Pakistan Journal of Pharmaceutical Sciences
Vol.9(1), January 1996, pp.43-54

QUALITY ASSURANCE IN NUCLEAR MEDICINE - BIOLOGICAL QUALITY CONTROL OF RADIOPHARMACEUTICALS

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ABSTRACT

Quality assurance is the sum of all parameters concerning the preparation and control of a finished product. It is a wide term commonly used for the confirmation and validity of various ways and measurements adopted to obtain a high quality procedure for intended use with guaranteed performance. Biological quality control of pharmaceutical products becomes essential as they are ultimately to be consumed by living organisms, in particular the humans. In this review, we have discussed the importance and significance of biological quality control in nuclear medicine. The current and new procedures for sterility, apyrogenecity and the biodistribution quality control, have been discussed and evaluated in view of the future needs and modern trends in this important area of research.

Introduction

Quality assurance is known to be a comprehensive, specifically designed, well documented and properly implemented system alongwith the relevant information of equipment and personnel involved during various steps of production and quality control, which is furnished to the users of a finished product with ensured quality appropriate for the intended purpose. Important elements of a production system, are the operators, premises, equipment, working and documentation procedures and different quality control measures. In the quality assurance, all such parameters are to be taken into account to obtain the required quality based upon the developmental work and good manufacturing practice. An appropriate quality assurance programme is essential to prepare the intended items in accordance with the specifications, containing the correct amount of pure ingredients, processed as defined, packed in suitable containers properly

labelled, stored and transported according to the established standards taking all necessary measures.

Quality control mainly concerns with the sampling and testing according to the established specifications and documentation systems which provide the basis for quality certification upon the release of finished products for proper utilization.

Quality in not an absolute term as the safety and efficiency of a drug can never be in a static state. The quality of a given product may be acceptable under some specific circumstances but not the others. The possibility of dynamic advancements always remain there to obtain more useful products, in accordance with the emerging technical and economic opportunities.

The objective of producing high quality pharmaceuticals, has remained the aim for providing the patients, the highest possible degree of safety and care (WHO 1975, 1977). Production of high quality radiopharmaceuticals is of paramount importance in the field of nuclear medicine (Frier and Hasalewood 1980, US Deptt. of Health & Human Services 1981, WHO 1982, Gertude 1984). Keeping in view the possibility of continuous improvements in the quality, some initial and basic standards are first established before starting the regular production of a radiopharmaceutical. While setting some standards for a pharmaceutical product, different factors are considered important mainly for the evaluation of its safety and the efficiency (Kristensen and Norbygarod 1984). In chemical terms, there is no difference between a non-radioactive and a radioactive pharmaceutical. In all the cases a complete and well tested production system is a pre-condition to obtain a radiopharmaceutical of uniform quality as in case of a non-radioactive pharmaceutical. Exposure to radiation is however an additional risk which poses the possibility of an extra toxic effect. The problem however exaggerates further in case of poor manufacturing and quality control conditions. The weightage of the associated risks and benefits has to be considered at the same time while prescribing a radiopharmaceutical for an individual patient (Seminar on Bad. Prot. Luxembourg 1976, Hospital Physicists Association Bulletin 1977, ICRP 1977). Many radiopharmaceuticals do not have any measurable pharmacodynamic effects. The purpose of radiopharmaceuticals utilization is most often diagnostic which normally takes a few minutes for administration to each patient. The short time avail-able for the quality control tests has thus led to the development of many fast procedures for the evaluation of some important parameters even the shorter half life of some radiopharmanuclides, in no way can now prevent from establishing a standard regarding the limits for potency and impurities along the same lines as in case of non-radioactive pharmaceuticals.

In many parts of the world, the developing and under developed countries in particular, radiopharmaceuticals are not still a subject under the control of health authorities. The greater part of the responsibility with respect to evaluating the quality of

radiopharmaceuticals still lies on the shoulders of individual physicians and most of the quality control analysis is carried on ready for use products in the hospitals just before the clinical application (Deptt. of Health and Social Security 1977, Trott 1978, Kirstensen 1979). It is also not always easy to get sufficient and timely response from the manufactures to evaluate and confirm the results of such analysis. A similar situation arises when the raw materials or semi-finished products like isotope generators and cold kit precursors of radiopharmaceuticals are the subject of quality control. This practice of course, may cause some complications in individual patients for the want of good quality due to lack of proper quality control facilities in the hospitals. It becomes therefore essential to perform some necessary quality control tests before the despatch of such substances to the hospitals. Preparation of these materials according to the good manufacturing practice (GM') and quality control rules to comply with the specifications prescribed in different pharmacopoeia (British Pharmacopoeia 1988, European Pharmacopoeia, US Pharmacopeiae XX, and XXII.) or those set by some technical authority or even the physician if no other option is available, can en-sure the quality of a product to a large extent upon its use in the hospitals.

