

Article

Risk Management in Good Manufacturing Practice (GMP) Radiopharmaceutical Preparations

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Abstract: Risk assessment and management during the entire production process of a radiopharmaceutical are pivotal factors in ensuring drug safety and quality. A methodology of quality risk assessment has been performed by integrating the advice reported in Eudralex, ICHQ, and ISO 9001, and its validity has been evaluated by applying it to real data collected in 21 months of activities of ^{18}F -FDG production at Officina Farmaceutica, CNR-Pisa (Italy) to confirm whether the critical aspects that previously have been identified in the quality risk assessment were effective. The analysis of the results of the real data matched the hypotheses obtained from the model, and in particular, the most critical aspects were those related to human resources and staff organization with regard to management risk. Regarding the production process, the model of operational risk had predicted, as later confirmed by real data, that the most critical phase could be the synthesis and dispensing of the radiopharmaceuticals. So, the proposed method could be used by other similar radiopharmaceutical production sites to identify the critical phases of the production process and to act to improve performance and prevent failure in the entire cycle of radiopharmaceutical products.

Keywords: quality risk management; ^{18}F -FDG PET production; good manufacturing practice



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1. Introduction

Positron Emission Tomography (PET) is a nuclear medicine technique used mostly for the diagnosis, staging, and follow-up of cancers [1]. ^{18}F -FDG is the most widely used radiopharmaceutical in PET clinical investigations; it is used in over 95% of the PET examinations performed [2].

Over the years, alternative radiopharmaceuticals to ^{18}F -FDG have been studied, but research in this environment is complex due to the high costs for development (from 20 to 60 million dollars in 2013), the long period for development (minimum 7–9 years) [3], and high risk (one new radiopharmaceutical for clinical use out of ten thousand molecules tested at the beginning) [4].

^{18}F -FDG will still be the most used radiopharmaceutical in nuclear medicine for years to come, although there are malignant diseases with poor uptake of F-FDG and other benign diseases that could cause false positives [5].

The radiopharmaceutical industrial production requires compliance with Good Manufacturing Practice (GMP): the guidelines for GMP implementation are enclosed in Volume 4 of the Eudralex “The rules governing medicinal products in the European Union” [6].

The GMP rules should be applied to all phases of a drug’s life cycle, starting from clinical trials through technology transfer and production until the final product’s retirement [6].

The Eudralex also suggests the use of other guidelines, among which ICHQ 10 guidelines (ICHQ: International Conference on Harmonisation of Technical Requirements for

Registration of Pharmaceuticals for Human Use) were finalized at setup for the pharmaceutical quality system (PQS) to be applied throughout the product life cycle.

ICHQ10 guidelines recommend the integration of the GMP regulations with the ISO 9001:2015 quality concepts related to the whole process [7], with the aim of harmonizing the entire production cycle of the drug.

A key aspect of the PQS is represented by Quality Risk Management (QRM), as described in another ICHQ guideline (ICHQ 9) [8].

In fact, to date, QRM has assumed a pivotal role in the (radio)pharmaceutical industries for the assessment, control, and communication of the risks associated with product safety and quality.

The literature reports several cases of QRM applied to radiopharmaceutical production, which are mostly applied to segments of the production process but not to the whole process [9–11] or are intended to prevent injury to the operators or patients [12] but without quantification of the risk throughout the product life cycle.

The analyzed literature also shows that the integrated application of some quality standards, such as GMP, ISO 9001, ICHQ, and EFQM (European Foundation for Quality Management), could contribute to obtaining the quality of a radiopharmaceutical [13] through quality risk assessment and guaranteeing performance and efficacy in the entire process.

Therefore, the application of different quality standards, such as GMP, ISO 9001, and ICHQ, guarantees the quality and safety of a radiopharmaceutical [13] and contributes to optimizing the performance and efficacy of the entire production process.

This paper describes the conceptualization and the setting up of a quality risk assessment methodology to be applied to the production of sterile PET radiopharmaceuticals under the GMP regulations.

This methodology has been developed in our public research institution, taking into consideration all phases of the product life cycle, starting from development, passing through technology transfer, and finally, commercial delivery.

This methodology of quality risk management has been performed by integrating the recommendations reported in Eudralex, ICHQ, and ISO 9001, and its validity has been evaluated by applying it to real data collected in 21 months of activities of 18F-FDG production at Officina Farmaceutica, CNR-Pisa (Italy), to confirm whether the critical aspects, which have previously been identified in the quality risk assessment, were effective.

2. Materials and Methods

The quality risk assessment has been carried out, highlighting criticalities at both management and operational levels. The flowchart in Figure 1 shows the rationale applied to develop the methodology.



Figure 1. Flowchart of quality risk assessment methodology to be applied to production of sterile PET radiopharmaceuticals under GMP regulations.

