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# RISK ASSESSMENT IN PET RADIOPHARMACEUTICALS PRODUCTION: PLANNING THE IMPLEMENTATION OF A PRODUCTION LINE COMPLIANT WITH GMP REGULATION

***Abstract:*** *The aim of this paper is to provide some indications for carrying out the risk assessment for the activation of a production line of a radiopharmaceutical containing a positrons emitting radionuclide. The risk analysis was performed by following the ICH Q10 guideline and ISO 9001:2015 standards and by using the risk-based thinking approach applied to the entire production cycle. The overall analysis has shown that hard and soft skills of the expert group are key factors of success both in technical and radiopharmaceuticals-related preparations as well as in risk management methodologies.*

***Keywords:*** *Radiopharmaceuticals, Risk assessment, Risk based thinking, GMP, Risk identification*

## 1. Introduction

Radiopharmaceuticals (RPs) represent a particular class of drugs that includes "any medicinal product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose ((EudraLex Volume 4; European pharmacopoeia 9th ed, 2018). Due to this intrinsic peculiarity, radiopharmaceuticals must be produced in compliance with both the legislation on medicines (Ballinger & Koziorowski, 2017; 2003/94/EC, 2003; 2017/1572, 2017; Decristoforo, 2011; Salvadori, 2008) and on radiation protection (2013/59/Euratom, 2013; de Jong, 2017).

Many types of radiopharmaceuticals are present in clinical field, and their use is linked to the type of radioisotope they include. The carrier molecule is the biological active ingredient while the diagnostic or therapeutic active ingredient is the emitted radiation. RPs containing gamma or positron emitting radionuclides are used in clinical field for diagnostic purpose (nuclear imaging techniques: positron emission tomography, PET; single photon emission tomography, SPECT), while those containing β- or alpha emitting radionuclides are mainly used as therapeutic agents (radio-metabolic/receptor therapy, brachytherapy, etc.). Besides the type of emitted radiation, another important aspect regarding the use of a specific RP is the half-life of the radionuclide that is the time required for the initial activity to be reduced by half. The half-life of these radionuclides can range from few minutes to hours or days. The short half-life is typical of radionuclides for PET

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radiopharmaceuticals; a selection of these, together with the production method, is showed in Table 1.

**Table 1**. Selection of radionuclides used in PET radiopharmaceuticals

| Radionuclide | Half-life | Production method |
|---|---|---|
| F-18 | 109,7 min | Cyclotron |
| C-11 | 20,4 min | Cyclotron |
| N-13 | 10,0 min | Cyclotron |
| O-15 | 2,0 min | Cyclotron |
| Cu-64 | 12,7 h | Cyclotron |
| Ga-68 | 67,6 min | Generator/Cyclotron |

The half-life value affects both the preparation of the RP and its clinical applicability: the shelf life of the radiopharmaceutical is linked to the life of the radioisotope therefore both synthesis method and clinical protocols must be optimized taking into account this parameter. A PET RP containing a radioisotope with a short half-life (e.g. carbon-11), although offers the advantage to perform repeated studies on the same patient, has the disadvantage of preparation only in those facilities equipped with a cyclotron (most of PET radionuclides in fact are produced from cyclotron; Table 1) and a laboratory onsite. The synthesis procedure of a RP must be quite easy and fast, compatibly with the half-life of the radionuclide. In addition, PET radiopharmaceuticals cannot be stored, and the number of batches produced per years is necessarily very high.

Due to its chemical-physical properties and sufficiently long half-life (109,7 min), the Fluorine-18, is one of the most versatile PET radionuclides as it allows the development of more complex syntheses consisting of several consecutive steps. Not surprisingly, the most used RP in imaging PET is just a fluorinated compound: the (2-[$^{18}$F]Fluoro-2-deoxy-D-glucose) ([$^{18}$F]FDG).

The short half-life of the radionuclide affects also the execution of the quality control: a PET radiopharmaceutical, must be used immediately, when some quality controls are still ongoing. A typical example is the result of sterility test whose implementation takes two weeks from the production (Yu, 2006).

The radioactive nature, the short half-life of radionuclides, the large number of daily productions, the release before the conclusion of quality controls and the parenteral administration, which requires the utmost care in aseptic handling make the production of a PET radiopharmaceutical a very complex process. The planning of a production line compliant with Good Manufacturing Practice (GMP) requires a careful risk assessment, in order to guarantee the requirements of safety, quality and efficacy peculiar of a drug and therefore the protection of patients (EudraLex Volume 4: Good Manufacturing Practice (GMP) guidelines, 2015).

