GOOD RADIOPHARMACY PRACTICE AND REGULATION

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Abstract

Production, control, distribution and clinical application of radiopharmaceuticals have not been subject to the same regulations and legislation developed for conventional pharmaceutical products. Generally the production of radiopharmaceuticals have started up at national nuclear energy research centres, where the products have been regarded more as radioactive tracers than pharmaceutical products. Gradually pharmaceutical philosophy and requirements have been introduced in the field and necessary changes in legislation have been introduced. The registration process to obtain official market authorisation for a radiopharmaceutical have been introduced in most countries. This process of registration is constantly changing with regards to the amount and the type of documentation required by the health authorities. Correspondingly the general requirements for the systems applied in pharmacy for the production, control, quality assurance and medical application have also become an integral part of the field of radiopharmacy. Is the present situation generally satisfactory? The ever increasing demands leads to increasing costs and thereby higher prices on the products for the end users. Do the present requirements generally ensure that the radiopharmaceuticals applied are safe and effective for the patient?

Radiopharmaceuticals have a short history compared to other drugs and medicinal products. The widespread use of radioactive nuclides for medical applications came as a direct result of the development of the atomic bomb during the Second World War. The construction of nuclear reactors in this context, opened up for the possibility of producing a whole range of new radionuclides by neutron activation of non-radioactive targets. Radionuclides that were not found in nature, could now be produced artificially in quantities that made it possible for use in scientific and medical applications.

Production, control, distribution and clinical application of radiopharmaceuticals have not been subject to the same regulations and legislation developed for conventional pharmaceutical products. The first important radiopharmaceutical product in routine clinical practice was Iodine-I-131, used for diagnosis and therapy of disorders of the thyroid gland. This was also the first true specific targeting radiopharmaceutical, and the spectacular success obtained in treatment of thyroid cancer brought the product and the practice of the new medical speciality nuclear medicine to the front page of newspapers and magazines. It was anticipated that new «Magic bullets» like the iodine-131 solution, which got the nickname: «The Atomic Cocktail», would be developed quickly and the diagnosis and cure for many other types of cancer would be obtained by using these radiopharmaceuticals. Time has

shown that it was not so easy as expected then and it is first in the last decade that a variety of new targeting radiopharmaceuticals have been introduced in routine clinical practice.

However the way radiopharmaceuticals were developed and introduced to the users were completely different from what was typical for conventional pharmaceutical products. The radioisotopes incorporated in the products were produced in reactors belonging to national nuclear research centres and institutes. Many regarded this production as a spin off of the general activities of the centres and as these reactors were built and operated with public funds, the radionuclides should be supplied to the public free of charge or at a very low cost. Therefore the radiopharmaceuticals developed during the first three, four decades of the new era were not priced according to the real costs of production of the radioisotope or the radiopharmaceutical. Furthermore it became prestigious for many countries to build and operate their own nuclear reactor. One of the ways to get political support and economic aid for such projects was the argument that the reactor also could be used for the production of radionuclides used in radiopharmaceuticals. This type of argument is one of the main reasons that we today find a widespread local production of radiopharmaceuticals all over the world, including many developing countries. However this hidden economic subsidy lead to the general expectation that radiopharmaceuticals should have a low price structure. This is clearly evident when the price of a multi dose vial of a generic technetium-kit is compared to the cost of a single dose vial with x-ray contrast media used in radiology. This tradition makes it very difficult to raise the price of the older radiopharmaceuticals to the correct level based on actual costs. This is an absolutely necessary requirement, now when many countries have privatised the production of radiopharmaceuticals

1. Good Radiopharmacy Practice

Generally the production of radiopharmaceuticals started up at national nuclear energy research centres and establishments. When looking at the major suppliers of radiopharmaceuticals in Europe, they all have their origin in such national research centres. However in these nuclear centres the products were more regarded as radioactive tracers than pharmaceutical products, and this had a had a major influence on the systems instituted for production, distribution and control of these medicinal products. Because the fields of nuclear science and pharmacy are far apart, the guidelines for Good Manufacturing Practice (GMP)

that were first introduced more than 30 years ago in conventional pharmaceutical practice, did not have any immediate impact on the general production of radiopharmaceuticals.