Our institution is authorized to manufacture radiopharmaceuticals for diagnostic use (^{18}F fluoro-2-deoxy-D-glucose and ^{18}F -Fluoromethylcholine) with marketing authorization, and it is also authorized to produce fluorinated radiopharmaceuticals intended for clinical trials.

Synthesis and dispensing of ^{18}F -FDG are carried out in a classified room in accordance with annex 1 of the EU; the raw materials and the finished product enter and leave the clean room bypass through ventilated boxes.

Inside the clean room, there are five shielded cells and a Class A class isolator equipped with a Class B transfer chamber. The shielded cells contain three automatic synthesis modules. Briefly, the production of ^{18}F -FDG is carried out with the fully automated IBA Synthera[®] multipurpose synthesizer, and the radiopharmaceutical is then dispensed into the single vials through the semi-automatic fractionation system, which is equipped with a dose calibrator. The product is dispensed in a grade-A environment and filtered through a 0.22-micron Millipore filter. After dispensing, the filter integrity is verified using the Bubble Point test system. The quality control of the finished product is made in an unclassified environment equipped with the instrumentation for chemical-physical and microbiological (content of bacterial endotoxins) tests.

2.1. Organizational and Management Risk Assessment

For the assessment of organizational and management risks, a matrix has been developed to identify the factors that influence the production of radiopharmaceuticals. These factors have been identified considering the indications contained in the ISO 9001: 2015 standard, which is considered a golden standard for the management of an organization. For each requirement of the ISO 9001 standard, we asked ourselves a number of questions, and based on the answers, we identified the relative risks. The aspects taken into consideration were the context of Organization, Leadership, Planning, Support, Operating Activities, Performance evaluation, and Improvement.

Table 1 reports management risks individuated based on the ISO 9001:2015 standard.

Table 1. Risks identification of the management process.

Requirement 9001:2015	What Did We Ask Ourselves	Main Risks Identified
Context of the Organization		
Understand the organization and its context	What are the factors of the context that influence the ability to achieve the expected results?	Risks related to the external context: legal, technological, competitive, market, social, cultural, national, and international. Risks related to the internal context: values, organizational capacity, and culture.
Understand the needs and expectations of stakeholders	Who are the stakeholders, and what are their needs?	Risks associated with failing to meet the needs of patients and the MA holder
Quality management system and related processes	Is there a QMS that meets the requirements of the standard?	Quality management system that is effectively an aid to the production process
Leadership		
Leadership	Does leadership show commitment to quality improvement by taking responsibility? Have goals and policies been defined?	Uncommitted leadership poses a great risk for a manufacturing site like ours, as the business is frowned upon by the scientific community.
Roles, responsibilities, and authorities	Has management assigned responsibilities? Are there personal assignments with duties and references to the QMS?	Responsibilities must be clearly defined to avoid gray areas.

Table 1. Cont.

Requirement 9001:2015	What Did We Ask Ourselves	Main Risks Identified
Planning		
Actions to address risks and opportunities	We have determined what the risks and opportunities are Have actions been planned to achieve the objectives?	Without the planning of actions to achieve the objectives, there is a risk of uncoordinated actions.
Support		
People	Have we determined and made the necessary people available? Have we determined the skills needed? Have we promoted staff awareness of the objectives to be achieved?	People are the wealth of the organization, and the risk is high if there are few people who are not adequately trained and not aware of the role they play in achieving the objectives.
Infrastructure	Is the infrastructure properly maintained? Have the critical parts been identified and periodically checked?	The risk is linked to inefficient infrastructure and is kept under control through the use of preventive maintenance and periodic calibration with primary standards.
Documented information	Do we have procedures and records?	The risk is mainly linked to redundant document systems that generate bureaucracy.
Operating activities (Treated separately with the FMAE method)		
Operational planning and control	We planned, implemented, and monitored the processes	(see FMEA Analysis)
Requirements for products and services	Have we determined and reviewed the requirements of the products?	The risk related to requirements not specifically defined
Design and development of products and services	During the design and development planning, have I taken into account all those factors that can guarantee the success or failure of the project?	The risk in the design phase is that of not properly evaluating the resources available to complete the project. Among the factors to be taken into consideration are the complexity of the activities and the available resources
External suppliers	Do the externally supplied processes comply with the specified requirements? How do we evaluate external suppliers?	The risk is linked to the possibility of entrusting parts of the process to unreliable suppliers.
Properties that belong to customers or external suppliers	Are we able to look after the property of customers or external suppliers?	The risk is linked to the possibility that the MA holder's information may be lost or disclosed.
Change control	In the event that a change is necessary, can we demonstrate that we have reviewed and controlled the process changes do not affect the quality of the product or process?	The risk is that changes may be made that affect the quality of the product.
Product release	Are there documents reporting the compliance of the products with the acceptance criteria? Are there documents proving traceability to the person(s) authorized to issue products and services?	The risk is the uncontrolled release of the product.
Control of non-compliant outputs	If there are outputs that do not comply with the requirements, are we able to identify them and keep them under control to prevent their inadvertent use or delivery?	The risk is the release of non-compliant products.

