

7. Main Text

7.1. Introduction

Radiopharmaceutical production constitutes the manufacturing of the radioactive isotope API, followed by formulation of the API into a FPP or using the API to radiolabel a molecule to form the FPP.

Radioactive isotope production, i.e. API's may be manufactured by one of the following methods: Neutron bombardment of target materials in a nuclear reactor; chargedparticleless bombardment of target materials in a cyclotron; nuclear fission of heavy nuclides after neutron or particle bombardment; or from a radionuclide generator (WHO, 2014, p. 169).

Radiolabeling is the incorporation of a radioactive isotope into the structure of a molecule for the purpose of determining the presence or biodistribution of the molecule in the patient's body, and may be performed by Radiosynthesis i.e. the incorporation of a radioactive isotope into the structure of the product, mainly by organic chemistry synthesis, mostly on automatic synthesizer units; radiolabeling of small molecules and macro molecules with a radioactive isotope; formulation of an API into a FPP.

Radiopharmaceuticals are pharmaceutical formulations which include radioactive substances which are used in the diagnosis and treatment of many diseases and are administered by specially trained physicians, either by injection, orally or via inhalation.

Thus, radiopharmaceuticals are required to follow the same regulatory processes as orthodox pharmaceuticals, in that manufacturers are required to demonstrate their quality, safety and efficacy prior to obtaining a Marketing Authorization (which, in South Africa, is equivalent to a registration license issued by the MCC) as well as a GMP Certificate in order to commercialize the product. Following the granting of a Marketing Authorization (throughout this paper, where marketing authorization is used, it includes the registration license as issued by the South African MCC) by the pharmaceutical Regulatory

Authority (RA), the radiopharmaceutical manufacturer is required to adhere to current Good Manufacturing Practice (cGMP) requirements during the manufacture of the product by ensuring that the manufacturing facility maintains its cGMP compliance status. Post-Marketing Surveillance studies, inclusive of pharmacovigilance studies, are another requirement which radiopharmaceutical manufacturers are required to adhere to.

For orthodox pharmaceutical manufacturers, the above is the extent of the regulatory requirements and restrictions to which they are required to adhere to. However, radiopharmaceutical manufacturers have the added regulatory requirements as specified by the applicable nuclear regulator.

Such additional requirements include, among others, the licensing requirements, which include regulatory hold points at the basic design, installation / construction, cold commissioning, hot commissioning and commercial operations, for the facility in which the radioactive material shall be handled, used and manufactured. Additional requirements exist in the area of process controls, as well as in the area of protection and monitoring of personnel involved in the manufacture of nuclear-based products. Such requirements are established by the applicable nuclear regulator, i.e. the National Nuclear Regulator in South Africa.

A classic example of a conflicting requirement between the two governing bodies exists in the ventilation requirements for a manufacturing facility. Pharmaceutical guidelines require that orthodox pharmaceutical products are manufactured under positive room pressure in order to allow for the flow of air out of the manufacturing suite, taking with it any environmental contaminants and ensuring that the product is kept free of any form of particulate contamination. Nuclear guidelines require that nuclear products are manufactured under negative pressure, ensuring that the flow of air is into the manufacturing environment thereby ensuring that radioactive contamination is contained within the manufacturing environment and prevented from spreading uncontrolled.

Each RA has its mandated objective and in order to achieve this, has established its individual set of regulations and guidelines to which the applicable industry is required to adhere. The pharmaceutical regulator has the mandated objective of ensuring the safety of the patient, by ensuring that the pharmaceutical products are consistently manufactured in a manner which produces a quality, safe and efficacious product, while the nuclear regulator's objective is ensuring the safety of both the personnel involved in the manufacture of nuclear products as well as that of the public at large.

Manufacturers who are able to clearly demonstrate their compliance to these applicable regulatory requirements ensure that the products manufactured are done so in a safe and responsible manner, while at the same time are safe to be administered to patients, even if such conflicting regulatory requirements exist.

Therefore, the aim of this research paper is to evaluate the appropriateness of current regulatory guidelines, as utilized in the manufacture of orthodox pharmaceuticals, on the manufacture of radiopharmaceuticals, by reviewing current guidelines in comparison to their application within the radiopharmaceutical industry, considering industry specific norms that have been adopted in order to ensure compliance to the various requirements. Due to the limited size of the radiopharmaceutical industry within South Africa, applicable guidelines from local as well as international RA's and governing bodies were reviewed. This serves to establish that the findings noted in this paper, are applicable to the global radiopharmaceutical industry, and not to the local industry only.

7.2. Literature Review

The Society of Nuclear Medicine and Molecular Imaging (SNMMI), estimates that approximately 18 million radiopharmaceutical procedures are performed annually in the United States and is a specialty which is rapidly increasing (SNMMI, 2004). However, as a result of major shortages of radiopharmaceuticals, many cancellations or delays of such procedures have been noted in the recent past and this has led to concerns regarding the reliability of reactor-based radiopharmaceuticals (Ruth, 2014, pp. 245).

Radiopharmaceuticals, are pharmaceuticals which are attached to a radioisotope. They are used either to treat or diagnose diseases safely, painlessly and early in the disease prognosis (SNMMI, 2004). During diagnosis, the radiopharmaceutical Final Pharmaceutical Product (FPP) aggregates in certain parts of the body, giving off gamma emissions in order to make the metabolic processes of that part of the body visible by special examination equipment, such as gamma cameras. However, during treatment the radioactive nature of the preparation is used to destroy the diseased cells (EANMMI, 2010).

Radiopharmaceuticals are required to meet the criteria of purity, identity, efficacy and safety, as for orthodox pharmaceuticals, and to comply with the precautions associated with the safe handling of radioactive materials (Westera and Johannsen, 1997, pp. BP5).

A basic regulatory strategy, which ensures the safety of public health, relies on product development, product manufacture, and Post Marketing Surveillance studies of the product (Tobin and Walsh, 2008, p. 21).

During product development, manufacturers are required to generate sufficient data, which proves the safety and efficacy of the product. Should the RA deem this data as acceptable, a Marketing Authorization (in the South African context this is equivalent to a manufacturing license) is issued, licensing the

commercialization of the product (Tobin and Walsh, 2008, p. 21). In addition, a GMP Certificate is required certifying the GMP Compliance of the manufacturing facility. This is a process which is similarly followed by the South African MCC.

Identifying the applicable RA, such as the Medicines Control Council (of South Africa) (MCC), as well understanding and implementing its regulatory requirements during the establishment of the Regulatory Strategy is essential to ensuring that the regulatory process runs smoothly.

Once the manufacturing facility is cGMP compliant and the Marketing Authorization is obtained and commercialization of the product begins, the RA focuses on ensuring that the manufacturing facility continues to comply with the applicable regulations, such as cGMP. This is ensured by the issuing of licenses such as manufacturing licenses and GMP Compliance Certificates, together with periodic inspections of the facility by the RA for compliance to the license requirements (Tobin and Walsh, 2008, p. 21). This process is followed by most RA's, including the MCC of South Africa.

Quality Assurance (QA) systems establishing the requirements pertaining to personnel, documentation, validations, corrective and preventive actions, and facilities and equipment, are essential to ensuring compliance to cGMP (Tobin and Walsh, 2008, p. 22).

Radiopharmaceuticals are required to be manufactured in accordance with cGMP as they are administered directly to patients, either by injection, inhalation or orally (WHO, 2014). Therefore, RA's such as the Medicines Control Council (MCC) of South Africa have established GMP guidelines for the manufacture of radiopharmaceuticals. These guidelines, together with various other supplementary guidelines are required to ensure that radiopharmaceuticals are manufactured according to the applicable cGMP requirements (MCC, 2003, p. 3).

Post Marketing Surveillance programs are required to be carried out for the lifetime of the product. This includes a system of reporting of adverse reactions by patients, as well as monitoring and reporting of incidents by the manufacturers to the RA (Tobin and Walsh, 2008, p. 22).

General Background:

One of the most significant differences between orthodox pharmaceuticals and radiopharmaceuticals is the very short shelf-life of the radiopharmaceutical as a result of the decay of the product, which involves its transformation from an unstable to a more stable isotopic configuration. This means that the radiopharmaceutical is usually prepared immediately prior to administration to the patient (WHO, 2014).

Another glaringly obvious difference is the fact that orthodox pharmaceuticals are generally used to treat diseases, whereas radiopharmaceuticals may be used to both diagnose and treat diseases. The gamma-rays emitted from products designed for diagnosis allow for non-invasive imaging providing information of the target organ, whereas the alpha- and beta-rays emitted from products designed for treatment destroy the diseased tissue (WHO, 2014).

Furthermore, radiopharmaceuticals are required to be administered by specially trained physicians (SNMMI, 2004), who have been trained in the administration and control of radiopharmaceuticals, as opposed to the generalized training received by physicians in the administration of intravenous pharmaceuticals.

Facility and Equipment Considerations:

Another difference between orthodox pharmaceuticals and radiopharmaceuticals lies in the facilities and equipment in which they are manufactured. The facilities must be dedicated and self-contained, in order to prevent the spread of radioactive contamination between products, and to the environment. It is

necessary that the equipment be dedicated to the manufacture of radiopharmaceuticals only (MCC, 2003).