Quality control of radiopharmaceuticals and cold kits usually include, test of physical appearance, pH, radiochemical purity, chemical and biological stability, sterility, apyrogenecity, toxicity, biological distribution and metabolic behaviour. Here we are going to evaluate the most essential and common biological quality control measures for radiopharmaceuticals.

Toxicity

Toxicology studies are usually carried out in the development stage. Through in-vestigations are needed to be recorded at this stage and the toxicological data on the basis of studies in animal models and human volunteers, are documented for future reference (Heywood 1990, Roe 1991, Balls 1992). Once the toxic properties of a product have been established, there is no need to check them in the routine synthesis of the products unless some problem with the preparation procedure leading to the formation of some harmful by products, is suspected. However toxicity properties of a product may at random or occasionally be checked to confirm the quality and reliability of the procedures under practice. Toxicology studies of the cold kits are usually undertaken just like the development of other non-radioactive pharmaceuticals. Radioactive pharmaceuticals however pose an extra risk of radiation exposure, this aspect is thus kept under check again at the developmental stage. Different nuclear properties are the prerequisite for a radionuclide depending upon its application for incorporation into a radiopharmaceutical. Both the half life (biological and chemical) and the energy of the emitted radiation are important. For diagnostic imaging radionuclides decaying by gamma rays of 100-200 Kev or position (B^+) particle emission having relatively short half lives are considered suitable to be utilized in the preparation of diagnostic radiopharmaceuticals (Saha 1984).

Diagnosis nuclear medicine heavily relies on the use of ^{99m}Tg which is best suited for the purpose having 6.02 hrs. half life with 140 Kev emission making it the ideal one for the purpose of diagnostic imaging (Stagman and Ecketman 1992, Sadiq et al., 1994). Radiotherapeutic applications however need a higher energy and relatively longer half life as it involves cell destruction. This requires radionuclides decaying by particle emission (alpha, beta, Auger electrons) usually having a half life between 1-10 days (O'Brien 1983, Mausner et al., 1988). The choice of a radionuclide is dependent upon the individual radiotherapeutic application keeping in view the particular energies of the emitted particles and the half lives of the radionuclides. However the radionuclides of higher energies and longer half lives pose higher risks of radiation toxicity and other associated health problems.

Stability

Majority of the radiopharmaceutical are organic, bioorganic or bioinorganic molecules with a radionuclide as an essential part. The cooperation chemistry of the radionuclide (usually a metal) determine the ultimate geometry and stability of the radiopharmaceutical. 1n-vivo stability and the biological properties are the two main considerations in the design and use of a radiopharmaceutical. *In-vitro* stability is different from chemical and thermodynamic stability and the stability for a radiopharmaceutical that is important, is its kinetic stability. The biological systems contain different body fluids, in particular the blood circulating at a pH 7.4 and temperature 37°C. The proteins (poly and oligo peptides), enzymes, cells, amino acids etc. which are obviously natural candidates for complexation with metals, potentially challenge the integrity of the radiopharmaceutical. The compound/product must be stable enough to reach its targeted position and preferably must remain intact during its stay in the body. Again the studies on the *in-vivo* stability of a compound are usually carried out in the developmental stage and not considered necessary when it comes into the routine production and clinical practice. However it is preferred to follow necessary tests on every new batch during the shelf life of the product (Bayly and Evans 1968). This equally applies to the cold kits and the labelled products.