Table 1. Cont.

Requirement 9001:2015	What Did We Ask Ourselves	Main Risks Identified
Performance evaluation		
Management review	Have we determined what and when needs to be monitored and measured?	The risk is linked to non-adherence to strategic objectives.
	Is the system reviewed to ensure alignment with strategic guidelines?	
Improvement		
Non-compliance and corrective and improvement actions	Do I keep track of non-conformances and take actions to keep them under control and correct them, or avoid their re-occurrence?	The risk is linked to the fact that I do not solve the problems.

Each identified risk was analyzed and defined as irrelevant, tolerable, moderate, effective, or intolerable by examining the impact of the risk on the production process and the probability of occurrence. Table 2 shows the risk quantification matrix.

Table 2. Matrix for risk quantification, risk index.

Impact/Probability	Not Very Likely	Likely	Very Likely
Low	Irrelevant	Tolerable	Moderate
Medium	Tolerable	Moderate	Effective
High	Moderate	Effective	Intolerable

Based on the obtained score, corrective and preventive actions have been identified to mitigate the risk. The actions were identified according to the criterion shown in Table 3.

Table 3. Corrective and preventive actions based on risk index.

Risk Type	Action Required
Irrelevant	No Action required
Tolerable	No further control actions are required. If necessary, improvement actions can be identified.
Moderate	Risk mitigation actions are required.
Effective	Resources must be assigned in order to reduce the risk.
Intolerable	Activities should not be carried out until the risk is reduced. If it is not possible to reduce the risk even with the use of adequate resources, the activities cannot continue.

2.2. Operational Risks

To assess the operational risk, a similar approach has been used, but rather than ISO9001, the Failure Mode and Effect Analysis (FMEA) methodology was used according to ICH Q9 because FMEA is able to identify and help us understand the risk sources, their causes, and their effects on the system by assigning priorities and implementing corrective actions to address the most serious risks.

At the beginning, the production process was divided into the main activities and then each identified activity was analyzed for the identification of the risks. Figure 2 shows the main process subdivided into the principal activities.

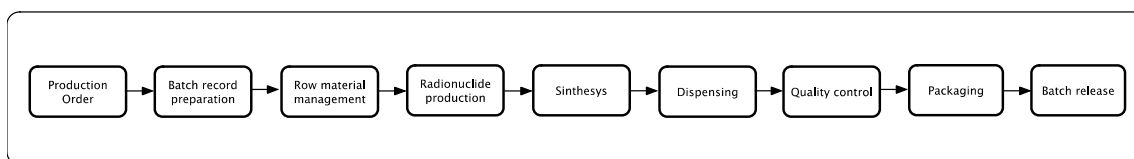


Figure 2. Principal activities of the main process.

For each step of the process, the most critical operations were identified, and the risks were quantified by evaluating the severity, detectability, and probability of occurrence according to the criteria reported in the following tables, attributing 3 points to a severe risk, 2 points to a medium risk and 1 point to a not-relevant risk (see Tables 4–6).

Table 4. Severity.

Score	Severity	Product	Economic Sustainability	Safety
3	Severe	GMP critical deviation	High economic damage (>10 k€)	Serious radiological accident (contamination beyond permitted limits or external impact on the production site);
		Product defect with potentially serious health impact or lethal risk	Severe image loss (public corrective actions); Loss of the customer	Harm to operators (risk of death, permanent impairment, or long duration ≥ 3 months)
2	Medium	Major GMP deviation	Substantial economic damage (€ 1000–9999);	Modest radiological incident (contamination within limits, event contained within the site)
		Product defect with potential protracted harm to the patient's health (e.g., risk of hospitalization or resolvable impairment with short-term disability)	Moderate damage to image (action limited to individual customers)	Medium-sized injury (disability/disability ≥ 7 days but <3 months)
		Process defect with impact on the pharmaceutical quality of the finished product	Repetition of a run	
1	Not relevant	Minor GMP deviation	Minor economic damage (<1000 €); higher consumption of reagents or raw materials in one run)	Minor radiological accident (contamination that can be removed by decontamination or removal of PPE)
		Non-compliance with GMP without risk to the patient's health	Deviations and non-conformities that do not lead to cost increases	Minor injury manageable with the help of the ward first aid kit)
		Deviations without impact on product safety	No economic damage	NEAR-MISS and deviations or non-compliance with GMPs that do not impact the health of operators and safety in the workplace.

Table 5. Probability of occurrence.

Score	Probability Scale	
	General	Almost inevitable or inevitable
1	Systems and technical-instrumental management aspects	Aspects possibility of frequent repetition (once a week)
	Batch production	Frequency of occurrence: risk event at least once every 10 batches produced

Table 5. Cont.