An additional difference lies in the ventilation pressure cascade of a radiopharmaceutical manufacturing facility. In order to contain the radioactive substances within the facility, the air pressure is required to be lower than that of the surrounding environment. However, the need to protect the product from environmental contamination still exists. Therefore, all operations should be carried out such that the risk of microbial and particulate contamination is abated, since the radiation emitted from the product is not sufficient to be deemed as sterilization of the product (MCC, 2003).

Manufacturing Considerations:

Guidelines such as the MCC's Guideline on the Manufacture of Radiopharmaceuticals are used to assist manufacturers on the required practices for the manufacture of radiopharmaceuticals. These guidelines specify the cGMP requirements over and above those specified in the cGMP Guide for the Manufacture of Medicines, and should be used to supplement these (MCC, 2003).

Not only do radiopharmaceutical FPP manufacturers have to obtain a manufacturing license from their local pharmaceutical RA, but the premises where any radioactive work is being carried out, is required to be licensed by the local radiological control authority as well. Furthermore, compliance to the applicable regulations pertaining to the production, supply, storage, transport, use and disposal of radioactive products is mandatory (MCC, 2003).

Quality and Safety Considerations:

As radiopharmaceuticals are considered to be potentially hazardous, special precautions are required to prevent cross-contamination; for the retention of radionuclide contaminants and for nuclear waste disposal (MCC, 2003).

The personnel involved in the manufacture (and administration) of radiopharmaceuticals, are required to be registered as radiation workers. The International Atomic Energy Agency (IAEA) has prescribed safety standards, such as the use of pocket dosimeters to monitor radiation doses of radiation workers. Another requirement is that the ALARA (As Low As Reasonably Achievable) principle be applied at all times. This dictates that at all times personnel should be exposed only to the lowest possible radiation doses (MCC, 2003).

The QA system of radiopharmaceutical manufacturers is a critical system as many radiopharmaceuticals are released prior to the completion of certain Quality Control (QC) analyses due to the short product half-lives. Therefore, it is required that the QA system be continuously assessed for conformance and effectiveness (MCC, 2003).

cGMP principles such as process validation, monitoring of process parameters and in-process controls are important factors to be taken into consideration, together with the environmental monitoring results, prior to the release of the product batch (MCC, 2003).

A formal recorded decision, based on the available production and QC data available at the time of release, is still required and this should be combined with an effective product recall system, should it become evident that the batch does not meet the remaining specifications. There should be a system in place to ensure that product recalls can be effected within a short period of time prior to the product being administered to patients (MCC, 2003). QC data such as sterility results are only available after the product is used, therefore to ensure product quality and patient safety, the applicable processes are required to be robustly validated.

In order to ensure that all the legal requirements are adhered to, the responsible person is required to be qualified and competent in the handling of both radioactive material, as well as pharmaceuticals. Astute knowledge of basic radiochemistry, pharmacy and radiopharmaceutical chemistry is a prerequisite for the

development and performance of radiopharmaceutical procedures (in Europe) (Westera and Johannsen, 1997, pp. BP5).

The European Association of Nuclear Medicine and Molecular Imaging (EANMMI) established post-graduate program of radiopharmaceutical chemistry / radiopharmacy provides the European community of radiopharmaceutical chemists and radiopharmacists, with the opportunity of a unified tutelage which may serve as a common basis for certification and licensing (Westera and Johannsen, 1997, pp. BP7). The European requirement for a qualified person to conduct the final release of FPP's is equated in South Africa to the requirement for these releases to be conducted by a pharmacist. However, the post-graduate program established by the EANMMI implies that being a qualified person is not sufficient on its own, to provide the necessary expertise and knowledge of the industry, to conduct these releases. Unfortunately, however, no such post-graduate training exists for pharmacists in South Africa.

Distribution and Packaging Considerations:

The IAEA transport regulations specify the maximum allowable radiation measured on the surface of final packaging. Also specified, are conditions under which the packages may be transported, which include the licensing requirements for the transport package itself. Health Physicists are required to check that transport containers are not radiologically contaminated, as well as to monitor the radiation levels emitted from the sealed package (MCC, 2003).

Conclusion:

The field of radiopharmaceuticals is one which is rapidly advancing and spreading. The demand for this advancement and spread is ever increasing, however like most other pharmaceuticals, it is an area which is not unfamiliar to its own crises.

With recent reactor stoppages around the world, the supply of radiopharmaceuticals has become vulnerable. Thus, manufacturers are looking for more innovative and reliable sources for the supply of radiopharmaceuticals.

This leads to the question regarding the guidelines required to manufacture radiopharmaceuticals and the literature review above highlights the basic differences, when compared to the manufacture of orthodox pharmaceuticals.

The EANMMI has formed the radiopharmacy committee to address issues such as the ever-increasing demands from cGMP regulations, for FPP radiopharmaceutical preparations (Decristoforo, Elsinga, Faivre-Chauvet, et al, 2008, pp. 1400).

Therefore, to qualitatively determine the appropriateness of the current regulatory guidelines on the manufacture of medicines within the radiopharmaceutical industry, a review of the current guidelines was conducted and compared to their applicability in a real-world setting when employed within the radiopharmaceutical industry.



7.3. Methodology

The method for gathering information in a research project depends on the nature of the information that is intended to be collected in order to arrive at recommendations in the identified area of improvement.

Hoepfl, 1997 and Denzin and Lincoln, 1998 (as cited in Golafshani, 2003, p 597), have defined quantitative research as methods which use experiments to test established hypotheses, after the researcher has familiarized himself with the problem. Quantitative research emphasizes the facts while presenting information in a mathematical term which is then analyzed and presented statistically. In order to achieve this, researchers are required to ensure the repeatability of the data gathered.

Repeatability, as defined by Joppe, 2000 (as cited in Golafshani, 2003, p. 598), is "...the extent to which results are consistent over time and an accurate representation of the total population under study..." and can be subdivided into three categories: the extent that the result remains the same, its stability over time and the similarity of the results within a time frame.

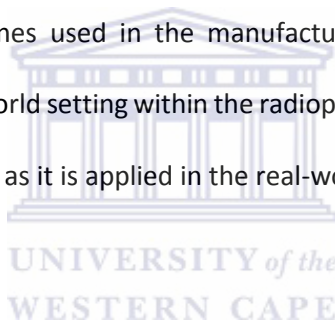
Golafshani (2003) explains in her paper that to ensure the repeatability of results, a high degree of reliability is required which is an indication of a high degree of stability of the results obtained.

Hand in hand with reliability goes the concept of validity. Validity has been defined by Joppe, 2000 (as cited in Golafshani, 2003, p. 599), as "whether the research truly measures that which it was intended to measure or how truthful the research results are".

Reliability and validity in terms of quantitative research, are the concepts which determine if research results are replicable and if the measurement is accurate and actually measuring what it intended to measure, respectively (Golafshani, 2003, p. 599).

However, the quantitative research technique was not considered a suitable method for this research paper as neither observational studies nor structured interviews, surveys or focus groups were appropriate to the collection of information related to the applicability of current regulatory guidelines on the manufacture of radiopharmaceuticals. This study also did not include any form of clinical trials nor laboratory studies, therefore, Case Report Forms and meta-analyses of laboratory or clinical trial data was also found to be not applicable.

Instead, the method of qualitative research was considered and adopted for this research paper based on the discussions found in Golafshani (2003). It explained that qualitative research aims to understand the research questions in a “real-world” setting, where results are not presented in a statistical form. As the review of current regulatory guidelines used in the manufacture of radiopharmaceuticals and their analysis and comparison to the real-world setting within the radiopharmaceutical manufacturing industry, aims to understand this phenomenon as it is applied in the real-world without presenting the results in a statistical form.



However, as explained above, the concepts of reliability and validity are commonly employed within the quantitative research methodology. Even though this may be the case, Golafshani (2003), has attempted to redefine these concepts in order for them to be relevant and applicable to qualitative research methodologies as well.

Golafshani (2003) in her paper titled Understanding Reliability and Validity in Qualitative Research, has presented two conflicting schools of thought on the applicability of reliability to qualitative research. One school of thought, led by Lincoln and Guba, 1985 (as cited in Golafshani, 2003, p. 601), states that the concept of dependability as utilized in qualitative research, closely corresponds to the concept of reliability as applied in quantitative research. This, together with the concept of trustworthiness, as described by Seale, 1999 (as cited in Golafshani, 2003, p. 601) are crucial in ensuring that the research study

is credible and the results obtained from a qualitative study are repeatable. This compared to the school of thought led by Stenbacka, 2001 (cited in Golfshani, 2003, p. 601) which claims that the concept of reliability is irrelevant to qualitative studies since reliability uses the concept of measurement, and there is no measurement in a qualitative study.

Lincoln and Guba (1985), (as cited in Golafshani, 2003, p. 601) go on to explain that even if the opinion of Stenbacka is adopted, since the concept of validity is reliant on the establishment of reliability, if the validity of a qualitative study is established then the reliability of the study is, by inference, established as well.

For validity to be established in a qualitative study, researchers are required to develop their own measurement of validity, as validity is affected by the researcher's perception of the studies validity (Golafshani, 2003, p. 602). Concepts of quality of the study design and results obtained as well as trustworthiness of the research conducted, are concepts which were adopted in ensuring the validity of this study. As already mentioned above, qualitative research is based on "non-numerical information and their phenomenological interpretation, which inextricably tie in with human senses and subjectivity" (Leung, 2015, p. 324). Researchers involved in quantitative research, usually try to distance themselves from the research process in order to ensure that results obtained are unbiased. However, in qualitative research projects, such as this project, the role of the researcher is vital to ensuring that real-world settings are used to evaluate the research topic on hand. In fact, Professor Leung (2015), notes that under the context of quantitative research human emotions and perspectives are undesirable, however under the context of qualitative research they are considered as essential and inevitable.