The first time the phrase «**Good Radiopharmaceutical Practice**» was coined, was around 1970, when a group of Scandinavian radiopharmacists came together to study how the GMP philosophy and guidelines could be applied within the field of radiopharmacy. The Good Radiopharmaceutcial Practice Code was defined to comprise the application of the GMP guidelines for pharmaceuticals with the relevant guidelines for radiation protection during production, distribution and hospital handling of radiopharmaceuticals to ensure the safety and efficacy of the product administered to the patient. In the beginning the discussions put much emphasis on how different radiopharmaceuticals were from non-radioactive medicinal products, and why it was important to make special legislation and requirements for these drugs. But over the years the discussions lead to the realisation that radiopharmaceuticals could not be considered as something extraordinary, and that the same quality standards would have to apply for these products as for conventional pharmaceuticals. However the radiation protection aspects make the situation more complicated, as personnel involved with the production, transport and preparation and administration in the hospitals as well as the environment has to be protected against the products.

So what makes radiopharmaceuticals that different from non-radioactive drugs?

1. The preparation of the radiopharmaceuticals in its final form does most often take place in the hospital department immediately prior to the administration to the patient.
2. Radiopharmaceuticals have a very limited period of use. (Short shelf-life)
3. Radiopharmaceuticals are frequently shipped directly from the manufacturer to the end-user without any formal control in a pharmacy or hospital pharmacy
4. A quality control must often be performed in the hospital upon the preparation of the radiopharmaceutical in its final form.
5. Manufacture, distribution and use of radiopharmaceuticals require special expertise in handling of radioactive materials

Gradually general pharmaceutical philosophy and requirements have been introduced in the field of radiopharmacy and necessary changes in legislation have followed. As a basis for the elaboration of such changes, it was necessary to characterise the various types of products most commonly used:

a) Ready-for-use radiopharmaceuticals, which contains radionuclides with a sufficiently long half-life to allow the product to be distributed in its finished form from the manufacturer

b) Radiopharmaceuticals prepared from semi-manufactured products. The use of radionuclide generator systems and preparation kits allows the preparation of radiopharmaceuticals with a relative short half-life in the hospital department.

c) Radiopharmaceuticals produced directly prior to patient administration
For radiopharmaceuticals containing radionuclides with ultra-short half-lives it may be necessary to both produce the radionuclide and prepare the radiopharmaceutical close to the patient for immediate administration. (PET radiopharmaceuticals are typical products of this group)

d) Radiopharmaceuticals based on biological material from the patient. Cells or plasma protein fractions from a patient may be labelled with a radionuclide and re-injected in the same patient.

In the discussions on Good Radiopharmaceutical Practice the complexity of the handling procedures for these products in the hospital environment increases from the first to the fourth of these categories.

The practice of radiopharmacy in the hospitals can also be classified according to the various types of work that is performed:

a) Dispensing of individual dosis from ready-to-use radiopharmaceuticals

b) Preparation of radiopharmaceuticals from radionuclide generators and preparation kits
Preparation is carried out in accordance to manufacturer's instructions and the finished pharmaceuticals is only intended for use within the department.

c) Centralised in-hospital dispensing and preparation
Dispensing and preparation of radiopharmaceuticals as described under a and b for use in other departments within or outside the hospital

d) Production of radiopharmaceuticals

Production and handling of radiopharmaceuticals not covered by a, b and c above. Included is the preparation and labelling of biological material from the patient.