This assessment can be designed following the guidelines of Quality by Design (QbD), an approach that dates back to the early nineties (Juran, 1992) and was even adopted in the pharmaceutical field (Lawrence, 2008). Pharmaceutical companies adopt the principles of QbD with the ultimate goal of achieving a more robust manufacturing process, also optimizing the costs and resources involved. The QbD consists of a systematic and scientific approach to the development and production of a pharmaceutical product, with a better control of its quality. This approach is described in the guidelines of the International Harmonization Conference (ICH) Q8, Q9, Q10 and Q11 patients (EudraLex Volume 4: Good Manufacturing Practice (GMP) guidelines, 2015; ICH Q8, 2014; ICH Q10, 2014; ICH Q11, 2013) and was designed to ensure product quality and encourage the use of quality risk management (QRM) techniques. Specifically, ICH Q10 describes a model of pharmaceutical quality system (PQS) that collects quality principles from the International Organization for Standards (ISO) and GMP regulations, and incorporates pharmaceutical development and QRM.

In 2013 a new revision of Chapter 1 of volume 4 of GMP guidelines has entered into effect in order to incorporate the concepts and terminology described in the ICH Q10 throughout the different stages of a production cycle.

This article deals with the QRM technique applied to the introduction of a new production line of a PET radiopharmaceutical in a manufacturing site GMP compliant. This approach is able to identify risks and take steps to control them also in relation to aspects of patient safety and radioprotection. (Chitto et al., 2013; Decristoforo & Peñuelas, 2009; Khalil, 2017; Kumar & Gupta, 2015; Liu et al., 2012; WHO Guidelines on Good Manufacturing Practices for Radiopharmaceutical Products, 2019). The analysis was performed using as "reference" a RP containing Fluoride-18, such as [$^{18}$F]FDG. The choice of a fluorinated compound makes it possible to discuss the topic in more detail, since its production involve almost always more complex synthesis steps and numerous quality controls respect to other PET RPs.

## 2. Materials and methods

The risk assessment regarding the implementation of a new production line compliant with GMP regulation was carried out taking into consideration the indications provided by the ICH Q10 guideline (ICH Q10, 2014), using the ISO 9001: 2015 standard suggestions (ISO 9001:2015, 2015).

The risk management process provides a solid support to optimize the performance of an organization (ISO 31000:2018, 2018). Each new project implies a risk; even in everyday life, risk assessments are continuously carried out, often based on intuition, reasoning and acquired experience. When the technical complexity of a project increases, the use of a standardized methodology to evaluate the effects of the risks is fundamental for the success of the project (Pritchard, 2015).

All projects should include a systematic and documented risk management as essential process but, in the pharmaceutical sector, this good practice becomes mandatory and drug manufacturers must use risk assessment methodologies to make decisions and to ensure product quality and patient safety.

Risk assessment in drug manufacturing must be carried out during the drug production cycle, from design to distribution (ICH Q10, 2014); with this aim, in 2005, the International Conference for Harmonization (ICH) published the Q9 Guide on Quality Risk Management and, in 2011, the EU adopted this guideline as Annex 20 of the GMPs (EudraLex Volume 4: Good Manufacturing Practice (GMP) guidelines, 2015).

The risk management process described in ICH Q9 is showed in Figure 1.

During the risk management process, the involvement of all stakeholders (Chapman, 1998) in planning meetings that are conducted to ensure a coherent and shared vision in terms of risk methodology used, project roles and responsibilities, timing, monitoring, etc., is fundamental. All plans are systematically reviewed to verify their correctness, completeness timeliness, and consistency. For the systematic review, checklists may be used to identify events that may occur and threaten the objectives of the project.

### 2.1. Risk Assessment

This is the first phase of the risk management process, where the *risk identification*, *risk analysis* and *risk evaluation* must be carried out.

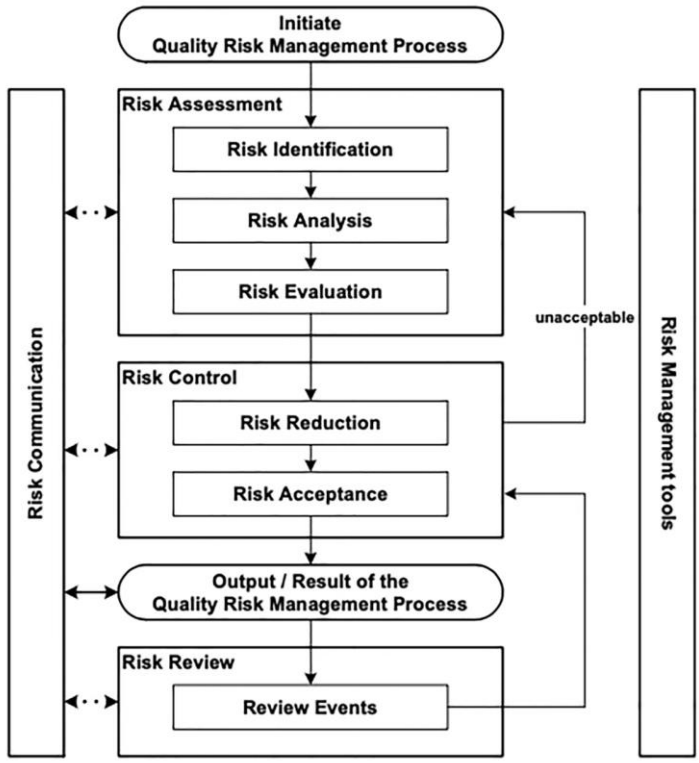


**Figure 1.** Quality Risk Management Process described in ICH Q9

### 2.2. Risk identification

Risk identification includes the identification of risk sources, their causes and their potential consequences. It is important in this phase preparing a complete list of risks that can influence (positively or negatively) the project and the patient safety: it is a critical phase, as the risk not identified in this phase will not be analyzed later.