Qualitative research has often been accused of "being merely a collection of personal opinions subject to researcher bias" (Noble and Smith, 2015, p. 34), therefore as the originator of this research is employed within the radiopharmaceutical industry, the risk of inherent bias does exist, and all efforts were made to

eliminate this risk, by employing methods which ensured the credibility of the results obtained, as well as the trustworthiness of the researcher in addition to the research topic.

The consideration of stability and internal reliability in a qualitative context were taken into consideration in order to ensure that the results obtained in this study were reliable and consistent with the research hypothesis. It was noted that the consideration of inter-observer consistency was not required as only one researcher was involved in the compilation of this paper. Measurement, internal validity and external validity were also taken into consideration in order to ensure that the results obtained were valid.

However, as discussed above, the concepts of reliability and validity are more suited to quantitative research projects even though Golafshani (2003) has attempted to redefine these for application to qualitative research. Therefore, the concepts of credibility, transferability, dependability and confirmability, were used in this qualitative context instead of the concepts of internal validity, external validity, reliability and objectivity, respectively (Shenton, 2004, p. 64).

Internal validity which in the quantitative context aims to establish if the study measures what it intended to measure, is, per Shenton (2004) equivalent to the concept of credibility in the qualitative context. Credibility is the concept which proves the extent to which the research project is aligned to reality (Shenton, 2004, p. 64). Therefore, it was noted that this concept proved to be vital as this research project aimed to identify the applicability of current guidelines to the manufacture of radiopharmaceuticals when compared to their real-world application.

External validity is the concept employed within quantitative research to prove the extent to which the results of a study can be applied to other fields. This concept would be equated to the concept of transferability within a qualitative research project. However, as the results of a qualitative research project are usually applicable to a particular environment, this concept may be impossible to prove (Shenton, 2004, p. 69). This was the case in this research project as it will only be applicable to the

radiopharmaceutical manufacturing industry, and it may not be possible to equate the findings from this project to other industries.

Another measure of validity, as noted by Noble and Smith (2015), is that of truth value. Truth value allows for the fact that multiple realities do exist and that personal experiences and viewpoints would lead to biases. Validity is thus addressed by ensuring that the perspectives of all involved, are clearly and accurately stated within the research results. This is the measure of validity, which was employed within this project, as the researcher's viewpoints and personal experiences drove the project.

Reliability, as discussed above, is the extent to which the study and its results are repeatable. This could be equated to the concept of dependability within the qualitative research environment (Shenton, 2004, p. 71). However, since a qualitative research study is based on the emotions and opinions of the researcher, this concept also proved difficult to achieve and the results obtained by each individual may be subject to the role which the researcher plays in the study.

The concept of consistency is one whereby an independent researcher may be able to achieve similar results to that of the original researcher based on a clear "decision-trail" being maintained by the original researcher (Noble and Smith, 2015, p. 34). Therefore, an independent researcher skilled in the art of radiopharmaceutical manufacture, GMP and radioisotopes shall be able to follow the thought processes and decision-trail of this study, and arrive at similar conclusions and recommendations.

Objectivity is the concept of using instruments which are independent of human influence within the quantitative context. However, as noted by Shenton (2004), "the intrusion of the researcher's biases are inevitable". The concept of confirmability may be employed within the qualitative environment by ensuring that the researcher declares his/her biases (Shenton, 2004, p. 72), as has been declared for this project. Confirmability may be an alternative method to that of reliability, as has been reported by Noble and Smith (2015).

Therefore, the method for data collection in this study was a mixed method comprising of a qualitative review of regulatory guidelines and an assessment of the applicability of these guidelines for the regulation of standards within the radiopharmaceutical industry.

The qualitative technique which was employed comprised of the collection and review of current guidelines which have been approved and published, and are currently implemented by the pharmaceutical and nuclear regulators, respectively. This review was then compared to industry specific compromises to determine the appropriateness and implementation of these guidelines within the radiopharmaceutical manufacturing industry. This was completed by reviewing the applicable and complementary guidelines from the two regulators side-by-side, for their implementation within their respective industries. Where conflicts were identified, these were compared to industry norms, to assess their applicability, as well as the compromises required from the industry in order to comply with the set requirements.

One method that has been recommended for ensuring the quality of a qualitative research project, is the use of the Critical Appraisal Skills Program (CASP) checklist for qualitative studies. This method ensures the clarity as well as the appropriateness of the research question (Leung, 2015, p. 325), and therefore was adopted (where possible) for the purposes of improving the quality of this research project. See appendix 10.2 for summary table of results obtained from the CASP Checklist.

7.4. Findings and Analysis / Discussion

General Background:

Radiopharmaceuticals are pharmaceuticals which consist of radioactive substances, intended as either diagnostic or therapeutic agents (WHO, 2014, p. 162).

Per the WHO Technical Report Series, No. 929 (2005), a Pharmaceutical Product is “any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state”.

Therefore, for the purposes of this paper, the term radiopharmaceutical, is used to describe both Final Pharmaceutical Product’s (FPP’s), as well as Active Pharmaceutical Ingredients (API). Where a distinction between the two is required, this shall be noted by either FPP or API.

Radiopharmaceuticals, as orthodox pharmaceuticals, are required to be manufactured in such a way that the processes comply to cGMP requirements, so that the end products are consistently manufactured to meet their established specifications for their intended uses. Therefore, the quality control of the product is of utmost importance in ensuring the continued compliance to cGMP. However, many differences exist in the manufacture of radiopharmaceuticals, when compared to that of orthodox pharmaceuticals. These differences in turn lead to many complications in ensuring compliance to the standard cGMP requirements as set for the manufacture of orthodox pharmaceuticals.

Therefore, during the execution of this research paper, applicable guidelines established by organizations such as the World Health Organization (WHO), the International Conference on Harmonization (ICH), the International Organization for Standardization (ISO), as well as the International Atomic Energy Agency

(IAEA), the National Nuclear Regulator (of South Africa) (NNR) and the MCC, were reviewed and compared for similarities as well as differences when applied to the manufacture of radiopharmaceuticals. Although many similarities were noted, some of the differences noted are highlighted below in an attempt to establish the applicability of these current guidelines on the manufacture of medicines within the radiopharmaceutical industry.

One of the most significant difference between orthodox pharmaceuticals and radiopharmaceuticals, is that radiopharmaceuticals rapidly decay over time, thereby limiting the shelf-life of the product (WHO, 2014, p. 162). This decay over time ensures that an unstable radionuclide reaches a state of more stability, which is dependent on the shedding of nucleons (and or gamma emissions). This in turn results in the emission of charged particles such as alpha or beta particles (WHO, 2014, p. 165) or gamma rays, which are responsible for the diagnostic or therapeutic properties of the radiopharmaceutical. Each radionuclide decays exponentially at its own constant rate (WHO, 2014, p. 171).

The physical half-life of the radionuclide of a radiopharmaceutical product, is the time it takes for a given quantity of a radiopharmaceutical to decay to half its original value (WHO, 2014, p. 165). This concept should not be confused with the serum or plasma half-life of pharmaceuticals, both orthodox pharmaceuticals as well as radiopharmaceuticals.

The purity and quality of the radiopharmaceutical ultimately influences the bio-distribution of the product; the interpretation of the nuclear imaging scan; as well as on the accuracy of the diagnosis of the procedure. Therefore, the physicochemical and biological QC tests are required to ensure that the product is of the required purity and quality (Vallabhajosula, Killeen, and Osborne, 2010, p. 222).

The physicochemical tests comprise of analyses to determine the chemistry, purity and integrity of the formulation (Vallabhajosula, Killeen, and Osborne, 2010, p. 222), such as radionuclidic purity and radiochemical purity, which are discussed below.

Chemical purity may be defined as the percentage of the chemical of interest in the specified chemical form (WHO, 2014, p. 163), while the radiochemical purity is the ratio of the radioactivity of a radionuclide in a particular chemical form, to the total radioactivity of that radionuclide within the preparation (WHO, 2014, p. 163). The radionuclidic purity of a preparation may be defined as the ratio of the radioactivity of the specified radionuclide to the total radioactivity of the preparation (WHO, 2014, p. 164).

The specific activity of a batch of a radiopharmaceutical is the radioactivity of a radionuclide per unit of mass of the element or of the chemical form of the radioactive preparation (WHO, 2014, p. 164). Generally, the higher the specific activity of a product, the more radioactive molecules can concentrate in a specific organ to produce the therapeutic effect of the product. The inverse is also true, in that the lower the specific activity, the more the cell receptors become saturated by the in-active molecules and the less radioactive molecules are available for diagnosis or therapy of that organ. This in turn results in more radioactive molecules concentrating in other vital organs of the body causing damage to these or poor image quality (Vallabhajosula, Killeen, and Osborne, 2010, p. 223).

The total radioactivity is the radioactivity of the radionuclide per unit of the dispensed formulation (WHO, 2014, p.164). The therapeutic effect of the radiopharmaceutical product is caused by the radiation dose of the product, and not because of the interaction of the pharmaceutical active ingredient with a biological target as with most orthodox pharmaceuticals.