Sterility

In the production of medicine, very strict hygienic and aseptic standards should be followed. Usually one living organism in a million units, is admissible in very extreme conditions. While this single microorganism can render a product non-sterile. For the sake of sterilization, autoclaving and radiation sterilization procedures are usually adopted. Sterility testing criteria vary in different pharmacopoeia. A method prescribed for the determination of bacterial contamination may be used as an in-process control as well as for the final test of the finished product. Test for microbial contamination in radioactive product is, in general, best carried out by the filter method (Kristensen 1979,

European Pharmacopia). In such procedures the whole sample may be filtered and the fdters are washed and incubated in two different media, one for bacteria and the other for fungi. There is an advantage in this procedure that any bacteriostats if present in the product, ar also removed with the microorganism. Sterile bacterial growth media like bouillon, are used for sterility testing (British Pharmacopeia 1988). An increased sensitivity is achieved if the filtration method is used to determine the number of microorganisms in the medium passed through the system or used to simulate the process. Thus procedure should however not be employed where risk of any influence on the performance of the system is involved. In the regular production of radiopharmaceuticals like ^{99m}Tc radiopharmaceuticals (British Pharmacopoeia 1988, IAEA 1992), typically 4-10 vials are picked at random from each batch and these vials are reconstitued with 1 ml sterile saline. The sterility tests are performed in two media I) fluid thioglycollate medium and 2) soyabean casein digest medium. The media are prepared according to the manufacturer's guidelines. In fluid thioglycollate medium incubation is done at 30-35°C for 14 days while in soyabean digest medium at 20-25°C for the same period. The media are regularly examined during the incubation period and finally at the end, for a macroscopic evidence of microbial growth. If this visual test does not indicate the presence of any growth, the product is considered sterile. These tests however are time consuming and less reliable as one has to rely on the visual recognition of the microbial growth.

The short time available for rapid quality control of radiopharmaceutical both in terms of short half life and the shelf life, has led to the development of fast methods of quality control (Khurshid 1993). The whole philosophy of sterility tests has generally changed very much in this direction. The much rapid radiometric sterility test has emerged on the base of $^{14}CO_2$ release from the microorganism consuming ^{14}C labeled substrate when incubated at 37°C. This method was actually developed and used by NASA to test life on Mars (Levin 1962) and later on its was utilized for the detection of bacteria (Chen et al., 1973, Brookes and Sodeman 1974). The procedure was optimized by Johnston laboratories and an automated procedure is now available in the form of a compact system known as Bactec unit (Johnston Labs. 1984). The release of $^{14}CO_2$ indicates the presence of microbial contamination in the product and the amount of $^{14}CO_2$ is considered proportional to the bacterial growth. The procedure is very rapid as the whole process takes only 6 hrs to complete and very sensitive as it can detect even a single colony of bacteria. By this method, some other microorganisms can also be detected which otherwise cannot be detected even by the procedures given in U.S. Pharmacopeia. The procedure have been earlier reproduced and evaluated by us to test various radiopharmaceuticals and found very sensitive, rapid and reliable as compared to conventional methods except in case of volatile radiopharmaceuticals (Khurshid 1993). The method has been successfully utilized for the routine biological quality control of different ^{99m}Tc radiopharmaceuticals, under the existing conditions in our laboratory (Khurshid and Karim 1981, Khurshid et al, 1988).

Apyrogenecity

Pyrogens may enter into a product from raw materials, personnel or equipment. One important source of pyrogens is water. Pyrogens cannot be removed by membrane filtration or autoclaving. Their introduction into the product must be avoided be using pyrogen free raw materials/utensils and preventing their entry at any stage during the production process and the storage. Pyrogen testing is carried out according to the prescribed recommendation in different pharmacopoeiae (British Pharmacopoeia 1988, European Pharmacopoeia, US Pharmacopeiae XX. and XXII.). It is checked through rabbit test where the temperature increase is determined after the intravenous administration of the radiopharmaceutical (US Pharmacopeiae XX and XXII). The exact amount of the test sample may vary in different investigations. For most of the radiopharmaceuticals e.g. ^{99m}Tc radiopharmaceuticals (IAEA 1992) it is assumed that the enter content of the kit vial will be injected into a normal average weight human subject. For the rabbit pyrogen test. 111th of the vial content of a kit is injected per kg. of the body weight of each animal. However, the maximum dose per animal (rabbit) may be the entire content a single vial. The total injected volume of the kit reconstituted in 0.9% saline, should not be less than 1 ml and not more than 10 ml. In case of cold kits, the tests may be carried out using the inactive preparation reconstituted in saline instead of the radioactive solutions like ^{99m}Tc-sodium perteebnetate solution. The test has shown some drawbacks in case of unpredictable behaviour of animals towards different compounds and development of immunity to different pyrogens. The test also cannot be carried out for drugs like epinephrine, methylene blue and steroids which have certain physiological effects interfering the test conditions (Cooper 1972, Cooper et al., 1977).

