proposed for the most critical failure modes defined in FMECA.

Steps	Failure modes	Measures proposed
Pharmaceutical validation	Poor or lack of information from the service on the new prescriptions	Increased information flow (Designated nurse)
Preparation of raw materials and entry into controlled atmosphere area	Prescription non-compliant because incomplete or refused by the pharmacist	Checklist Computerisation and protocolization of prescriptions
	Poor decontamination of vials	Audit practices Add a timer
	Labeling error of the repackaged product	Write operating method
	Error about the nature of the repackaged product or their stability	
	Defect in the report of pressure, temperature and bio-cleaning	Checklist: entry into controlled atmosphere area + the action to be taken if there are malfunctions
	Non-compliant dressing/poor handwashing	Add a timer for handwashing Job training (video support) Audit practices
Preparation of controlled atmosphere area	Poor decontamination of the hood	Write operating method Job training Audit practices Microbiological monitoring Media fill test
	Failing or not turned on hood	Job training Write degraded operating method
	Poor organization of the working field	Procedural document Job training
	Handling does not respect the rules of asepsis during assembly	Procedural document Job training (video support) Media fill test
	Automated compounder assembly error/product reversal	Automated compounder/prescription interface Dosage control Impression of an end of production report The scan of the product barcode Performance qualification
	Incorrect transcription of the volumes to be withdrawn	Double checking Checking the final volume of the bag
	Poor circuit purge	Double checking Procedural document Job training Performance qualification
	Circuit contamination/non-compliance with aseptic rules when handling	Procedural document Job training (video support) Media fill test
	Balance failure or bad calibration	Maintenance and daily balance calibration
	Contamination of the sampling.	Procedural document Job training
Dispense	Storage of an invalidated bag	Definition of a specific place in the cold storage Procedural document

In order to identify the critical risks of our future PN bag manufacturing process and to establish an action plan to implement it, we chose the FMECA method over other risk-analysis methods such as Preliminary Risk Analysis (PRA) which is a more general tool that concerns a global process [7]. The FMECA method is commonly used to evaluate the risks in pharmaceutical production [5, 6, 8–14]. Our pharmaceutical production team had

previously used a FMECA process to analyze the activity of preparation for advanced therapy drugs [5]. The experience acquired by part of the working group during this FMECA allowed, prior to the meetings, a good organization.

The overall CI of our process was 5,723: other studies found different results, from 2,280 [12] and 2,381 [11] to 3,415 [10] and 4,744 [6], it is difficult to analyze and compare this data. On the other hand, we can compare the number of failure

modes: 50 failure modes were identified in our process, which is coherent with results found in the literature [6, 8].

The strength of the FMECA method is the pooling of ideas and knowledge of all members of the working group [8, 11]. In addition, this way of working allowed each member of the pharmaceutical team to become aware of the overall functioning of the activity. These multi-disciplinary meetings made it possible to exhaustively identify the failure modes of our process. The rating of these failure modes is another advantage because it allowed us to prioritize them and thus to prioritize the barrier measures to be implemented. The results obtained during this first FMECA can also be used as a basis for comparison in a future FMECA evaluating the impact of our corrective and preventive measures. The analysis of our process made it possible to secure the automatization of the manufacture of PN bags and also to develop a quality culture within the pharmaceutical team. The main limitation of this exercise remains the subjectivity of the failure mode rating, which is also described in other studies [6, 8, 11]. Indeed, the feeling of the different members of the working group concerning the failure modes can vary according to experience, habits and the function occupied. Despite the use of the working tools (rating scales), a consensus on the evaluation of each failure mode can be long to find, making this approach time-consuming [6, 11]. Although the analysis was limited to the pharmaceutical part of the process, the number of sessions required for the FMECA to be successful remained significant. In addition, bringing together all the members of the working group remained an organizational challenge [8].

Conclusion

The risk analysis allowed us to analyze the failures of both the actual and the future manufacturing processes. Once the most critical failure modes were identified, specific recommendations were proposed and an improvement plan was established. First, the compounder needs to be fully qualified. Then, the quality manual of the PN process will be reviewed and updated. Once these steps are completed, the pharmacy professionals (pharmacists, pharmacy technicians) will be trained and the PN production will be performed using the automated compounder on a daily basis.