Score		Probability Scale	
2	Possible	General	Reducible or deferrable
		Systems and technical-instrumental management aspects	Moderate repetition (once a month)
		Batch production	Frequency of occurrence: the risk event at least once every 10–30 batches produced
3	Rare	General	Almost completely avoidable
		Systems and technical-instrumental management aspects	Low repeatability (less than once a month)
		Batch production	Frequency of occurrence: risk event once over 30 batches produced

Table 6. Detectability.

Score		Detectability Scale	
3	Hardly detectable	General	Post-facto evidence
		Systems and technical-instrumental management aspects	Possibility of maintenance over time without identification
		Batch production	Evidence downstream of use
2	Detectable	General	Detection before the end of the expected function
		Systems and technical-instrumental management aspects	Detection before the start of a production process
		Batch production	Detection before use of the product
1	Immediately detectable	General	Certain detections before starting the performance of the expected function
		Systems and technical-instrumental management aspects	Detection even in the absence of a process to start
		Batch production	Detection during the process

By multiplying the severity of the damage (S) with the probability of occurrence (O) and the detection index (D), the risk index was obtained according to the formula $RI = S \times O \times D$.

Based on the risk index (RI) calculated, 3 different risk categories are individuated:

Risks with indexes 27, 18, and 12. They are high risk (NOT acceptable) and require immediate mitigation action.

Risk with index 9 or 6 medium risk: requires corrective actions to be implemented as soon as possible (days).

Risk with index from 4 to 1: low risk; they may require improvement actions to be implemented in the medium–long term (annual planning).

3. Results

Tables 7 and 8 show the results of risk assessment defined as the “Risk Index” performed based on theoretical analysis of the entire production cycle divided into management (Table 7) and operational process risks (Table 8).

Table 7. Risk assessment of the management's risks.

9001:2015 Requirement	Key factor	Risk Identification	Impact	Probability	Risk Index
Contest	Safety and radiation protection regulatory	Radiation protection, chemical risk, load handling	High	Rare	Moderate
	Organizational Skills, culture	Industrial activity carried out in a public organization	High	Possible	Effective
Leadership	Commitment	Uncommitted leadership represents a great risk in a production site like ours as the activity is frowned upon by scientific community	High	Rare	Moderate
	Policy and Strategy	Decisions not based on facts, uncoordinated decisions	Medium	Possible	Moderate
	Objectives definition	Failure to achieve objectives	Medium	Rare	Tolerable
Planning	Actions to address risks and opportunities	Failure to achieve objectives, uncoordinated decisions	High	Rare	Moderate
Support	Human Resources/ Staff Skills	Not enough staff Not competent staff Not motivated staff	High	Possible	Effective
	Management of Infrastructures	Incorrect management of infrastructures	Medium	Possible	Tolerable
	Documented Information	Loss of traceability	Medium	Rare	Tolerable
Operational activities	Planning and development	Bad evaluation of the complexity of the activities and of the available resources	High	Rare	Moderate
	Management of suppliers	Not compliant supplies	Medium	Possible	Moderate
Performance evaluation	Management review	Uncoordinated decision not based on facts	Medium	Rare	Tolerable
Continuous improvement	Not-compliance/ corrective and improvement actions	Not resolution of issues	Medium	Rare	Tolerable

Table 8. Risk assessment of the operational process. The green scale represents the severity of risk.

Failure Mode and Effect Analysis (FMEA)					
Main Process	Activity	Ipoteticals Risks	Effects	Type of Damage	SxOxD
Production order	Preparation of the production plan (PP)	PP not present Delayed PP Wrong PP Insufficient radioactivity	Customer dissatisfaction, loss of production	Sustainability	2
Batch record	BR Preparation	Incomplete or wrong registration forms	Operator error Loss of traceability	Sustainability	1

Table 8. Cont.

Failure Mode and Effect Analysis (FMEA)					
Main Process	Activity	Ipoteticals Risks	Effects	Type of Damage	SxOxD
Raw material management	Entry into the warehouse	Difference between ordered material and arrived material	Insufficient material and loss of production	Sustainability	4
		Missed or incorrect registration including labeling	Loss of traceability	Product safety	1
			Exchange of material, approval of non-conforming material		2
		Sampling	Lack of Retention Sample Loss of traceability	Product safety	1
	Storage	Expired material	Loss of production Non-conformities of the finished product	Product safety	2
		Insufficient inventory		Sustainability	2
		Incorrect storage conditions		Product safety	2
	Exit from the warehouse	Exchange of material	Loss of production Non-compliant finished product	Product safety	2
Radionuclide production	target irradiation	Boot failure	Delayed product shipment or lack of synthesis	Sustainability	2
		Human error in target selection			
		Failed to load the target	Delayed product shipment or lack of synthesis	Sustainability	4
		Failure irradiation	Delayed product shipment or lack of synthesis	Sustainability	4
	Delivery of radionuclides	Failure to transfer	Lack of synthesis	Sustainability	6
		Incomplete transfer	Loss of production, reduction in the transferred activity	Sustainability	6
		Transfer to the wrong cell/module	Delayed product shipment or lack of synthesis	Sustainability	2
Product preparation	Clean room management	Parameters out of specification	Production delay or loss of production	Sustainability	1
			OOS final product	Product safety	1
	Shielded cell management	Inefficient cell	Production delay or loss of production	Sustainability	1
		Loss of radioactivity	Operator contamination	Operator safety	1
	Isolator management	Fault DTC-SAS-LAF	Production delay or loss of production	Sustainability	6
			OOS final product	Product safety	6
Radiopharmaceutical synthesis	Synthesis	Pretest times too long	Production delay	Sustainability	4
		Preliminary tests not passed	Loss of production	Sustainability	4
		Low yield	Customer dissatisfaction	Sustainability	6
		Synthesis failure	Loss of production	Sustainability	6