In order to identify risks, the use of tools and techniques consistent to the objectives and capabilities of the organization is mandatory. It is important that the collected information is up to date and provided by people who have appropriate knowledge in each specific area.

Although not exhaustively, the most common risk identification techniques are shortly described here below.

The *collection of information* (Braem & Turner, 2019; Pritchard, 2015) is a particularly useful technique for identifying risks. The goal is to obtain a simple and clear description of the project risks.

The *expert interview* is a common technique that involves people who are competent in a specific area in the risk assessment. These experts are consulted on the risks in their areas of expertise. In this technique, interviews can be conducted individually or in groups. Often experts, in groups or individually, analyze the documentation (document review) asking to themselves "what are the risks?" of the specific process.

Comparison with past or similar projects is also important in the risk management method. The similarities can be related to technology, production processes, regulatory aspects or other. The use of historical data or

"lessons learned" is an example of application of this technique (Pritchard, 2015).

In the *Delphi technique*, the project manager or facilitator translates the insights of the experts into common terms that are easier to evaluate.

The *Brainstorming* is an information sharing, in which participants answer the facilitator's questions. Brainstorming encourages thinking outside conventional boundaries in order to generate new insights and possibilities.

The *SWOT analysis* consists in identifying the strengths and weaknesses, opportunities and threats of an organization (Baumann et al., 2016).

### 2.3. Risk analysis

The risk analysis takes into account every risk source, quantifies its positive or negative effects (i.e. risk impact), and establishes the probability of occurrence. The combination of both the impact of the risk and the probability of occurrence provides an estimate of the level of risk.

Risk analysis can be qualitative, semi quantitative or quantitative, or a combination of these, depending on the circumstances.

### 2.4. Risk evaluation

The risk evaluation compares the identified risks with previously defined criteria.

The result of a risk evaluation can be a quantitative estimate or a qualitative description of a range of risks. When the risk is expressed quantitatively, a ranking is defined previously. Alternatively, the risk can be expressed using qualitative descriptors, such as "high", "medium" or "low" (EudraLex Volume 4: Good Manufacturing Practice (GMP) guidelines, 2015).

### 2.5. Risk Control

The second phase of the risk management process is the *risk control*: this phase includes the decision-making process to reduce and/or accept risks. The purpose of risk control is to reduce the risk to a specified acceptable or tolerable level if possible.

In the risk control, all the measures and controls are considered to reduce the risk and their effectiveness and efficiency

Communication and consultation with internal and external stakeholders should be ensured during all stages of the risk management process: knowing the needs of internal and external stakeholders is the first step to obtain an effective and productive process of evaluation.

### 2.6. Risk Review

The risk review process allows the evaluation of the risk trend and the effectiveness of the actions taken. The frequency of review should depend on the level of risk.

ICH Q9 provides a list of risk management tools but does not offer a precise guidance and recommends to adapting these tools as needed, using a combination of methodology to facilitate the application of risk management principles. In addition, the ISO 9001:2015 standard encourages the use of QRM: one of the cornerstones of ISO 9001:2015 is Risk-Based Thinking in the requirements for planning, reviewing and improving the quality management system.

The first step of the risk management process, according to ISO 9001:2015, is understanding the external and internal context in which the organization operates. Some guidelines of the application of ISO 9001:2015 provides indications on the main external and internal factors of the context that should be taken into consideration.

In general, for the external context, the social, cultural environment and the

perception of external stakeholders should be taken into account. Technological, regulatory and economic-financial aspects including market trends should also be taken into consideration. For the internal context, governance, organizational structure, roles and responsibilities, policies, objectives and strategies should be taken into account.

Other factors to be considered are the availability of resources in terms of people, knowledge/skill, infrastructure and technologies. The main categories and some examples of the external and internal context factors, which should be considered in the evaluation, are summarizes in Table 2 and 3, respectively.

**Table 2.** The main categories of the external context

| *Categories* | *Some examples of external context factors* |
|---|---|
| Legal aspects | Mandatory / Regulatory<br>Internal regulations<br>Code of ethics |
| Technologies | New technologies available<br>Equipment<br>Materials<br>Intellectual Property Rights |
| Competitive factors | Market segments<br>Similar or replacement products<br>Trends of market<br>Growth trends in the specific area<br>Market stability<br>Service stability<br>General economic situation |
| Social / cultural / political factors | Public investments<br>Local infrastructures<br>Commercial agreements |

The risk factors related to the implementation of a production line of radiopharmaceuticals compliant with the GMP regulation, have been identified based on the methodology suggested by ICHQ9 and ISO 9001:2015 standard and on the experience of the team in the field of radiopharmaceuticals production and in quality management systems (Chapman, 1998). Internal and external key stakeholders are involved to identify risks: context factors are systematically reviewed to identified risk and opportunities of improvement. The identified stakeholders (patients, industry, institutions, employees, scientific community etc) have different skills and needs and have been involved according to the covered topics.