Facility and Equipment Considerations:

The pharmaceutical manufacturing facility shall be designed in such a way, so as to ensure that the orthodox pharmaceutical products manufactured within that facility are of the highest quality standards. This concept is not only limited to the architectural design of the facility, but to the design of the HVAC and utility systems of the facility.

According to the WHO Supplementary Guideline on GMP for HVAC Systems for Non-Sterile Pharmaceutical Dosage Forms (2016a), the architectural and HVAC designs go hand in hand, in that one influences the other. Therefore, the two shall be considered and established during the concept design phase of the facility. This will ensure that the contamination and cross-contamination, as defined by GMP, are prevented thereby ensuring that the quality of the product is not compromised as a result of the design of the facility and its utilities.

The WHO Supplementary Guide (2016a), furthermore states that even though engineering design requirements and standards may vary from manufacturer to manufacturer, they should still comply with all the regulatory requirements in ensuring that product quality and safety is not compromised.

HVAC systems within facilities in which radiopharmaceuticals are manufactured, are designed according to the requirements of the ISO 17873:2004 International Standard (2004) which specifies the design and use requirements for the ventilation system in a nuclear installation such as a radiopharmaceutical manufacturing facility.



The WHO guideline has been drafted with the aim of ensuring the protection of the product from contamination which is usually of a chemical or microbial nature, or protection of personnel from dust or fumes while ensuring comfortable working conditions, or the protection of the external environment from dust, fumes or effluent discharges from the facility (WHO, 2016a, p. 8). In comparison, the ISO guideline for the criteria of ventilation systems for nuclear facilities was established to ensure the safety and protection of the workers, public and environment from the spread of radioactive contamination (ISO, 2004, p. 1).

Another difference noted between the two guidelines is that of pressure cascades. Per the WHO guideline, the facility design should be such that the required pressure cascades can be achieved (WHO, 2016a, p. 16). The difference in pressure between areas is to ensure the different levels of cleanliness, as

well as to prevent cross-contamination between the different areas (WHO, 2016a, p. 17). Usually, orthodox pharmaceutical manufacturing facilities should be maintained at a positive pressure relative to the atmosphere to prevent the ingress of environmental contaminants (WHO, 2016a, p. 51). As discussed above, the purpose of the ventilation system in a nuclear facility is to prevent the spread of radioactive contamination. One way of achieving this is by implementing the concept of dynamic confinement whereby the pressure is lowest in the areas of highest radioactive contamination, thereby ensuring that airflow is from the area of low contamination in to the area of higher contamination (ISO, 2004, p. 10).

Similarly, the orthodox pharmaceutical guidelines require that doors open into the higher pressured area, in order to ensure firstly that the doors are held closed by the pressure cascade, and secondly, for the air flow to be out of the room, which ensures that contaminants (particulate and dust) do not enter into the room while the doors are open (WHO, 2016a, p. 57). This requirement would then also be in direct conflict to the requirements for radiopharmaceutical manufacturers, where the basic concept of containment applies. This means that the doors of the facility should open into the more negative area, to ensure that the air flows into the room, which would ensure that the radioactive contamination is contained within the manufacturing area (the HEPA filters at the supply end of the ventilation system may be relied on to ensure protection from environmental contamination, however since closed-systems are used, there is a very low risk of environmental contamination of the product).

Another requirement for achieving dynamic confinement in a nuclear facility is the inclusion of one or two HEPA filters, as well as, where required, activated carbon columns at the exhaust end of the ventilation system in order to decrease the amount of radioactivity being released into the environment (ISO, 2004, p. 11). This differs from orthodox pharmaceutical requirements, which specifies that HEPA filters should be installed in the supply end of the ventilation system in order to protect the product from particulate and / or dust contamination (WHO, 2016a, p. 27). This implies that radiopharmaceutical manufacturers

would be required to install HEPA filters at both the supply and exhaust ends of the system to meet both the requirements.

However, the biggest challenge which radiopharmaceutical manufactures may face, is the orthodox pharmaceutical manufacturing facility requirement for HEPA filter integrity tests. Regulation states that the filter media, frame and seal should be tested for each HEPA filter, and that the integrity testing should be conducted from within the room. Therefore, filter housings are required to have ports for measuring the upstream concentration and penetration concentration of the filter (WHO, 2016a, p. 72). However due to the radioactive nature of radiopharmaceuticals, this would prove to be impossible as the HEPA filters would be highly contaminated with radioactivity, making access to them impossible. Although in-line monitoring of the pressure differential across the HEPA filter may be possible, it may be required that the HEPA filters be replaced on a more frequent basis as a preventative measure.

Manufacturing Considerations:

Radiopharmaceuticals may be manufactured by one of the following methods: Neutron bombardment of target materials in a nuclear reactor; charged particles bombardment of target materials in a cyclotron; nuclear fission of heavy nuclides after neutron or particle bombardment; or from a radionuclide generator (WHO, 2014, p. 169).

The development of an orthodox pharmaceutical process is carried out in most countries according to the ICH Q11 guideline. Although this guideline does not make an exclusion of radiopharmaceuticals, it does not make specific reference to it either. The guideline covers the process control, selection of starting materials, process development and lifecycle management, all specifically from a chemical attribute point of view, and does not explore the radioisotopic characteristics of a radiopharmaceutical product.

When providing guidance on the process development, it does not take in to account in-house built closed- or semi-closed systems, such as those required for the manufacture of radiopharmaceuticals.

Furthermore, the small batch sizes produced during the manufacture of radiopharmaceuticals, as well as the concept of volume vs radioactivity produced, are critical to identifying the Critical Quality Attributes of the product, as well as the effect of these on the identified Critical Quality Attributes.

In the selection of starting materials the main aspects that should be considered for orthodox pharmaceuticals, is the effect of the materials on the stability and impurity profile of the product (as well as on the establishment of the product specifications), generally with the view of toxicity profiles to the patient. However, the ICH Q3 guidelines exclude radiopharmaceuticals, and do not consider the sensitivity of many radiopharmaceuticals to even trace amounts of impurities. Many radiopharmaceutical API products are required to be of an ultra-pure specification in order to ensure the adequate control and manipulation of the FPP for patient administration. One aspect which has not been taken in to account, is the fact that the ultra-pure starting materials are supplied by a limited number of suppliers only, making their control and release (e.g. QC testing on receipt, as well as qualification of the supplier) a challenge, albeit critical, due to the lack of equipment and analyst capabilities. In addition, the potential to contaminate these with impurities introduced by analytical grade reagents used during the QC process, also poses a concern. Therefore, extra controls in the form of supplier qualifications, method validations, standardized procedures and stringent training programs may be required.

The process validation guidelines referred to in the Q11 guide are applicable to orthodox pharmaceuticals and do not take in to account the challenges posed by radiopharmaceuticals, due to the inherent nature of the products themselves.

In the adoption of the lifecycle approach, although risk based, it does not take into consideration the handling of the radioactive waste generated by the manufacturing process (this is regulated by the applicable nuclear and/or radiation protection regulator). In the development of a radiopharmaceutical manufacturing process, the identification and management of waste streams is critical in ensuring the

proper and safe treatment of radioactive waste, so as to ensure that the process operators, facilities and surrounding environments are not contaminated by the waste.

Quality and Safety Considerations:

A sample is a representative unit, collected according to the sampling procedure, to allow for QC testing, as well as for the retention sample (WHO, 2005, p. 63).

A retention sample is one which is collected following the original sampling process and stored for future testing. The purpose of a retention sample is for potential future evaluation, for example in the event of a potential product recall or customer complaint. Therefore, the retention sample for each batch of an orthodox pharmaceutical manufactured should be appropriately stored for at least one year after the expiry date (or three years after the final distribution, whichever is longer) of the batch and should be sufficient to conduct two full compendia or specification analyses (WHO, 2005, p. 63 and ICH, 2000, p. 25). However, in the case radiopharmaceuticals, at the end of the retention period the radioactivity of the product would have decayed completely, limiting the evaluation of the sample to the chemical analysis only.

Sampling of orthodox pharmaceuticals (for QC testing) is required to be carried out in dedicated facilities, except when in-process samples are being taken (WHO, 2005, p. 65). This is to ensure that the environment is not contaminated by the product but also to ensure that the sample is not contaminated by the environment. Due to the radioactivity associated with radiopharmaceuticals, this is not possible. Therefore, in order to ensure that the samples are free from contamination additional controls such as the use of once-off consumables and tools are implemented.

Sampling tools used for the preparation of the samples are required to be made of inert materials, and kept scrupulously clean (WHO, 2005, p. 68). This is to ensure that the tools themselves do not become a source of contamination during the sampling process. However, in the manufacture of

radiopharmaceuticals new sampling tools are required for each batch manufactured to eliminate the spread of radioactive contamination.

The requirements for sampling and storage of retention samples stems from GMP, and no similar requirements exist within the nuclear regulations. Nevertheless, the requirements for As Low As Reasonably Achievable (ALARA), as well as the facility limitations (sample sizes are required to be adequate for the minimum prescribed analyses only so as to ensure that the storage of multiple samples do not violate the facility license) with respect to allowable limits of radioactivity, are to be adhered to. Therefore, additional controls are implemented in order to adhere to both the GMP requirements, as well as the nuclear regulations.