Other recommendations are more complicated to implement such as the prescription's transmission to the pharmacy or softwares interfacing

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: None declared.

Informed consent: Not applicable.

Ethical approval: Not applicable.

References

1. Haute Autorité de Santé. Recommandation de bonne pratique: Nutrition parentérale en néonatalogie. [Internet]. HAS. Disponible sur: https://www.has-sante.fr/upload/docs/application/pdf/2018-06/argu_np_neonat_2018-06-28_11-18-23_280.pdf [Cité 20 janvier 2021].
2. Haute Autorité de Santé. Méthodes et Outils des démarches qualité pour les établissements de santé. [Internet]. HAS. Disponible sur: https://www.has-sante.fr/jcms/c_272145/fr/methodes-et-outils-des-demarches-qualite-pour-les-etablissements-de-sante [Cité 20 janvier 2021].
3. Haute Autorité de Santé. Analyse des modes de défaillances et de leurs effets (AMDE) – fiche 26 [Internet]. HAS. Disponible sur: <https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-04/fiche26.pdf> [Cité 20 janvier 2021].
4. Landy G. AMDEC: Guide pratique. La plaine Saint-Denis: Afnor éditions; 2011.
5. Hugerot H. Définition et mise en œuvre des prérequis à l'ouverture d'une unité de préparation de médicaments de thérapie génique au CHRU de Brest [Ph.D. thesis]. Nantes: Nantes University; 2018.
6. Ducret E. Management du risque à l'hôpital: Méthode AMDEC et actions de sécurisation appliquées à l'activité de nutrition parentérale pédiatrique au CHU de Nantes [Ph.D. thesis]. Angers: Angers University; 2016.
7. Le Pêcheur V, Spiesser-Robelet L, Vrigaud S. Using preliminary risk analysis (PRA) to ensure safety in the preparation process for parenteral nutrition bags in hospital pharmacy. *Pharmaceut Technol Hosp Pharm* 2016;1:63–72.
8. Royer M, Libessart M, Dubaele J-M, Tourneux P, Marçon F. Controlling risks in the compounding process of individually formulated parenteral nutrition: use of the FMECA method (failure modes, effects, and criticality analysis). *Pharmaceut Technol Hosp Pharm* 2019;4:105–12.
9. Boulé M, Lachapelle S, Collin-Lévesque L, Demers E, Nguyen C, Fournier-Tondreau M, et al. Failure mode, effect, and criticality analysis of the parenteral nutrition process in a mother-child hospital: the AMELIORE study. *Nutr Clin Pract* 2018;33:656–66.
10. Bonnabry P, Cingria L, Sadeghipour F, Ing H, Fonzo-Christe C, Pfister R-E. Use of a systematic risk analysis method to improve safety in the production of paediatric parenteral nutrition solutions. *Qual Saf Health Care* 2005;14:93–8.
11. Grattelle A. Evaluation des Pratiques Professionnelles liées au processus de production des nutriments parentéraux pédiatriques au Centre Hospitalier Universitaire de Bordeaux : application de la méthode Analyse des Modes de Défaillance, de leurs Effets et de leur Criticité (AMDEC) [Ph.D. thesis]. Limoges: Limoges University; 2016.

12. Mourkogianni E, Karatza A, Vinni E, Papadimitriou E, Avgoustakis K, Panagi Z. Assessment and optimization of the pediatric parenteral nutrition preparation process in a hospital pharmacy. *J Parenter Enteral Nutr* 2020;44:928–39.
13. Bourika K, Koutras A, Kalofonos H, Vicha A, Tsiata E, Papadimitriou E, et al. Improvement of chemotherapy solutions production procedure in a hospital central chemotherapy preparation unit: a systematic risk assessment to prevent avoidable harm in cancer patients. *Clinical medicine insights. Oncology* 2019;13:1179554919852933.
14. Reece KM, Lozano MA, Roux R, Spivey SM. Implementation and evaluation of a gravimetric i.v. workflow software system in an oncology ambulatory care pharmacy. *Am J Health Syst Pharm* 2016;73:165–73.