**Table 3.** The main categories of the internal context

| *Categories* | *Some examples of internal context factors* |
|---|---|
| Organization strategies | Values<br>Policy<br>Targets |
| Economical | Availability of financial resources |
| Flow of information | Internal communication |
| Normative | Laws, rules and organizational models adopted |
| Product | Design<br>Production<br>Performance of the quality management system organization |
| Relations with stakeholders | Customers<br>Suppliers<br>Employees |
| Contracts | Contracts with suppliers<br>Contracts with companies<br>Conventions |
| Resources | Infrastructure<br>Operating environment<br>Capital<br>Time<br>People<br>Knowledge<br>Organizational knowledge<br>Processes<br>System<br>Technologies |
| Governance | Rules and procedures for decisions<br>Decision-making processes (formal and informal)<br>Organizational structure / roles and responsibilities |

According ICH Q9 guidelines, a risk assessment of the production process of radiopharmaceuticals has been made using the Failure Mode and Effect Analysis (FMEA).

FMEA is a method used to: a) identify and understand the risk sources, their causes and their effects on the system or on the end users; b) assess the risk associated with the identified risk sources by assigning priorities; c) identify and implement corrective actions to address the most serious risks.

FMEA analysis is performed by a multidisciplinary team of experts who analyse the manufacturing process. The goal is the identification of the system weaknesses and of the corrective actions that should reduce the risk associated in the various segments of the production process before the product release.

The experts of the multidisciplinary team were chosen for their hard skills developed in the twenty-year experience in the production and quality control of radiopharmaceuticals for research and diagnostics and for a similarly long experience in the field of Quality Assurance. Soft skills, such as capacity of dialogue, flexibility and the absence of manifest conflicts within the group, also represented equally important selection criteria.

The tool used was the brainstorming: during the meeting, each one brought his experience and supported the project with his ideas that, in some situations, became actions for improvement.

The initial output was the identification and categorization of the risk sources thereafter the risk was quantified and specific improvement actions were identified. Internal and external context factors were compared with past or similar projects and experiences using historical data or lessons learned.

## 3. Results and discussion

In the first stage of the process, brainstorming was used to create the checklist with the risk sources based on the analysis of the main factors of the external and internal context reported in Tables 2 and 3, respectively.

The analysis was carried out on the entire production process, the identification of risks began with a breakdown of the processes into elementary activities, also taking into account the safety of the process, the integration of the various activities, the internal and external interfaces and any variables that could prevent the entire system from functioning as expected. Then brainstorming was carried out with the experts of the entire production process, involving radiochemists, Quality Control and production operators and quality experts. Potential risks were identified for each segment of the process using historical non-conformance analysis and expert knowledge.

Once the risks were identified, the probability of occurrence (O), the severity of the consequences (S) and detectability (D) were analysed. The probability of occurrence, severity and detectability have been entered in a matrix for the calculation of the risk index.

$$RI = OxSxD$$

The severity of the consequences includes the evaluation of the product defect with potentially health risk of the patients.

Figure 2 shows the source of the risks identified for the activation of a new production line of a GMP radiopharmaceutical.