In addition to sampling for QC analysis, the requirement for in-process sampling also exists. In-process sampling takes place during the manufacture of the orthodox pharmaceutical product to ensure that the process is in control and shall yield a product of the desired quality and purity (WHO, 1999, p. 68). However, due to the radioactive nature of radiopharmaceuticals as well as the risk of radiologically contaminating the product, in-process sampling before all process steps have been completed is not possible. The high levels of radioactivity would render the product not safe to be handled by the process or QC operators.

Sterile FPP's are required to exclude microbial contamination, which is determined using the standard method for testing of sterility, as used for orthodox pharmaceuticals. Unfortunately though, due to the short shelf-life of the products, it is not always possible to obtain the results of such tests prior to the release of the products. Therefore, a system of parametric release should be implemented to ensure that the product is manufactured according to approved procedures of a validated method. In this case, the final sterility results are used as confirmation of the control of the manufacturing process (WHO, 2014, p. 177).

Many radiopharmaceutical FPP's are formulated as parenteral products, thereby requiring that they be sterile before administration. The MCC guide for the Manufacture of Radiopharmaceuticals has noted that the radioactive nature of radiopharmaceuticals is not sufficient to produce a sterilizing effect (MCC, 2003, p. 4). Therefore sterile radiopharmaceutical products are required to be terminally sterilized either by autoclaving or by filtration. Either way, the manufacturer shall ensure that the sterilization cycle was effective by conducting appropriate sterility testing of the product. No guideline exists which provides guidance on the sterility procedures which may be applied to radiopharmaceuticals. Therefore, the standard methods for sterility testing, as employed for orthodox pharmaceuticals, should be applied. The European Pharmacopoeia cites two methods of which the most applicable method should be employed. The European Pharmacopoeia General Monograph for Radiopharmaceutical Preparations recommends the membrane filtration method of sterility testing, in order to limit the exposure of personnel to the radioactivity of the product (Council of Europe, 2014, p. 762). However, due to the small batch size of most radiopharmaceutical products, this method is not always the most suited method, due to the size of the sample required. In cases where the sample size required is larger than the batch size, the direct inoculation method is preferred. During the validation of the direct inoculation method, to assess its applicability to the product, the introduction of a control culture encourages the growth of micro-organisms to prove that their growth is not suppressed by the nature of the product. This means that bacterial growth is encouraged during the method suitability testing of the method. It is for this reason that the method suitability testing is conducted on a sample of radiopharmaceutical which has decayed sufficiently, so as to ensure that the radioactivity of the product does not hamper the growth of the control cultures. Should the sterility testing be conducted on a sample which has not sufficiently decayed, the radioactivity of the product will destroy the bacteria, thereby effectively killing them, resulting in no bacterial growth. However, as has already been stated, the self-sterilizing effect of radiopharmaceuticals cannot be claimed. This implies that the sterility sample is required to sufficiently decay (about 10 physical

half-lives of the isotope), prior to the initiation of the sterility testing, which in itself requires 14 days of inoculation before a result of the sterility of the batch can be assessed.

The measurement of the radiochemical purity and radionuclidic purity of a radiopharmaceutical, are the methods which may be employed in order to determine the purity and level of impurities of a radiopharmaceutical product. These are determined in orthodox pharmaceuticals by chemical analyses for purity and impurity levels.

The radiochemical purity is the ratio of the radioactivity of a radionuclide in a particular chemical form, to the total radioactivity of that radionuclide within the preparation (WHO, 2014, p. 163). Radiochemical impurities may form during the radiolabeling process of the FPP, or as a result of decay, radiolysis or radioactive degradation. Radiochemical impurities may result in an altered bio-distribution and poor imaging quality, should the impurities be too high (Vallabhajosula, Killeen, and Osborne, 2010, p. 223). Radionuclidic purity of a preparation however, may be defined as the ratio of the radioactivity of the radionuclide to the total radioactivity of the preparation (WHO, 2014, p. 164), which is dependent on the quantities of the radionuclide as well as other contaminants, their half-lives, as well as the changes in their quantities over time (Vallabhajosula, Killeen, and Osborne, 2010, p. 222).

Following the manufacture, the batch of product is released for use to the market. Generally for orthodox pharmaceuticals this is done only once all the QC results, comprising of both physicochemical as well as biological testing, is available and the QA department has confirmed the batch's compliance to all applicable specifications. However, for sterile orthodox pharmaceuticals the concept of parametric release is available, whereby the manufacturer may release the batch prior to the availability of the final sterility results, and / or following a reduced physicochemical testing program, if they have implemented an adequate sterility assurance program. This authorization to implement parametric release is however subject to approval by the regulatory body (PIC/S, 2007a).

However, due to the short shelf-life of radiopharmaceutical products the need may arise whereby the product is required to be released from the control of the manufacturing company before all the QC results are available. This is to ensure that it is accessible to the patient before it has decayed completely (or to unusable radioactivity levels) (MCC, 2003, p. 4). In addition, the concept of parametric release may be applied to sterile radiopharmaceutical FPP's, in order to ensure that the patients receive the product timeously.

The Q7 guideline for GMP requirements for API's requires that during supplier qualification the first three batches of a raw material shall be tested for the full range of impurities possibly present, and thereafter, one batch shall be periodically tested (ICH, 2000, p. 17). To establish the requirements surrounding the testing of elemental impurities in orthodox pharmaceuticals the ICH Q3D guideline shall be applied. However, the Q3D guideline excludes radiopharmaceuticals from its scope, meaning that this guideline does not apply to radiopharmaceutical products (ICH, 2014, p. 1). Additional controls pertaining to the supplier qualification, as well as the laboratory control may however be implemented to ensure that the raw materials used in the manufacture of radiopharmaceuticals, are of the required quality. In addition to this, the requirements pertaining to Good Distribution Practices shall also be employed to ensure that the quality of the materials is not compromised during the transport of the material from the manufacturer.

Distribution and Packaging Considerations:

Good Distribution Practices for orthodox pharmaceutical products ensure the quality and identity of orthodox pharmaceuticals during all aspects of distribution, from procurement up to distribution and transportation. This is to ensure that the quality of the products is not compromised as a result of the supply chain, while at the same time ensuring that counterfeit products are not introduced into the market via the distribution chain (WHO, 2010b, p. 236).

The WHO Technical Report Series no 957 annex 5 provides guidance on Good Distribution Practices for orthodox pharmaceuticals and is applicable to both prescription as well as Over-The-Counter products. However, it does not make the explicit inclusion nor exclusion for radiopharmaceuticals (WHO, 2010b, p. 237 – 238). This guideline establishes the requirements for Good Distribution Practices, to which a distributor is required to conform, similar to that of GMP to which a manufacturer is required to adhere in order to establish a Pharmaceutical Quality System (PQS). It also includes the specific requirement to ensure that the transport of the orthodox pharmaceutical is done so in a manner which does not compromise the distribution chain (WHO, 2010b, p. 255 – 256).

In addition, radioactive materials are required to be transported in such a manner and under such conditions that the safety of the personnel and the environment is assured (IAEA, 2012, p. 2). The IAEA Safety Standard Regulations for the Safe Transport of Radioactive Material set out these regulations, including the packaging requirements for the radioactive materials.

The type and limitations of each package (which is designed based on the “Russian-dolls” concept in order to provide the required amount of shielding and containment) is based on the material being transported and is required to be licensed by the applicable regulator. The license is based on the evidence provided from drop tests and/or fire tests confirming that the package is able to provide sufficient protection, both during routine transport, as well as during emergency situations.

Although the requirements for the transport and distribution of pharmaceuticals ensure the overall integrity of the entire supply chain, the additional regulations, as discussed above, pertaining to the transport of radioactive materials ensure that sufficient protection is provided for the nature of the radiopharmaceutical products.

8. Conclusions and/or Recommendations

General Background:

Radiopharmaceuticals are fast becoming the option of choice for fast and painless diagnosis and treatment of many cancers, as well as cardiac, neurological and endocrinological conditions, amongst others.

In addition to the advantage of radiopharmaceuticals being applied to both diagnostic as well as therapeutic applications, they are capable of detecting diseases very early in their progression, making the patient outcome and disease prognosis far more positive, than with conventional diagnostic and therapeutic applications.

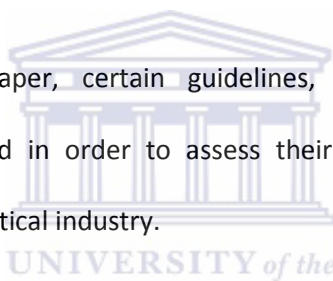
As the radioactive nature of the radiopharmaceutical itself is used to produce the diagnostic or therapeutic effect of the product, concepts such as the total radioactivity, radioactive concentration, radionuclidic purity and radiochemical purity of the product are important aspects to be monitored by the radiopharmaceutical manufacturer. The radioactivity of the product should be of such a concentration to produce the desired effect without compromising the health of the patient further. Furthermore, as the radiopharmaceutical is administered by introducing it into the patient's body, for example by injection, it is required to be manufactured according to the applicable guidelines. Therefore, the product shall be manufactured in a facility, which meets the applicable environmental air quality requirements, using a process which has been developed to consistently produce a product of the acceptable quality standards for its intended use. Following the manufacture, the product shall be analyzed using applicable QC methods, to confirm that the manufacturing process has yielded a product of the desired quality. Thereafter, the radiopharmaceutical shall be released and transported as per the pertinent transport

regulations, within the shortest possible time, to ensure that the final user of the product receives it before the product has completely decayed.