Alternatively a limulus amoebocyte lysate (LAL) test is available (US Pharmacopeiae XX and XXII) which does not need animal subjects. The principle of this test, is based upon gelation or precipitation of clottable proteins of lysate amebocyte of limulus polyhemus (horse show crab) when incubated with a solution containing pyrogens in the form of bacterial endotoxins (Jorgenson and Smith 1973). This test cannot be used to detect synthetic pyre dal substances which means that it cannot entirely replace the conventional pyrogen tests It has the advantage of high sensitivity, as a very small volume required and relatively rapid performance as it takes only 1 hr. as compared to rabbit test which needs atleast 3 hrs. The disadvantage is that chemicals/reagents present in the kit content, can possibly interfere which may lead to wrong conclusions. This test has shown to respond to a long range of endotoxins and is compatible to the majority of radiopharmaceuticals (Brown and Baker 1986). Certain metal complexes and a few ^{tat}l labelled compounds however inhibit this test.

Biodistribution

Biodistribution study is one of the most important parts of the development and routine testing processes of pharmacological products. A good quality control practice,

includes a thorough check of the biodistribution and metabolic properties of a pharmaceutical product. Pharmacological studies are first done in animal models rather than directly on human beings (Sadiq and Khurshid 1995). The information so obtained is then applied to the human beings during clinical applications. Good quality control in animal studies consists of the accountability of 100% of the administered product within the animal system (Sadiq and Khurshid 1995a). In the biodistribution studies of radiopharmaceuticals, the advantage of incorporated radioactive nuclide is taken, as the qualitative determination of the radionuclide is readily achieved by the assay of radioactivity in different organs/tissues and body fluids. In-vivo imaging is performed for the qualitative clinical tests. For the biodistribution studies small laboratory animals like mice, rats, and rabbits are used due to the greater ease, lesser expenses and better control during the housing and experimentation. Animals are chosen which would be ideally human like in different characteristics e.g. organ to body weight ratio, enzyme system, metabolic rate per unit surface area etc. (Adolph 1949). The principle for the quantification in pharmacological studies is to keep a check on the administered dose, how much of it goes into the system, distributed in different organs/tissues/fluids and excreted. Generally healthy rats and mice weighing 120-150g and 20-25 g, respectively, are used in the biodistribution experiments (IAEA1992). The task of biodistribution is most easily accomplished in case of radiopharmaceuticals having a gamma emitting radionuclide like ^{99m}Tc incorporated into its molecule (IAEA 1992, Sadiq et al., 1994). The animals to be used in a set of experiments should be preferably of some, sex, strain, flock and of about the same weight. The drug formulations are prepared according to the specific requirement of different radiopharmaceuticals. The ready for injection dose is then used for pharmacokinetic studies. About 0.3 ml and 0.5 ml of the formulated preparation in case of mice and rats respectively, is injected intravenously into the already anesthetized animal. Radioactivity of the radionuclide is selected depending upon the sensitivity of the measuring device, its half life and the post injection time period (IAEA 1982 and Khurshid et al., 1993, Sadiq et al., 1995). Care is taken to keep the amount of chemicals to be injected at about the same level on per gram basis as to be used in human subjects otherwise one may encounter abnormal distribution. After the time period specified for the radiopharmaceutical under the test, the animals are humanly sacrificed and dissected for the separation of individual organs/tissues and fluids. Usually liver, spleen, lungs, kidneys, stomach, intestines, femur, urinary bladder with urine and thyroid glands are removed. Urine is collected very carefully to avoid any losses which may lead to wrong results. Animals are preferably kept in metabolic cages during the post injection period and urine and other excreta are collected very carefully. The removed organs/tissues are blotted with cotton or tissue paper pads, wrapped and placed in suitable containers for radioactivity counting. If the required data are to be expressed on per gram basis, the individual organs are weighed. For the collection of blood samples, a measured aliquot is taken by cardiac puncture, weighed and counted. Total activity in blood is usually counted assuming the blood weight to be 7% of the total body weight. The total activity injected may be calculated either from the net activity in the syringe, just before