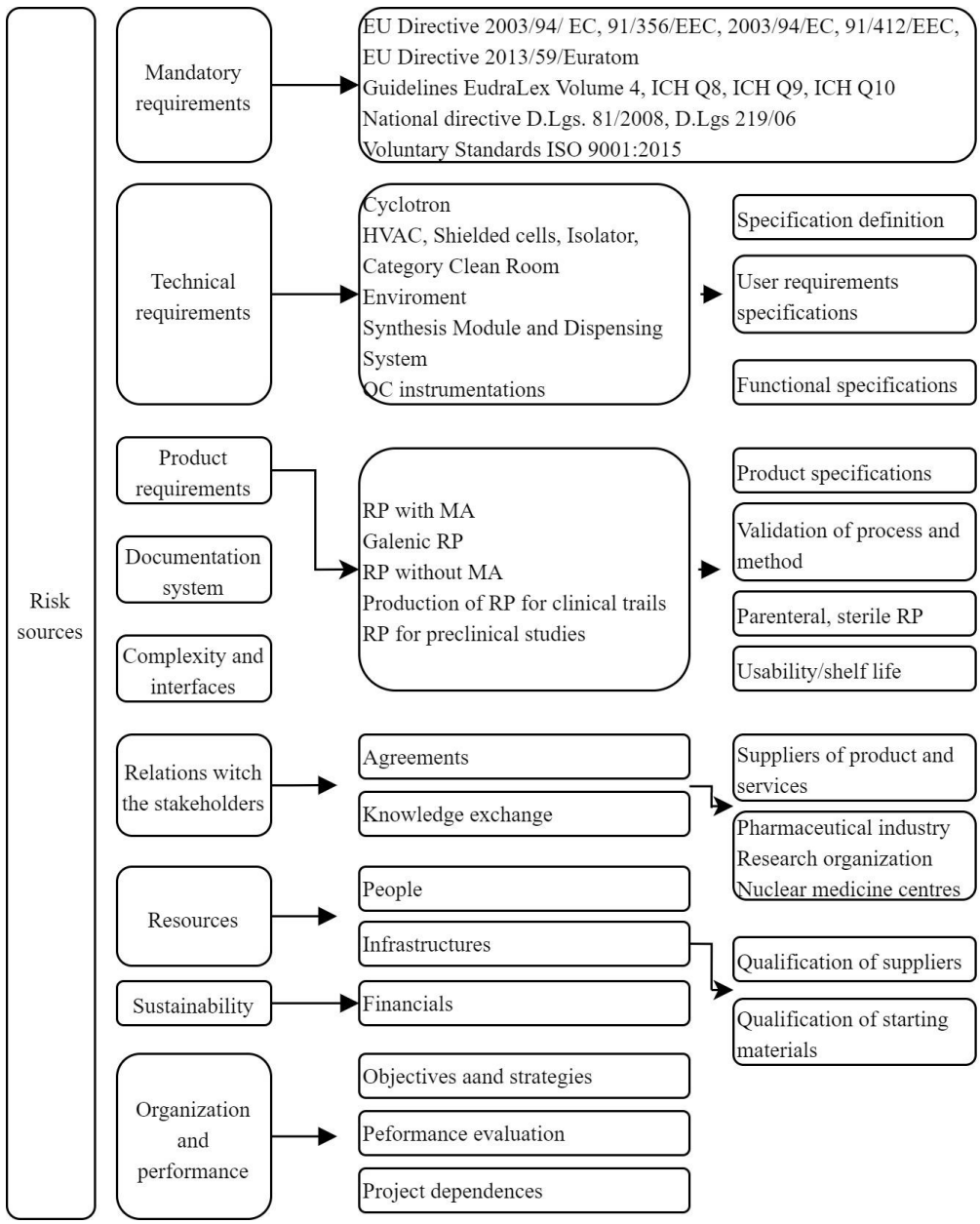


**Figure 2.** Risk sources

The list of risks showed in Figure 2 is apparently traceable to that of any drug. The main aspects that distinguish "classical" from radiopharmaceutical drug are related to the "mandatory" and "technical" requirements. In general, regulatory about radiation safety is not present in the "classical" pharmaceutical industry: the respect of its rules instead deeply affects the technical requirements of radiopharmaceutical's manufacturing sites. Both the environments and the production equipment must guarantee the compliance with GMP guidelines and radiation

protection rules. The use of radioactive substances introduces a complex series of potential, additional risks that must be taken into account: all stages of RPs production must be design in order to protect the workers and the environment by radiation. Suitable shields and monitoring systems must be adopted to confine and control the radioactivity emission. Safety measures must also be adopted for the handling and the distribution of the finished product. The packaging of RP vials must be performed using particular containers suitable to preserve the product and to protect the external environment by radioactive emission. The use of these special containers, generally made of lead or tungsten, introduces a further element of risk linked to the handling of heavy loads.

### 3.1. Mandatory requirements

The production of radiopharmaceuticals needs compliance with several regulatory requirements and guidelines, regarding both the aspects of medicinal preparation and of radioprotection. The mitigation actions as the adoption of the Pharmaceuticals Quality System reduces the risk of non-compliance with mandatory legislation which could result in a defect in the quality of the RP and in patient safety. The voluntary adoption of ISO 9001 standards also helps in documenting control and compliance with legal requirements.

### 3.2. Technical requirements

Technical risks are linked to both the production area (clean room) and the equipment, i.e. all the devices involved in the preparation and quality control of radiopharmaceuticals (Lange et al., 2015; Poli et al., 2012). A first potential risk is represented by the correct design of pressure stages and double door system, heating, ventilation, air conditioning, and air filtering (cleanroom HVAC).

The cleanroom design is very complex work which requires a proper risk assessment process. Many important aspects, such as pressure stages, environmental parameters, personnel and material flow, type and position of monitoring probes, etc., must be taken into consideration and careful evaluated at the planning, in order to guarantee the compliant with the production requirementes. In radiopharmaceutical field, additional requirements are necessary.