Table 8. Cont.

Failure Mode and Effect Analysis (FMEA)					
Main Process	Activity	Ipoteticals Risks	Effects	Type of Damage	SxOxD
Dispensing	SAS-LAF material entrance	Blocking moving parts or operating software	Production delay or loss of production	Sustainability	1
		Sanitization of raw materials	DTC bacterial contamination	Product safety	1
	DTC material entrance	Sanitization of raw materials	bacterial contamination of the finished product	Product safety	1
	CRP6 Set-up	Error in assembling the kit	Production delay or loss of production	Sustainability	6
		CRP6 software communication problems	Production delay or loss of production	Sustainability	6
		Incorrect labeling of the vial	OOS final product	Product safety	6
		Vial packaging	Production delay/customer dissatisfaction	Sustainability	6
	Bulk product transfer to DTC	Incomplete transfer to the DTC	Customer dissatisfaction	Sustainability	6
		Failure to transfer to the DTC	Loss of production	Sustainability	6
	DTC-SASLAF operation	Delay in dispensing	Customer dissatisfaction	Sustainability	2
		Inability to continue with dispensing	Loss of production	Sustainability	4
		Loss of the product into the DTC	Personal and environmental contamination	Operator safety	6
		Mixup of the vial and shielded container	Customer dissatisfaction, complaint	Product safety	3
	Delivery	Breakage of the vial in the delivery output	Personal and environmental contamination	Operator safety	6
			Customer dissatisfaction	Sustainability	6
		Vial blocked in the delivery output	Production delay or loss of production	Sustainability	6
			Break of the vial	Sustainability	4
		Fall of the container	Personal and environmental contamination	Operator safety	4
	Bubble point test	Test failed	Loss of production	Sustainability	3
CQ	PH measurement	Value out of range in calibration	Production delay or loss of production	Sustainability	1
		Failure of the instrument	Production delay	Sustainability	1
		Value out of range in sample measurement	OOS final product	Product safety	2
	Half-life analysis (dose calibrator)	Device faulty or not calibrated	Production delay or loss of production	Sustainability	1
		Value out of range in sample measurement	OOS final product	Product safety	2

Table 8. Cont.

Failure Mode and Effect Analysis (FMEA)					
Main Process	Activity	Ipoteticals Risks	Effects	Type of Damage	SxOxD
CQ	Analysis LAL test	Device faulty or not calibrated	Production delay or loss of production	Sustainability	1
		Value out of range in sample measurement	OOS final product	Product safety	4
	GC residual solvent analysis	Error in the standards preparation	Production delay	Sustainability	2
		Device faulty or not calibrated	Production delay or loss of production	Sustainability	1
	Chemical and radiochemical purity analysis by HPLC	Value out of range in sample measurement	OOS final product	product safety	4
		Error in the standards preparation	Production delay	Sustainability	4
		Device faulty or not calibrated	Production delay or loss of production	Sustainability	2
	Chemical and radiochemical purity: TLC analysis	Value out of range in sample measurement	OOS final product	Product safety	4
		Error in the standards preparation	Production delay	Sustainability	1
		Device faulty or not calibrated	Production delay or loss of production	Sustainability	2
	Radionuclide purity: gamma spectrometry analysis	Value out of range in sample measurement	OOS final product	Product safety	2
		Device faulty or not calibrated	Production delay or loss of production	Sustainability	4
	Chemical purity: determination of kriptofix	Value out of range in sample measurement	OOS final product	Product safety	3
		Loss of samples, shipment not carried out	GMP deviation	Product safety	2
	Sterility control	Value out of range in sample measurement	GMP deviation	Product safety	3
		Value out of range in sample measurement	GMP deviation	Product safety	1
	Microbiological control	Value out of range	OOS final product	Product safety	2
		Device faulty or not calibrated (oven and SAS)	GMP deviation	Product safety	1
Packaging of the final product	Preparation for shipment	Suitcases not available	Inability to ship	Sustainability	8
		Shipping documents not available	Shipping delay	Sustainability	1
		Mixup of the shielded container and Suitcases	Customer dissatisfaction	Product safety	2
	Delivery to the carrier	Courier not available	Inability to ship	Sustainability	2
Batch Release	BR verification	Human error in data verification	release of non-compliant product	Product safety	3

The most critical activities (productivity, reliability, non-conformities) were analyzed as suggested in Chapter 1 of the EUGMP guidelines Volume 4 for a period of 21 months of activity of the production site after restart.