How can all these requirements be taken care of without making impossible restrictions affecting the daily routines in the nuclear medicine departments? In most countries the radiation protection aspect is taken care of by the licensing of the premises by the national boards of radiation, which would define the radionuclides and quantities allowed in each particular case. The pharmaceutical aspects could be covered by inspections by the general medicinal inspectorate. But in many countries the legislation demands that a pharmacist should be registered as the qualified person for the radiopharmaceuticals and take the responsibility of the handling, production and preparation in the hospital. The authorities in Denmark have established an interesting system, that may serve as a model for other countries. Each nuclear medicine department is visited by a team of two inspectors/advisors. One of the members of the team is a representative from the National Institute of Radiation Hygiene while the other is a radiopharmacist from the national Isotope-pharmacy, which is a laboratory belonging to the national board of health. The inspectors review the premises and equipment available and the qualifications and training of the personnel. Based on their findings each department is given a licence describing the type of work they are authorised to perform taking into consideration all the above mentioned factors. The classification process is the most important task for the team, but they are also welcomed in the departments as advisors on practical topics, such as design of the various working areas, application of working techniques, local radiation protection issues etc.

2. Regulations and legislation

For radiopharmaceuticals the legal requirement for marketing authorisations or an official registration of the products came late. Some countries did include the new products under the general legislation for medicinal products from the start. But the introduction of special requirements on distribution and sale of the products often made a direct link between radiopharmaceuticals and the national nuclear research centres.

The first formal systems for obtaining market authorisation for radiopharmaceuticals were established in the USA, United Kingdom and Denmark. It was obvious that the requirements

used for non-radioactive drugs could not be applied directly to the radiopharmaceuticals. Several special characteristics of the radiopharmaceuticals had to be taken into consideration. The drugs were then mostly used for medical diagnosis. They were usually given to the patient only once or occasionally a few times and they contained only very small physical quantities of carrier substance and radionuclide. In general most requirements concerning documentation of the safety and efficacy of a non-radioactive drug would also apply to radiopharmaceuticals. But it must be recognised that most radiopharmaceuticals do not have a measurable pharmacodynamic effect. In addition to the general requirements it is also necessary to include staff and patient radiation protection aspects and patient dosimetry parameters in the documentation. Certain points therefore did differ considerably from the documentation of non-radioactive drugs:

a) Radiopharmaceuticals have a changing composition with time due to the radioactive decay of the radionuclide. The radioactive concentration and the specific activity of the product would therefore change all the time from the production day to expiry date.

b) For certain radiopharmaceuticals containing ultra-short lived radionculides it would be impossible to perform quality control of the product before administration to the patient. For example radionuclide generators and cyclotrons may be used for production of an ultra-short lived radioactive gas which is inhaled directly after production by the patient. All quality control would have to be performed retrospectively and the quality assurance program would concentrate on the reproducibility of the chosen production process to provide a final radiopharmaceutical fulfilling all quality specifications.

c) The labelling of radiopharmaceuticals do not follow the same pattern as for non-radioactive drug. The label on the inner container contains only basic information, as this label is not supposed to be studied in detail by the user. Most of the relevant information is contained on the label attached to the lead-shielding surrounding the inner container and in the packaging insert.

d) The extent of toxicology studies would depend and the intended clinical use of the radiopharmaceutical. Part of the studies should be performed on the non-radioactive form of the radiopharmaceutical. Studies of chronic toxicity would only be required in special cases. If studies of mutagenic, oncogenic or carcinogenic potential are required, they should be performed using the non-radioactive form of the new chemical entity.

Radioactivity is in itself an important risk factor for the introduction of such biological changes.

e) Clinical documentation would normally be more limited than for non-radioactive drugs. The administration of radioactivity to a patient would always be subject to a risk/benefit evaluation. No application of a radiopharmaceutical should take place if the benefit of a better diagnosis, better treatment etc., outweighs any risk induced by the radiation dose and other properties of the product. To give radioactive substances to healthy volunteers would have to be subject to ethical evaluation in each case. It would therefore not be ethical to perform large, comparative studies of radiopharmaceuticals with other diagnostic or therapeutic tools.

Now most countries have established national registration procedures to obtain official market authorisation for a radiopharmaceutical. But less than a decade ago many European countries did not have a drug legislation that did also cover radiopharmaceuticals. Several of these countries did finally get their legislation for these products as part of the directives on radiopharmaceuticals issued to the member-states of the European Union.