By designing and implementing a radiopharmaceuticals site of production, a compromise solution between the requirements coming from the pharmaceutical standards and those of the radioprotection rules must be adopted. This represents a critical step because the two regulations are in contrast. The rooms, classified from the point of view of radiation protection, must designed in “cascade” and under pressure with respect to the uncontrolled surrounding area, in order to ensure that the external airflow always goes towards areas where the risk of radioactive contamination is greatest, and never the other way around. The rooms, classified from a microbiological and particle point of view, must be designed in cascade and in overpressure with respect to the surrounding areas with a lower or none classification, so that the external (dirty) air flow does not reach the production area. The HVAC must simultaneously guarantee the maintenance of the requirements requested by the radiation protection rules and GMP standards. This is possible by planning within the radioprotection-controlled area, a “depression room”, that is a room with a pressure lower than both the radiopharmaceutical production area and the rest of the controlled area. Air with a lower purity coming from the outside or other laboratories goes towards this particular room that, therefore, prevents its entry into the clean area. Similarly, the air coming from the production rooms, which, in the event of an accident can be radioactive, is directed into this room, preventing the

contamination spreads in the surrounding areas.

Ensuring that the production area is a microbiological "clean" environment is essential especially when the radiopharmaceuticals are not finally sterilized. Usually, the production of PET RPs is performed at least in “class C” areas (Annex 3 of GMP). As for the classical drugs industry, the class maintenance is monitored by particles counts and microbiological controls. Staff access to the clean room through a series of cascading locker rooms, wearing appropriate clothing. The plant must be therefore equipped with a control system designed to monitor the basic operating parameters, such as the difference of pressure of the clean room and related areas as well as a radioactivity-monitoring system in order to guarantee the safety of both operators and environment.

The fractioning of final product in liquid form must be carried out inside a “class A” for example an isolator, a special suitable shielded cells equipped with gloves and a pre-chamber that allows introduction/extraction of materials in total containment. Technical risks coming from this critical step are mitigated through training and qualification of personnel for the production in asepsis that also implies the periodic execution of specific *mediafill* tests. During these tests, the dispensing is performed without the use of sterilizing filters, using as “bulk” a culture medium that is later incubated under controlled conditions. If there is no bacteria or fungi growth, the dispensing process and the operators are considered *qualified*.

Radioprotection rules impose to adopt all safety measures, depending on the type of radionuclide, to protect the workers by radiation. RPs productions are carried out using automated synthesis and fractionation/sterilization modules. These modules are equipped by mechanical (electronic and/or pneumatic devices such as actuators, valves etc., and monitoring sensors) and chemical (i.e. a series of interconnected containers in which reagents are placed) parts, able to perform automatically a sequence of operations remotely managed from a laptop (Aerts et al., 2014). All synthesis operations are carried out sequentially and in such a way that the product is always confined within the process line. A human or mechanical error during the synthesis phase is difficult to solve and can lead to the risk of loss of production.

Differently from any other drug, the manipulation of radioactive substances requires the use of suitable shielded cell, where automatic synthesizers and dispensing module are placed. The synthesis modules are prepared with reagents and disposables prior the transferring of the radioactive isotope, which represents the first step of the synthesis.

During the production steps, the cells are usually “sealed”, without the possibility of opening the door to access inside. “Manual” operations must be performed from outside the shielded cell using specific device e.g. tele-pliers or analogs. A bug in one of these “hot cells” (e.g. problems with interlocks of the door, unsecured pressure values, malfunctioning of radioactivity detector systems, etc.) represents a major risk for the safety of the operator and for the environment.

Potential risks coming from QC equipment regard mainly the unreliability of the produced results, due to an incorrect functioning or unsuitability of the instrument. In addition to the equipment for “standard” quality control, in the case of radiopharmaceutical production also instruments dedicated to determination of radionuclidic purity and the measure of radioactivity must be present. Instruments dedicated to determination of radiochemical purity must be equipped with a traditional detector (e.g. UV, electrochemical, etc.) and a radioactivity detector. All operations must be performed carefully, following the

radiation protection procedures to avoid the risk of contamination of the operator and the premises.

In order to mitigate technical risks for all production equipment and QC instrumentation, the user requirements specifications, the functional requirements and the qualification documentations should be defined in accordance with EudraLex Volume 4 Annex 15 "Qualification and Validation". Also quality control methods, as well as the synthesis processes, have to be validated. The infrastructure management should be carried out in accordance with Chapter 3 Volume 4 "Good Manufacturing Practice (GMP) guidelines". For complex equipment the qualification documentations should be include Factory Acceptance Test (FAT), Site Acceptance Test (SAT), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

All facilities and instrumentations should be included in a maintenance and calibration plan and there should be an active maintenance contract (Todde et al., 2017)

The instructions for use and maintenance should be clear and easy to find for the operator. In order to avoid repeating the same errors, a database for collecting the failures of each equipment should be present. This is an important requirement from the point of view of the radiation safety since the repetition of an error affects not only the quality of the product but also the safety of the operator.

### 3.3. Product requirements

The legislation provides that radiopharmaceuticals can be produced industrially as medicines with or without a marketing authorization (MA). For the industrial preparation with MA, the requirements are described in the pharmaceutical dossier. General requirements are described in Annex 3 of GMP regulation dedicated to the "Manufacture of Radiopharmaceuticals".