However, the radiopharmaceutical manufacturer has the added obligation of ensuring that the processes involved in the manufacture of the radioactive product, does not cause harm to those employees involved in its manufacture, QC, or transport, nor does the manufacturing process result in excessive amounts of radioactivity being released in to the surrounding environment.

To ensure that these requirements are met, and that the product is available to those patients in need of them, the radiopharmaceutical manufacturer shall adhere to all applicable regulations related to these processes.

During the completion of this paper, certain guidelines, applicable to the manufacture of radiopharmaceuticals, were reviewed in order to assess their applicability to the manufacture of medicines within the radiopharmaceutical industry.



Although several similarities, between the nuclear regulations and the pharmaceutical regulations were noted, the main conflicts were highlighted and evaluated above, and their corresponding conclusions are presented below. Such conflicts, if reviewed in isolation, and not implemented, would result in the radiopharmaceutical facility being non-compliant to the requirement in question, and therefore certain compromises were found to be critical in ensuring that the facility would still be compliant to the intent of the requirement, while not being able to implement the requirement itself as specified.

Facility and Equipment Considerations:

From the discussion above, it is clear that the cGMP and nuclear requirements for ventilation systems in a manufacturing facility conflict, particularly in the area of their respective functions, as well as in the area of pressure cascades. Should either one of the two guidelines discussed above, be implemented in

isolation of the other, the facility in question shall not meet the requirements as established in the conflicting guideline. This in essence implies, that should the ISO requirements for nuclear facilities be implemented without consideration of the GMP requirements, then the facility shall not be deemed as GMP compliant by the pharmaceutical RA and therefore not worthy of certification as such. The opposite scenario applies as well.

One industry norm or concession which may be implemented to overcome this, is the implementation of a positive pressure cascade, for example in the form of a Laminar Airflow Cabinet, within a negatively pressured environment. This will ensure that the negative pressure cascade is maintained, thereby ensuring that the radioactive contamination is contained within the area of highest radioactive contamination, whilst still ensuring that the positive pressure cascade prevents the contamination of the product with any environmental or particulate contaminants.

Therefore, it is recommended that the GMP guidelines be adapted to incorporate the requirements for nuclear facilities to ensure that should this guideline be adopted in isolation of other requirements, the applicable facility shall still comply to all applicable requirements governing the manufacture of radiopharmaceuticals.

Alternatively, radiopharmaceutical manufacturers may choose to adopt the WHO Technical Report Series No. 957, 2010, Annex 3, which specifies the GMP requirements for the manufacture of pharmaceutical products containing hazardous substances, together with the ISO 17872:2004 guideline. Even though this GMP guideline is applicable to the manufacture of pharmaceutical products containing hazardous substances such as steroids, cytotoxines and hormones, many of the requirements are more closely aligned with those of the nuclear facility requirements than the standard GMP guidelines discussed above.

As the primary focus of the WHO guideline relates to the HVAC system of a facility (WHO, 2010a, p. 193), requirements for ensuring the quality of the product, such as the protection from contamination, are

based on the standard GMP Guidelines (WHO, 2010a, p. 198). Therefore this guideline, albeit closer to the requirements for radiopharmaceutical facilities, is not sufficient to be implemented in its entirety in isolation to the other guidelines, as discussed above, and certain concessions may still be required. Even though this guideline makes provision for a negative pressure cascade in relation to the environment, it still requires that normal pharmaceutical pressure cascade requirements be adhered to. This implies that a positive pressure cascade is still required in order to prevent contamination from environment contaminants, and therefore a positive pressure cascade may still be required within the negative pressure environment, as discussed above.

Manufacturing Considerations:

A radiopharmaceutical manufacturing facility is required to be licensed by the applicable regulator to handle the radioactive material. This license and its limitations are based on the established process methods and parameters, including the identified waste streams. Furthermore, the facility is required to ensure the safety of the personnel as well as the surrounding environment. These limitations are described in detail by the applicable nuclear regulator. However, the applicable GMP guidelines fail to provide guidance in this regard to ensure that neither the product quality and patient safety, nor the personnel and environmental safety is compromised.

Quality and Safety Considerations:

Due to the inherent nature of the radiopharmaceutical, the sampling process is one which poses a great concern from a nuclear/radiological protection point of view. The samples are required to be prepared with extreme caution and care so as not to contaminate the sample or increase the radiological exposure of the personnel involved in the process, as per ALARA (As Low As Reasonably Achievable) principle. Furthermore, the care with which the samples are required to be handled and stored extend to the QC analyses and retention sample storage as well.

As the size of a radiopharmaceutical batch is exponentially smaller than the standard size of an orthodox pharmaceutical batch, the sampling tools and methodologies, as well as the size of the samples, described in the WHO guideline for sampling of pharmaceutical products and related substances, are not suitable for the sampling requirements for a radiopharmaceutical product. However, no alternatives have been described in the aforementioned guideline. In addition, the WHO guideline for sampling prescribes the number of samples, which are required to be analyzed as is, without any further manipulations, in order to obtain a result which is a true reflection of the batch in question. The implementation of this requirement proves to be difficult in the manufacture of radiopharmaceuticals. Each radiopharmaceutical facility is licensed for the possession and use of radioactive materials, which includes facility specific radioactivity limitations. This means that for a QC laboratory to receive the QC samples, and conduct the analyses, the sample in question may be required to be diluted to an activity range which is within the QC laboratory's facility license as well as the QC equipment activity limitations. This concept is further supported by the activity requirements as specified for the QC method, for example within the pharmacopoeia, which implies that the sample is required to be diluted prior to the QC analyses being conducted as the activity of the batch would be far greater than that which is required by the method.

The primary guidelines for GMP for API's (ICH Q7) makes a direct requirement pertaining to the testing of impurities (in raw materials), however the supplemental guideline (ICH Q3D), which is recommended to be consulted in order to ensure compliance to this requirement, does not apply to radiopharmaceutical products. No replacement guideline has been established to fulfill this requirement, and since this requirement originates from GMP principles, no such guideline exists within the nuclear regulatory environment. As noted in section 7 above, the control of impurities in raw materials is paramount to ensuring the quality and purity of the product, which in turn ensures its successful application, i.e. the quality of the scan, etc.

In order to ensure that radiopharmaceutical products reach the applicable patients before they have decayed completely (or to unusable radioactivity levels), they are required to be released to the market prior to all the QC results being available. Sterile radiopharmaceutical FPP's may be released under a parametric release authorization granted by the regulatory authority, which may assist in ensuring that the product reaches the market timeously. However, the concept of parametric release does not apply to radiopharmaceutical API products, and since the requirement to have the API reach the FPP manufacturer with sufficient time to manufacture the FPP and release this to market also exists, the onus rests with the API radiopharmaceutical manufacturers QA department to ensure that the product meets the applicable specifications. In addition to this, orthodox pharmaceutical API products are not required to be manufactured under the direct control of a responsible pharmacist or qualified person. Therefore, the release of the batch, prior to the availability of all QC results, lies with the QA department only.

As has been discussed above, the sterility testing methods for orthodox pharmaceuticals as is required to be applied for radiopharmaceuticals, has its own challenges and short-comings. For example in the size of sample required for testing, as well as the time required to allow for the decay of the sample prior to testing, which in many cases may be longer than the shelf-life of the product itself rendering the testing baseless. However, one option which has been employed within the orthodox pharmaceutical industry, to decrease the lead-time required to obtain the sterility results, is the rapid sterility test. This method has its basis in the positive identification of bacterial growth in a sample, based on the release of carbon dioxide gas which is given off by the bacteria during its growth. This method however has been found to not be effective for radiopharmaceutical products, due to the fact that carbon dioxide gas is given off by radiolysis during radioactive decay, possibly leading to false-positive results (Chen, Rhodes, Larson, et al, 1974, p. 1143). Another method of the rapid sterility test, is based on the consumption of oxygen by the bacteria during its growth, however the same effect is seen during decay, and therefore renders this method also ineffective. It is therefore noted that the sterility testing for orthodox pharmaceuticals is

found to be inadequate for implementation for radiopharmaceutical products, and no alternative guidelines are provided by the applicable regulators. However, the sterility process is validated according to conventional sterility methods in order to ensure that the methods are adequate for their intended use to support parametric release.

In addition, orthodox pharmaceuticals are required to be analyzed using a higher grade of reagent than those used during manufacturing to ensure that the product sample is not contaminated with impurities during the QC process. However, as mentioned above, the control of impurities in a radiopharmaceutical product, and therefore the limits associated with these impurities are usually far stricter than for orthodox pharmaceuticals. In addition, the laboratories available to analyze these reagents, which possess the competencies and equipment required, are few and far between. In this case, the analytical grade reagents recommended for the QC of the orthodox pharmaceutical is of a lower grade than the reagents used during the manufacture of many radiopharmaceutical products. However, due to the lack of guidance in this area, no concessions or industry specific norms exist, thereby making the control of materials used in the manufacture of radiopharmaceuticals, according to standard GMP principles, a challenge. One way of overcoming this challenge is to obtain robust assurances from the raw material manufacturer of its quality systems, as well as its distribution chain, in order to mitigate the risk of obtaining materials which are of sub-quality. In addition, assurances from the QC laboratory, will also assist in ensuring that the methods employed do not contaminate the sample by introducing additional impurities into the sample. These two assurances combined, should provide the radiopharmaceutical manufacturers with the confidence that the raw materials are of the required quality, to ensure that these will not be the contributory factor to a final product which is not of the required specification.