the injection, minus the activity remaining at the site of injection or by adding the count rates in all the organs, remaining body and the carcasses. Ideally, for the sake of ease and accurate calculations, primary standards of the same activity as to be injected, are also prepared and secondary standards are prepared from the primary standard and run with the body parts for standardization and comparison. The individual ratios between the standards and animals are determined and applied to subsequent calculations to obtain the values of percent activity per sample. These ratios are corrected by the aliquot factor to get the real per-cent activity in the sample taking in to consideration the radionuclidic decay factor. For rapid and accurate calculations and evaluation of data, certain computer programmes have been developed. We have carried out extensive studies of the biodistribution behaviour of indigenous kits for ^{99m}Tc radiopharmaceuticals (Imran and Khurshid 1993, Khurshid et al., 1993, Sadiq et al., 1995) and have developed a computer programme for the calculation of organ distribution of various ^{99m}Tc radiopharmaceuticals in rats/mice (Imran et al., 1994). The programme has been successfully applied in biodistribution studies of different ^{99m}Tc radiopharmaceuticals produced in our laboratories.

The biological behaviour may also be tested alternately or supplementarily in rabbit using a gamma camera (IAEA 1992). The dissection step is automatically eliminated in this method. For scanning purpose healthy and adult rabbits are chosen. The formulated preparation of the radiopharmaceuticals is injected through the ear vein. Normally 3 ml volume, at the maximum, of the formulation in injected containing radioactivity and the chemical ingredients proportional to the body weight as expected to be used in human subjects. After an appropriate time interval which varies from pharmaceutical to pharmaceutical, the animal is anesthetized and the whole body gamma camera or scanner image is taken from both posterior and anterior views using a multipurpose collimator and organs accumulating the radiopharmaceutical, are clearly visualized. For serial imaging the injection is given under the camera, scanning is started immediately after the injection and the clearance of the injected drug from blood, uptake and release by the organs and excretion from the body is constantly monitored. In very particular cases data may also be collected by carrying the whole body scanning of human volunteers administered with a specific radiopharmaceutical (Tsui et al., 1981).

Miscellaneous Considerations

There are many other considerations, although minor but not less important in any respect, which should be kept under regular and careful assessment during the process of biological quality control of radiopharmaceuticals. In this regard quality control analysis of the raw materials, packing material etc. is of equal importance. Personnel involved in the production and quality control work should be regularly monitored because human are an important source of microbial and particulate contamination and can largely contribute to environmental disturbances through various activities. Human body

provides an excellent environment for microbial growth. Microorganisms of different species may find a place suitable to multiply on the body surfaces in the nose, throat, oral cavity and the intestines etc. Strict hygienic measures should therefore be undertaken to keep the atmosphere sterile for the manufacture and quality control of radiopharmaceuticals (British Standards Institution 1976). Similarly all the laboratory instrumentation (Rhodes 1977, Albert 1983) and other facilities like ventilation systems and air filters etc. should be regularly checked.

Laboratory animals like other living organisms are susceptible to many pathological disease which may pose a challenge to the sterility and apyrogenicity of the product. Therefore high care must be taken to keep the animals healthy and pathogen free (Coates and Gustafsson 1984).

As a part of in-vivo stability and the biocompatihility of the products and for the surveillance of over all quality of the radiopharmaceutical agents, active efforts are needed to collect the information about the drug defects and any sort of consequent adverse reaction during the clinical utilization. Such data should be frequently analyzed and even minor deviations in the characteristic chemical, biochemical or biological behaviour, should not be ignored and must be properly recorded. Such abnormalities may be useful when viewed in conjugation with other events and malfunctions if any. The manufacturers should be kept informed about the relevant information for further modifications and alterations to improve the quality of the product to get even better radiopharmaceuticals. Biological quality control tests (sterility and apyrogenicity, in particular) must of course also be performed for the distilled water used in experimentation or in the formulation of injections. For this purpose radiometric detection method is good one to check the sterility of water and other materials (Iqbal and Khurshid 1987, Khurshid et al., 1987, Khurshid and Bibi 1991) used in the preparation and control of radiopharmaceuticals.

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