Non-industrial production (involving sites such as hospital pharmacies, nuclear medicine departments, PET centers), can be prepared as officinal (according to pharmacopoeia requirements) or magistral (according to a medical prescription) preparation. The Guidelines on "Good Radiopharmacy Practice (GRPP) in the preparation of radiopharmaceuticals" (Aerts et al., 2014) and the guidance on the "current GRPP (CGRPP) for small-scale preparation" (Elsinga et al., 2010) provided by EAMN (European Association of Nuclear Medicine), clearly indicate how a quality management system in the production of radiopharmaceuticals should be implemented in non-industrial sites.

Radiopharmaceuticals can be produced also for clinical trials (Todde et al., 2014) or for preclinical studies.

In both cases, pharmaceutical legislation requires the adoption of quality systems designed to ensure the integrity of data and products. Good practices can be represented by:

- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)

The rules of GCP provide an international standard of ethics and scientific quality for designing, conducting, recording and reporting clinical studies involving human subjects.

GLP defines the principles by which laboratory research (studies) are planned, conducted, controlled, recorded and reported, in order to obtain high quality experimental data.

In general, when defining the production method, the needs of stakeholders should be checked, taking into consideration all the risks related to the requirements of the product and the opinion of all experts: nuclear physician, radiopharmacists, manufacturers and researchers.

### 3.4. Documentation system

The management of the documentation is a very important aspect in this field. All documents regarding the entire production process (worksheets, standard operative procedures, analytical methods, etc.) must be always available to the staff and present in their most recent revision. When an updated version of a process document is issued, the old revision must be withdrawn, in order to avoid the circulation of multiple versions of the same document.

The risk of an uncontrolled documentation system is mitigated with the management of documentation in compliance with Chapter 4 Volume 4 "Good Manufacturing Practice (GMP) guidelines".

### 3.5. Complexity and interfaces

The Management of complexity and interfaces is necessary to avoid cross contamination in management of multi-partner, multi-product and multi-project.

Cross-contamination is one of the main challenges in the pharmaceutical industry: in multi-product pharmaceutical production plants, the production of more than one product on the same line can affect the safety and quality of the products (Sargent et al., 2016).

Cross-contamination is influenced by many factors and only with a careful risk assessment it is possible to identify effective mitigation actions.

### 3.6. Suppliers

The use of unsuitable suppliers involves a high risk for the safety and quality of the product as well as an economic loss linked to the failure of the syntheses. The reliability of a supplier, in addition to the quality of the materials, also concerns the ability of products supplying and delivery times.

In order to mitigate the risk, each supplier should be qualified in accordance with the provisions of Chapter 7 of the EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. For example, three supply batches of materials can be analyzed to verify compliance, or a quality certification (e.g., GMP, GLP etc.) can be evaluated to qualify the supplier. The qualification of the suppliers is re-evaluates (by audit, filling of questionnaires, etc.) periodically according to a defined time list, and in the event of significant anomalies and out of specification of the materials supplied, in order to verify the reliability.

### 3.7. Resources

The management of human resources and infrastructures is one of the major risk factor: non-competent or unaware personnel or improperly maintained infrastructures can lead to the failure of the project. A human error can cause the loss not only of a batch but also of the entire production day for the reasons discussed above concerning the peculiarity of RPs production. For this reason, continuous training of the staff is a fundamental element. Some indications to mitigate the risk linked to these factors are available in chapter 2 Volume 4 - Good Manufacturing Practice (GMP) guidelines, chapter 3 Volume 4 - Good Manufacturing Practice (GMP) guidelines and in chapter 7 of ISO 9001: 2015.

### 3.8. Sustainability

All aspects related to income and expenses must be considered to assess the sustainability of the project, also through the support of experts. The economic plan must be evaluated over the medium and long term and it should also take into account any unforeseen events that could occur (e.g. a broken instrument that must be replaced, failure in the Fluorine-18 production, an extraordinary maintenance, etc.) and lead to an increase in costs. In the RPs production, these unforeseen events can be of several type and occur quite often. Since PET

radiopharmaceuticals cannot be stored and have to be produced daily, any problem can cause a production stop for a relatively long period. Therefore, the economical aspect must be evaluated very carefully. In order to mitigate the unexpected events and to prevent large losses, all possible precautions must be adopted (e.g., keeping all instrumentation / equipment under full risk maintenance contract instead standard).

### 3.9. Objectives and strategies and Performance evaluation

The formalization of strategies in a strategic plan or in the quality policy reduces the risk of uncoordinated actions unrelated to the achievement of common goals. The re-examination of the objectives according to the GMP Pharmaceuticals quality system and the ISO 9001 ensures that the decision-making process is based on real data. These risks are mitigated applying what is described in the PQS, especially with the drafting of the Product quality Review (PQR), in ICH Q10 and ISO 9001:2015.

### 3.10. Project dependences

The production of the radiopharmaceutical is closely linked to the availability of the radionuclide. It is important that the interactions between the radionuclide and radiopharmaceutical production process are correctly mapped and synchronized. In addition, the slowness of the procedures due to relations with the Public Administration, bureaucratic constraints, etc. can be mitigated by the adoption of strategies that allow to remove the obstacle (e.g. making orders in advance, etc).