3. Status today

The procedures for obtaining market authorisation is a dynamic process, and the requirements set by the health authorities for documentation will change constantly over the years to come. For the manufacturers of radiopharmaceuticals it seems that there is an never ending process requesting more and more documentation, while the users in the hospital departments feel that the demands with regard to premises, equipment, education and supervision are getting stricter and stricter. It is obvious that the consequence of the situation will be higher prices for radiopharmaceuticals and increased problems in the nuclear medicine departments, which already are fighting with serious economic constraints. It is easy for authorities and regulators to introduce new demands and requirements, but these must be balanced against the benefits gained and the ultimate goal: To ensure a reliable supply of safe and effective radiopharmaceuticals at a price that is affordable for public and private health services. The standards we establish must be set with this goal in mind and must not be based on purely political or juridical motives.

4. The future

The question is therefore how to reach this common goal without using too much labour and economic resources. One evident solution must be global and regional collaboration in various fields of radiopharmacy. How can this be achieved?

a) Joint projects to elaborate manuals and guidelines for Good Radiopharmaceutical Practice. Some do already exists! In Scandinavia the Nordic Council of Medicines formed a group of radiopharmacists that elaborated guidelines for the preparation and control of radiopharmaceuticals in the hospital environment. These guidelines have been the model for similar projects around the world. It has been realised that guidelines should be established for other areas of radiopharmacy as well, such as centralised radiopharmacies and the local, small-scale production of radiopharmaceuticals. Currently a manual is being established under the auspices of International Atomic Energy Agency covering these fields of radiopharmacy and intended for use in the region of Central and South America .

b) Collaboration and harmonisation on radiopharmaceutical monographs in the pharmacopoeias. These monographs are very important to establish the quality requirements for the products on the market. Today it is difficult to find experts to take part in the work on these monographs who have the access to laboratories that have the time and economic backing to perform the necessary laboratory work to establish and validate the various analytical methods that are to be included in the monographs. Working with radiopharmaceuticals the analytical equipment will be contaminated with radioactivity, and not many centres or companies are willing to work with this type of problem. It may therefore be of interest to look at this work on new monographs globally instead of regionally, in order to get a good scientific background for the new monographs. The harmonisation process has already been started on monographs for the Ph. Eur, the U.S.P and the Japanese Pharmacopoeia.

c) Could this work be extended to include a regional process for the granting of market authorisations? Yes, within the European Union this possibility does already exist. By applying through the «Centralised Procedure» a product could be granted a market authorisation in all the member states of the union. This type of collaboration is a very sensible idea. It must be regarded as a waste of time and money if all nations should designate personnel and money to evaluate the same data supplied as documentation in the

applications for marketing authorisation for a radiopharmaceuticals. A thorough study performed by a competent authority will be much more valuable than the study of an individual health authority with little experience and expertise to handle and evaluate applications for a radiopharmaceutical product.

d) The question of joint projects for regional production of radiopharmaceuticals has been raised. It has become more and more evident that transport and logistics will become very important issues in the future of radiopharmacy. This year has showed clearly how difficult the transport by air will become, if firm commitments for long periods of time for shipment of radiopharmaceuticals are not granted by the various air companies. To avoid this problem the idea of setting up local production centres are getting more and more interesting. But this idea of local production does already exist because of national interests. Could this idea be of more importance by expanding it from a national interest to a regional interest? It is a very difficult topic, as nobody really wants to give up or transfer the production to another company in the region. Denmark, Norway and Sweden had such discussions 30 years ago. But the negotiations stranded as nobody at that time were ready to give up their production of ^{131}I-iodinated Hippuran! Political and professional issues will always make it difficult to make this type of arrangements. Could the establishment of commercial centralised radiopharmacies make an impact? These pharmacies are already well known in USA and are now being introduced in south-east Asia. But they are still an almost unknown entity in Europe. The practice of centralised radiopharmacy may change the way of marketing and distribution of radiopharmaceuticals in certain areas, but may also help to increase the standards of Good Radiopharmaceutical Practice and reduce the total costs in areas with the necessary population density and transport infrastructure.