Distribution and Packaging Considerations:

Once again there is very little overlap between the GMP and nuclear guidelines in terms of distribution and transportation of radiopharmaceuticals. The Good Distribution Practices guidelines primarily focus on ensuring that the product quality is maintained throughout the supply chain and that the distribution chain remains intact so as to ensure the authenticity of the product. While the transport regulations applicable to radioactive materials primarily focus on ensuring that the radioactive nature of the products are contained to such a level so as not to pose a threat to the personnel and surrounding environment.

Each guideline in isolation is insufficient to ensure that radiopharmaceuticals are transported and distributed adequately and therefore the risk remains of non-compliance, should only one of the two be implemented. Therefore, both regulators requirements shall be met.



Tabulated below is a summary of the main conflicting regulations and the current or proposed solutions:

Chapter	Conflicting regulations		Current / Possible solutions
	Radiopharmaceutical	Pharmaceutical	
General Background:	Rapid decay, limiting shelf-life to between hours to weeks.	Shelf life ranges from days to years.	Limited shelf life requiring immediate administration to patients.
	Therapeutic and diagnostic effect.	Therapeutic effect due to pharmacological effect of the pharmaceutical.	Diagnostic or therapeutic effect as a result of shedding of radioactive particles, using minute concentrations of the radiopharmaceutical resulting in biodistribution at a molecular level.
	Shelf-life is determined by physical half-life of the radionuclide and/or the stability of the API or FPP.	Shelf-life is determined by the stability of the pharmaceutical.	Product with short-shelf requiring immediate administration to patients.
	Purity and quality influences bio-distribution, quality of the nuclear scan and accuracy of diagnostic procedure as well as the therapeutic effect i.e. impurities could cause damage to non-target organs.	Purity and quality ensures the therapeutic effect and prevents adverse effects as a result of the product.	High purity starting materials in order to ensure high purity end products.
	QC testing includes physicochemical, radionuclidic purity, radiochemical purity as well as sterility testing.	QC is generally limited to physicochemical and sterility testing.	Highly-Sensitive QC instrumentation and test methods.
Facility & Equipment:	HVAC system designed to protect personnel and environment and prevent spread of radiological as well as environmental contamination.	HVAC system designed to protect from dust, chemical & microbial contamination.	HVAC system designed to meet radiological and pharmaceutical requirements.
	Negative pressure cascade.	Positive pressure cascade.	Negative pressure cascade with biological safety cabinets.
	Facility door open into lower pressured area.	Facility doors open in to higher pressured area.	Facility door open into lower pressured area.
	HEPA filters at supply and exhaust end of ventilation system.	HEPA filters at supply end of ventilation system.	HEPA filters at supply and exhaust end of ventilation system.

	Radiological contamination prevents HEPA Filter integrity testing.	HEPA filter integrity testing required from within room.	In-line monitoring of differential pressure, more frequent replacement of filters.
Manufacturing:	Neutron bombardment of target materials in a nuclear reactor; charged particles bombardment of target materials in a cyclotron; nuclear fission of heavy nuclides after neutron or particle bombardment; or from a radionuclide generator.	Standard solid, liquid or ointment formulation according to Q11 guideline.	Manufacturing process applicable to the radiopharmaceutical product.
	Use of in-house built closed- or semi-closed systems.	Standard off-the-shelf equipment.	In-house built closed (or semi-closed) systems.
	Starting materials based on sensitivity of the process.	Starting materials based on Q3 guideline.	Q3 guideline to be updated to include radiopharmaceutical products
	Use, control and release of ultra-pure starting materials.	Use, control and release of pharmaceutical grade starting materials.	Extra controls in the form of supplier qualifications, method validations, standardized procedures and stringent training programs may be required.
	No guideline for validation of radiopharmaceutical products.	Q11 guideline used for validation of pharmaceuticals.	Q11 guideline to be updated to include radiopharmaceutical products.
	Radiological & chemical waste streams.	Chemical waste streams only.	Waste streams to be identified and controlled.
Quality & Safety:	Retention sample Size and storage period not possible due to radiological activity and decay of the sample.	Retention sample size sufficient for two full analyses, stored for 1 year after expiry.	Retention sample stored for 3 months with sufficient activity to conduct 2 full analysis at time of sampling.
	In-process sampling not possible due to radiological contamination.	In-process sampling required.	Sampling and testing of all reagents used in production, as well as of the final product.
	Sampling tools should eliminate the spread of radiological contamination.	Sampling tools should not be a source of contamination.	New sampling tools are required for each batch manufactured.
	Batch size = very small volumes.	Batch size = thousands of tablets or capsules or solutions.	Small volume batch sizes.

	Sterility test results available 14 days after testing, however radiopharmaceutical had usually already decayed.	Sterility test results available 14 days after testing.	Sterility test results available post shelf life, and therefore serves as confirmation of the sterility assurance program only.
	Sterility testing according standard sterility testing methods.	Sterility testing according standard sterility testing methods.	Sterility assurance program (including validation of the sterility testing method) and parametric release.
Distribution & Packaging:	Distributional according to Good Distribution Practices and IAEA transport regulations.	Distribution according to Good Distribution Practices.	Good Distribution Practices and IAEA transport regulations used for the distribution of radiopharmaceutical products.
	Licensed packaging according to "Russian-doll" concept.	Approved primary and secondary packaging based on the impact to the product.	Transport packages licensed by applicable regulator, shielding sufficient to prevent radiological contamination.



Recommendations:

Based on the findings and discussions above, it has been noted that the only concise and explicit guideline available for the manufacture of radiopharmaceutical products, are the MCC guide for the manufacture of Radiopharmaceuticals as well as the pharmacopoeia chapter on Radiopharmaceuticals. All other guidelines are applicable to orthodox pharmaceuticals mainly, with most making the exclusion for radiopharmaceuticals. Furthermore, the MCC guide does not explicitly refer to API's, and is very general in its guidance to radiopharmaceutical manufacturers.

Even though most guidelines make the disclaimer that all applicable regulations should be adhered to, a gap exists where no or very limited guidance is provided in the control of the manufacture of radiopharmaceuticals. Where guidance does exist, this is very vague and general, and does not specify the need for concessions that may be required in order to comply with all conflicting regulations governing this industry.

Even though all applicable guidelines make the statement that local and applicable requirements shall be adhered to, and that requirements may vary from application to application, they still require that all regulatory requirements are adhered to. However, from the information presented above, it is clear that many cases exist in the radiopharmaceutical industry, where the requirements from one regulator conflict with those of the other regulator and when the requirements of one regulator are adopted over the requirements of the other regulator, it is obvious that the requirements of the latter shall not be met.

Therefore, industry norms and concessions are required in order to ensure that radiopharmaceuticals are manufactured to the standards required and that the industry is regulated adequately and consistently.

To ensure consistency within the concessions allowable within this industry, it is recommended that the current GMP guideline governing the manufacture of radiopharmaceuticals (MCC Radiopharmaceutical Manufacturing guideline) should be reviewed and revised, in consultation with radiopharmaceutical

experts. This review should identify areas where the manufacture of radiopharmaceuticals may be compromised because of conflicting requirements and should also include acceptable concessions, which may be consistently implemented within the industry. This shall ensure that radiopharmaceuticals are manufactured and the industry is regulated to the same standards as orthodox pharmaceuticals, without being subjected to requirements which are difficult to implement.

Although it is the responsibility of the manufacturer to ensure that they adhere to all applicable regulations, it is the responsibility of the RA to assess the level of compliance based on the implementation of said guidelines. If industry norms and concessions are not standardized within the applicable guidelines, firstly radiopharmaceutical manufacturers may be found to be “non-compliant” to certain requirements, and secondly, the adoption and implementation of industry norms and concessions will be open to interpretations. This would then be subject to personal biases, experience and knowledge, both within the industry as well as the RA.

Therefore, if the guidelines are reviewed and improved to include the industry norms and concessions, such as those discussed above, these will become the new standardized requirements to which the radiopharmaceutical industry will be required to adhere. These will then no longer be subject to personal interpretations, and will thus also enable the RA to ensure that the industry is compliant to the set requirements and therefore regulated as adequately as the orthodox pharmaceutical industry.

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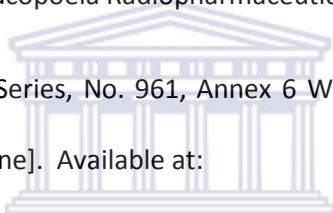
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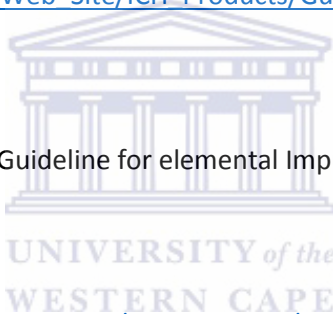
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10. Appendices

10.1. Research Proposal

Title:

A qualitative evaluation on the appropriateness of current regulatory guidelines, on the manufacture of medicines within the radiopharmaceutical industry.

Introduction:

Although radiopharmaceuticals have been employed in patients for more than 60 years, it is a field which is constantly being refined and renewed, in order to ensure that only the latest technologies are available to patients.