The results of these analyses are summarized in the following figures.

The first analysis concerns the productivity of the site evaluated through the number of productions/months. Figure 3 shows that over those 21 months, the productivity went from 2 productions per month to 27 productions per month.

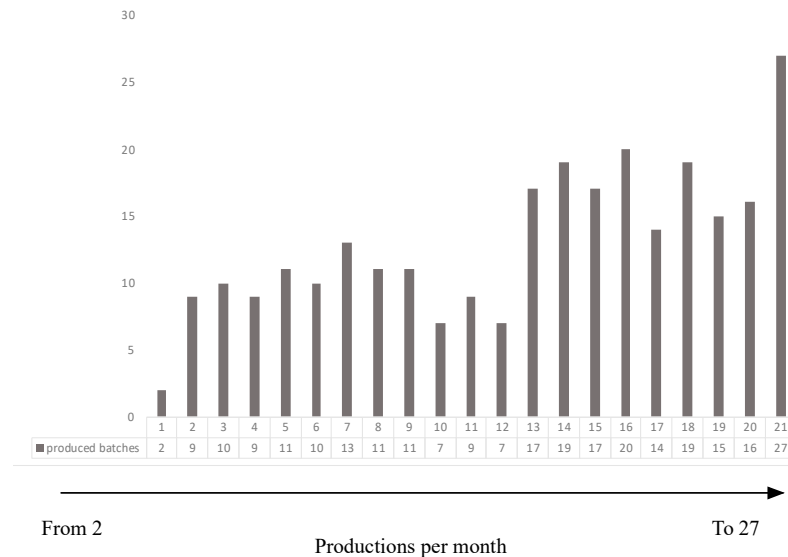


Figure 3. Increase in productivity.

Regarding reliability evaluation, the collected data were grouped into 17 slots of 20 productions, and for each slot, the reliability percentage value was calculated using the following formula: $\text{Reliability} = \frac{\text{scheduled lots}}{\text{released lots}} \times 100$.

The average reliability is 84%, and the trend is positive, as shown in Figure 4.

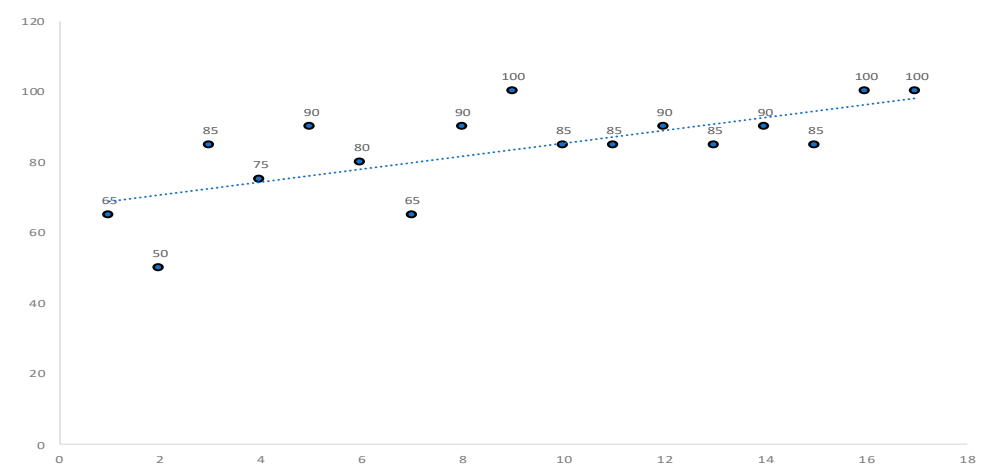


Figure 4. Increase in reliability over time (each circle represents the % scheduled lots/released lots).

All non-conformities ($n = 143$) were recorded in the 21-month period and were analyzed in accordance with the internal procedures that contemplate a classification related to the items reported below:

- Production process deviations;
- Quality control deviations;
- Raw material deviations;

- General site deviations;
- Documentation deviations.

Figure 5 shows how non-conformities are distributed within these five areas.