All aspects discussed above are summarized in Table 4 that shows the results risks identification for a production line implementation and the relative mitigation actions.

**Table 4.** Risk identification and mitigation actions

| *Categories* | *Risk* | *Mitigation actions* |
|---|---|---|
| **Mandatory requirements**<br>EU Directive 2003/94/EC,91/356/EEC, 2003/94/EC, 91/412/EEC<br>EU Directive 2013/59/Euratom<br>Guidelines EudraLex Volume 4, ICH Q8, ICH Q9, ICH Q10<br>National directive<br>Voluntary standards ISO 9001:2015 | Non-compliance with mandatory legislation | The adoption of the Pharmaceuticals Quality system (The Rules Governing Medicinal Products in the European Union Volume 4 EU Chapter 1 Pharmaceutical Quality System) reduces the risk of non-compliance with mandatory legislation. The ISO 9001 (ISO 9001:2015) voluntary adoption supports documentation control and compliance with legal requirements. |
| **Technical requirements**<br>Cyclotron<br>HVAC, Shielded cells, Isolator<br>Synthesis Module and Dispensing Systems<br>QC instrumentations | Unsuitable environments<br>Unsuitable tools and equipment<br>Unqualified tools and equipment | Define the functional requirements and manage the equipment in accordance with EudraLex Volume 4 Annex 15 "Qualification and Validation" Chapter 3 Volume 4 "Good Manufacturing Practice (GMP) guidelines" |
| **Product requirements**<br>Radiopharmaceuticals with MA<br>Radiopharmaceuticals without MA<br>Radiopharmaceuticals for clinical trials | | Taking into consideration all the risks related to the requirements of the product, the opinion of all experts: Nuclear doctors, radiopharmacists, manufacturers, researchers is desirable. |

| | | |
|---|---|---|
| New radiopharmaceuticals | | |
| **Documention system** | Uncontrolled documentation system | Management of documentation in compliance with Eudralex Chapter 3 Volume 4 "Good Manufacturing Practice (GMP) guidelines" |
| **Complexity and interfaces** Multi-partner, multi-product, multi-project | Cross contamination | Management of cross contamination according to a risk assessment process |
| **Supplier** | Safety and quality of the product | Each supplier should be qualified in accordance with EudraLex Chapter 7 Volume 4 "Good Manufacturing Practice (GMP) guidelines". Suppliers should be qualified in order to verify the reliability and quality of services and/or materials. |
| **Resource** | Non-competent or unaware personnel or improperly maintained infrastructures | Resources management in accordance with EudraLex Chapter 2 and Chapter 3 Volume "Good Manufacturing Practice (GMP) guidelines". Resource management according to chapter 7 of ISO 9001: 2015 |
| **Sustainability** | Failure of the project | All aspects related to income and expenses must be considered to assess the sustainability of the project Providing the support of an expert to evaluate the sustainability of the project |
| **Objectives and strategies** | Uncoordinated actions | Formalization of strategies in a strategic plan or in quality policy reduces risks of uncoordinated actions. |
| **Performance evaluation** | Decisions not based on data | Product quality Review and annual Management Review according to PQS GMP and in the ISO 9001 ensures a decision-making process based on real data. and also mitigates the risks associated with poor performance evaluation. |
| **Project dependences** | Slowness of procedures bureaucratic constraints, etc. | Identify strategies that allow to remove the obstacle, e.g. making orders in advance, etc. |

## 4. Conclusions

The production of radiopharmaceuticals is a very complex process that put together the critical issues related to the production of sterile drugs and those related to management of radioactive compounds. In this paper, a risk assessment analysis regarding the implementation of a radiopharmaceutical production line has carried out. For this study, the risk-based thinking approach, recommended from the guidelines, has been followed and applied to the entire production process, starting from the early design stages until the final release. The brainstorming was carried out with a team of people, who are competent in a specific area, able to contribute with their hard and soft skills.

The twenty-year experience in the production and quality control of radiopharmaceuticals for research and diagnostics and the long experience in the field of Quality Assurance, the soft skills,

such as capacity of dialogue, flexibility and the absence of manifest conflicts within the group, represents the key factors of success of the risk management process.

The risk factors were identified and analyzed, taken into consideration the peculiar aspects of these pharmaceutical productions, that is the short half-life times, the large number of produced batches, the administration before the results of the sterility control, and addressed with appropriate mitigation actions.

The identification of risks should not be limited to technical risks but should also be extended to organizational, sustainability, and programmatic risks related to the availability of resources although risk related to mandatory and technical requirements make the difference between a "standard" drug and a radiopharmaceutical. Regulatory about radiation safety are, in general, not present in the "classical" pharmaceutical industry: the use of radioactive substances introduces a whole series of potential additional risks that must be taken into account.

This study showed as the experience in the production of radiopharmaceuticals is one of the essential requirements for identifying risks throughout the production process as well as the knowledge of risk assessment techniques can result one of the key factors for the success of the project.

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