Radiopharmaceuticals, in the treatment and diagnosis of diseases, permit the collection of information and identification of abnormalities, long before they would become apparent using other diagnostic methods. This in turn allows for diseases to be diagnosed and treated early enough to ensure a positive prognosis, or influence the treatment plan, and monitor the patient's response to the treatment.

Radiopharmaceuticals are used to detect abnormal lesions deep within the body, or even if certain body organs are functioning optimally. Furthermore, radiopharmaceuticals may be used to treat hyperthyroidism, bone pain or certain types of cancers (SNMMI, 2004).

The gamma rays emitted from the radioactive isotopes allow the radiopharmaceutical to be traced or imaged non-invasively, providing information of the target organ or tissue, as part of the diagnosis process. During therapy, the alpha or beta rays emitted from the radioisotope partially or completely destroy the diseased tissue (WHO, 2014).

Because of the rapid and widespread growth in the use of radiopharmaceuticals, novel radiopharmaceuticals have been and are constantly being researched and introduced into the commercial market.

Since these radiopharmaceuticals are introduced into the patient's body, either via injection, orally or inhalation, they are required to be manufactured according to current Good Manufacturing Practices (cGMP). In addition to this, these radiopharmaceuticals are required to be evaluated and approved by the applicable pharmaceutical regulators prior to being marketed and used.

One of the main differences between radiopharmaceuticals and orthodox pharmaceuticals, is the short shelf-life of the radiopharmaceutical product, which stems from the short half-life of the radionuclide, which is a result of the isotopic decay of the product (WHO, 2014).

As with orthodox pharmaceuticals, radiopharmaceuticals may be classified as Active Pharmaceutical Ingredients (APIs) or Final Pharmaceutical Products (FPP's). An example of a radiochemical API is the product obtained from the chemical extraction of a radioisotope from irradiated target plates, and an example of a radiopharmaceutical FPP, is a radionuclide generator system, which utilizes a relatively long-lived parent radionuclide, which decays to a daughter radionuclide that has a shorter half-life. The daughter radionuclide is then separated from the parent radionuclide on the generator either by a chemical or physical process (WHO, 2014).

Medicinal products manufactured within the orthodox pharmaceutical as well as the radiopharmaceutical industries are currently regulated and manufactured according to the same set of guidelines, even though comprehensive differences exist in the manufacturing processes within these two industries. Therefore, this research paper aims to evaluate the appropriateness of the current regulatory guidelines, on the manufacture of radiopharmaceuticals.

Hypothesis: If current regulatory guidelines (as utilized for the manufacture of orthodox pharmaceuticals), are employed for the manufacture of radiopharmaceuticals, without industry specific concessions, then radiopharmaceuticals may not be as appropriately regulated as orthodox pharmaceuticals.

Methodology:

The method for gathering information in a research project, depends on the nature of the information that is intended to be collected, in order to arrive at recommendations in the identified area of improvement.

To arrive at recommendations for improvement in the field of regulatory guidelines employed for the manufacture of radiopharmaceutical products, the identified method of data collection shall be a mixed method, comprising of a qualitative review, while comparing its applicability within the radiopharmaceutical industry.

The qualitative technique which is envisaged to be employed, shall comprise of the collection and review of current guidelines, in comparison to their appropriateness and applicability within the radiopharmaceutical industry, using industry specific nuclear norms as the basis for the comparison. As the originator of this research is employed within the radiopharmaceutical industry, the risk of inherent bias exists, however, all efforts shall be made, to eliminate this risk.

The consideration of stability and internal reliability shall be taken, to ensure that the results obtained are reliable and consistent with the research hypothesis. It is envisaged, that the consideration of inter-observer consistency shall not be required, as only one researcher shall be involved in the compilation of this paper.

Measurement, internal validity and external validity shall also be taken into consideration, to ensure that the results obtained are valid.

Refer to Gantt Chart below for project milestones.

Ethical Considerations:

When conducting research, it is important to ensure that the rights of the research participants are upheld and protected. Researchers (together with research ethics boards) are required to obtain valid consent from the participants, protect their confidentiality, and maintain sensitivity, while at the same time respect cultural diversity.

Since not all countries include ethics in the applicable laws of the country, a universal code of ethics exists, which provides guidance for a common standard, across all disciplines. This universal ethics code, is comprised of The Nuremberg Code, The Declaration of Helsinki, and the International Conference on Harmonization of Good Clinical Practice (ICH GCP).

Ethical principles originating from the Declaration of Helsinki, should be taken into consideration when developing a research project comprising of a clinical trial. The rights, safety and well-being of the participants prevail over the interests of society and science. Therefore, compliance with standards such as the ICH GCP Guideline, provides assurance of this, in consistency with the principles of the Declaration of Helsinki, and that the clinical trial data obtained from the study is credible (EMA, 2002).

However, not all research projects require ethical consideration and approval from research ethics boards. Research projects, which do not include interventional studies, studies using patient samples, or studies asking sensitive questions do not require ethical consideration and approval.

Since it is planned that this research paper shall not include any interventional studies, using patient samples, nor asking sensitive questions, it is concluded that ethical consideration and approval for this paper is not required.

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Gantt Chart:

May 2016	June 2016	July 2016	August 2016	September 2016	October 2016
1. Project Planning Duration 28 Days Start: 2016/05/01 End: 2016/05/28					
	2.Proposal Compilation Duration 20 Days Start: 2016/05/29 End: 2016/06/17				
		3.Literature Collection Duration 27 Days Start: 2016/06/18 End: 2016/07/14			
			4.Detailed Literature Review Duration 31 Days Start: 2016/07/15 End: 2016/08/14		
				5.Detailed Literature Analysis Duration 35 Days Start: 2016/08/15 End: 2016/09/18	
					6.Thesis compilation Duration 43 Days Start: 2016/09/19 End: 2016/10/31

Gantt Chart: Detailed break-down of tasks

No	Task Name	Duration (days)	Start	Finish
1	Project Planning	28	2016/05/01	2016/05/28
1.1	Topic Identification	4	2016/05/01	2016/05/04
1.2	Proposal and Methodology Planning	5	2016/05/05	2015/05/09
1.3	Ethical Considerations	5	2016/05/10	2016/05/15
1.4	Preliminary Literature Review	14	2016/05/16	2016/05/28
2	Thesis Proposal Compilation	20	2016/05/29	2016/06/17
2.1	Draft 1 Compilation	14	2016/05/29	2016/06/11
2.2	Draft 1 Review	3	2016/06/12	2016/06/14
2.3	Proposal Finalization	2	2016/06/15	2016/06/16
2.4	Thesis Proposal Submission	1	2016/06/17	2016/06/17
3	Literature Collection	27	2016/06/18	2016/07/14
3.1	Preliminary Research	7	2016/06/18	2016/06/24
3.2	Detailed Research	20	2016/06/25	2016/07/14
4	Detailed Literature Review	31	2016/07/15	2016/08/14
4.1	Data Mining	7	2016/07/15	2016/07/21
4.2	Selection of Valid Data	7	2016/07/22	2016/07/28
4.3	Draft 1 Detailed Literature Review	14	2016/07/29	2016/08/11
4.4	Review of Draft 1 Detailed Literature Review	3	2016/08/12	2016/08/14
5	Detailed Literature Analysis	35	2016/08/15	2016/09/18
5.1	Review of collected data	14	2016/08/15	2016/08/28
5.2	Analysis of collected data	15	2016/08/29	2016/09/12
5.3	Finalization of Literature Review	5	2016/09/13	2016/09/17
5.4	Submission of Literature Review	1	2016/09/18	2016/09/18
6	Thesis compilation	43	2016/09/19	2016/10/31
6.1	Compilation of Draft 1 of Thesis	22	2016/09/19	2016/10/10
6.2	Review of Draft 1	3	2016/10/11	2016/10/13
6.3	Compilation of Final Draft of Thesis	12	2016/10/14	2016/10/25
6.4	Review of Final Draft of Thesis	4	2016/10/26	2016/10/29
6.5	Finalization of Thesis	1	2016/10/30	2016/10/30
6.6	Final Submission of Thesis	1	2016/10/31	2016/10/31

10.2. CASP Checklist – Summary

Screening Questions:	Result:	Comment:
1. Was there a clear statement of the aims of the research?	Yes	The aims are further clarified in the research proposal section.
2. Is a qualitative methodology appropriate?	Yes	Although it is noted that a survey within the industry may have proven to be more appropriate, however this was not considered due limited size of the industry, as well as the large amount of proprietary information associated with the topic.
3. Was the research design appropriate to address the aims of the research?	Yes	This is further confirmed by the comments from Examiner two.
4. Was the recruitment strategy appropriate to the aims of the research?	Not applicable	The study design did not include the recruitment of any study participants.
5. Was the data collected in a way that addressed the research issue?	Yes	Most of the important information on the topic was reviewed and considered.
6. Has the relationship between researcher and participants been adequately considered?	Not applicable	No participants were recruited in this study.
7. Have ethical issues been taken into consideration?	Yes	Although no participants were recruited in this study, ethical considerations were included in the research proposal.
8. Was the data analysis sufficiently rigorous?	Yes	An additional side-by-side review is tabulated to summarize the findings.
9. Is there a clear statement of findings?	Yes	Most important findings are included.
10. How valuable is the research?	-	The research is valuable to the radiopharmaceutical industry, and requires a wider audience, as comment by Examiner 1.