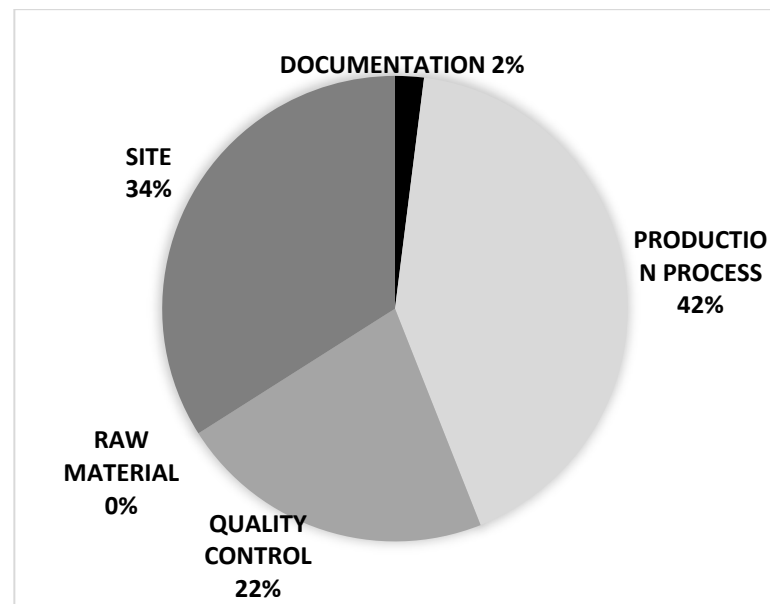


Figure 5. Non-conformities distributed within these 5 areas.

To verify if the risk assessment process had correctly identified the most critical segments of the process, we further subdivided the registered non-conformities along the entire production process as scheduled in Figure 6 (main steps process), as shown in Figure 6.

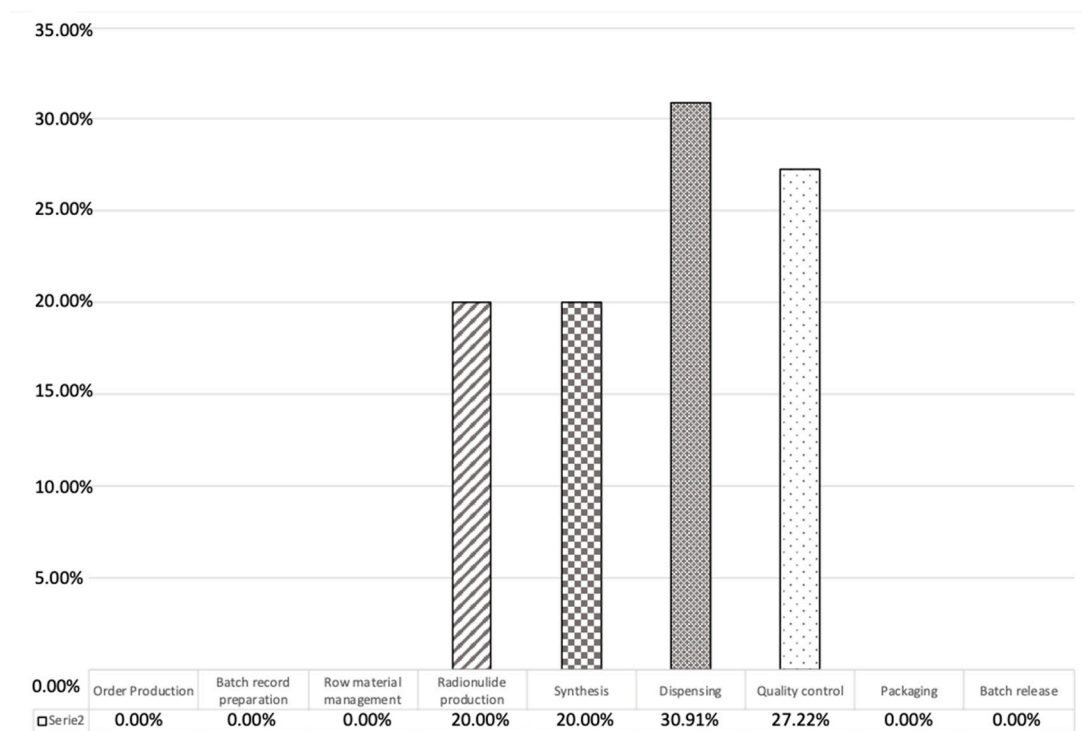


Figure 6. Percentage distribution of registered non-conformities along the entire production process steps.

We have also quantified the impact of the non-conformities on the three types of failures identified during the risk assessment: product quality, personnel safety, and sustainability.

In general, the risk to the quality of the product never occurred because the system was able to detect potential risks to product quality, including with sterility control. To guarantee the sterility of the finished product, specific actions are adopted to ensure that the entire production chain takes place in quality assurance conditions, despite the test result being available to the patient at least 15 days after the injection.

For the operator risk, the data analysis shows that the most critical process is the dispensing in 8.6% of non-conformities; radioactive material has leaked out, especially inside the shielded isolator, due to incorrect assembly of the sterilization filter. This aspect was carefully monitored, and corrective actions were taken, which led to risk mitigation. Another risk for operator safety is the breaking of the vial in the delivery channel (1.2% of non-conformities), but also, in this case, the radioactivity monitoring systems have effectively detected the contamination, and the automatic locking systems for the opening of the cells have prevented the contamination of the operator.

As regards the failure to sustainability, the failure to release the lot generally had an important impact on the site's sustainability.

Figure 7 shows the main causes of the rejection of a lot of radiopharmaceuticals.

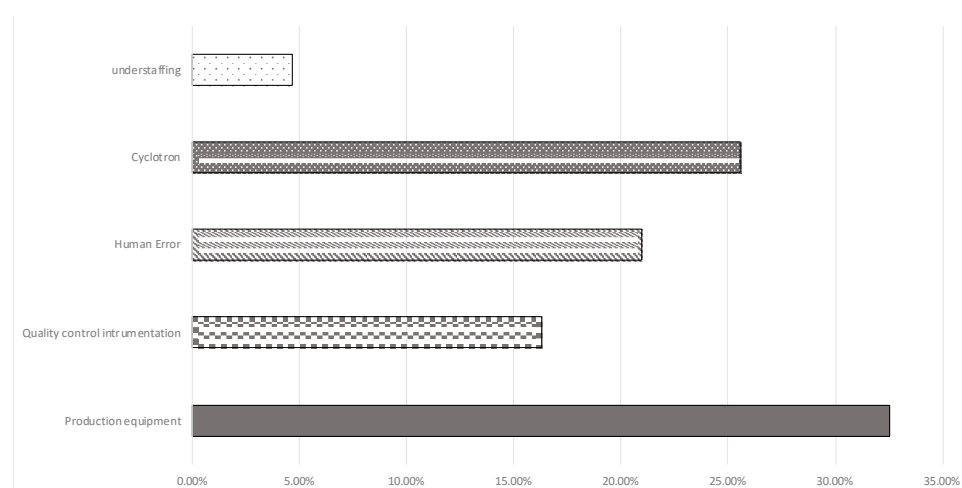


Figure 7. Main causes of lot rejection.

4. Discussion

In general, the radiopharmaceutical manufacturing process starts with the production of the radionuclide and continues with the synthesis of the radiopharmaceutical according to the formulation described in the Marketing Authorization (MA) dossier or Pharmacopoeia Monograph [14].

The production of PET radiopharmaceuticals is extremely complex due to a series of factors [15]: the delivery of the final product that takes place with the sterility control still in progress; the short half-life of the tracer; the very high number of batches produced compared to conventional drugs; the activity carried out mainly during the night; and the handling of radioactive substances. The complexity of this system implies that risk assessment is even more necessary than in other production systems.

Fortunately, the GMP standard helps us keep the critical aspects of the production process under control by indicating the tools to be used “to manage” the risk [16,17].

Our GMP experience has allowed us to develop a risk assessment, which is conducted by separately considering organizational and management risks and operational risks.

This report describes the experience of a public radiopharmaceutical site that has adopted the GMP standards and which, therefore, produces radiopharmaceuticals following the indications of the EU-GMP for industrial production [18]. Since the start of GMP

radiopharmaceutical production, the site has used an approach founded on risk-based thinking and followed regulatory updates over the years.

In 2021, the production site radically changed the production process, moving from production with final sterilization in an autoclave to production using aseptic techniques. Before starting with the new production process, a risk assessment was carried out, which identified the most critical segments of the process. Twenty-one months after the restart of the production, which was intended for distribution on the national territory, the data that emerged were collected and analyzed to verify if the risk assessment process carried out ex ante had been able to identify the main risks.

Compared to the initial risk assessment, the evidence collected during these twenty-one months allows us to state that the method, adopted both for the assessment of management risks and operational risks, is a suitable tool for identifying the critical phases of the process.

At the managerial level, the greatest criticality was mainly linked to personnel management.

The results of the analysis also show that production is the most critical phase of the process (asepsis and radioactivity). In particular, the dispensing phase has proven to be the most critical, implying a delay or even a loss of production along with customer dissatisfaction. In addition, there are problems during the dispensing phase; as an example, the breakage of a product vial could result in personal and environmental contamination and put an operator's safety in danger (Table 2).

In general, the preventive actions to be undertaken to mitigate the risk can be grouped into two main types: the continuous training of staff, with attention to motivation and awareness of the complexity of the system, and the increasingly detailed processes so that the risks can be reduced as much as possible and, therefore, achieve an overall risk reduction.

In conclusion, having a risk management process in place is critical for GMP production facilities, and the identification of risks in the matrix is a useful tool. Our implemented model has identified and quantified the risks, and, given the overlap between the risks identified and the analysis of real data, the proposed method could be used by other similar radiopharmaceutical production sites to identify the critical phases of the production process, improve the performance, and prevent damages to the entire cycle of the radiopharmaceutical product.

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