# 2. The Purity of Radiopharmaceuticals

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## 1. Introduction

With the experience of the pharmaceutical and fine chemicals industries as a background, radiopharmaceutical manufacturers have from the first applied controls to the purity of their products. Awareness of the standards required, and the means to achieve them and to test them, have emerged only gradually. Enough is now known to merit a detailed review of the subject.

The term purity, as applied to a radiopharmaceutical, can include radionuclidic purity (widely referred to as radioisotopic purity), radiochemical purity and chemical purity, together with the normal pharmaceutical requirements of sterility and freedom from pyrogens.

## 2. Radionuclidic Purity

(**Note**: The term 'radioisotope' is used almost universally in contexts where the term 'radionuclide' should be employed. It is not surprising therefore that the term 'radioisotopic purity' is used where 'radionuclidic purity' is meant. The author has a strong preference for the term 'radionuclidic purity', as the term 'radioisotopic purity' can lead to ambiguities. The term 'radiochemical purity' has often been used in the past, and indeed is still used, to denote what we now term 'radionuclidic purity'.)

Radionuclidic purity may be defined as the proportion of the total activity which is in the form of the stated radionuclide: daughter nuclides are often excluded. Consideration of examples shows that a statement such as "the product is 99% radionuclidically pure" is often of little value: it is the nature of the impurities that is important.

Radionuclidic impurities may be nuclides of the same element(e. g. $^{60}$Co in a preparation of $^{58}$Co)or of a different element. In the production of a radioisotope, the proportions of isotopic impurities can be controlled by the isotopic composition of target material, by the types of nuclear reaction chosen for production, by control of the energies of the particles used in the nuclear reactions, and by control of irradiation and decay times: isotopic impurities can be detected by physical means only. Non-isotopic impurities can in theory be separated from the product by chemical means, although it is often better to keep them out by suitable control of the production process: they can most conveniently be detected by combinations of chemical and physical means.

A number of radiopharmaceuticals involve questions of radionuclidic purity. They include $^{47}$Ca and $^{197}$Hg, where the isotopic composition of the target is important: $^{86}$Rb where the chemical purity of the target is important: $^{74}$As, $^{123}$I and $^{198}$Au where control of the nuclear reaction used in production may be required. Of special importance are the very short-lived isotopes now being widely used in diagnostic work, especially those derived from cow systems: the presence of traces of long-lived radionuclides in these can be very harmful.

## 3. Radiochemical Purity

Radiochemical purity is the proportion of the stated radionuclide which is present in the stated chemical form: thus if we say that a preparation of L-selenomethionine, $^{75}$Se, is 99% radiochemically pure, we mean that 99% of the $^{75}$Se present is in the chemical form of L-selenomethionine.

We may distinguish various types of radiochemical impurities:

(a) Impurities of completely different chemical molecules from the stated chemical form, e. g. iodide ion in a preparation of L-thyroxine, $^{131}$I.

(b) Impurities differing in the position of labelling, e. g. L-thyroxine-3 (:5)-$^{131}$I in a preparation described as L-thyroxine-3′(:5′)-$^{131}$I.

(c) Impurities differing in the sign of optical rotation, e. g. D-thyroxine-3′ (:5′)-$^{131}$I in a preparation described as L-thyroxine-3′(:5′)

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$^{131}I$. Special cases arise when there is optical asymmetry due to the presence of the radioisotope itself.

Included in the general term radiochemical purity are such diverse considerations as the immunological properties of iodinated insulin, $^{125}I$, and the particle size range of gold colloid, $^{198}Au$.

Radiochemical impurities may arise:

(a) During the synthesis of the compound

(b) During storage or subsequent treatment

The synthesis involves not only the normal considerations of impurities arising in chemical syntheses but also those of exchange reactions taking place, and of radiation decomposition during synthesis. The storage and subsequent treatment (such as autoclaving for sterilization) may also lead to decomposition. Radiation decomposition is an especially troublesome factor, and the pharmaceutical manufacturer must give particular consideration to means to minimize it – variation of specific activity, the strength of the solution and the nature of the solvent, the use of protective agents, and so on. It must be realized that normal chemical decomposition can take place also – certain iodine-labelled compounds are rather unstable on this account.

Radiochemical purity can be studied by a variety of techniques, but paper chromatography, and more recently thin-layer chromatography, are of particular importance. Inverse dilution analysis is important in special cases.

## 4. Chemical Purity

This refers to chemical purity as normally defined and no consideration of radioactivity enters into it. As applied to radiopharmaceuticals, freedom from toxic chemical elements is of obvious importance. Perhaps the most important example for medical users is that of the chemical purity of "carrier-free" iodide, $^{131}I$, employed in the very exacting procedures used in the labelling of certain proteins such as insulin and human growth hormone. The chemical scale of such iodinations is so small that the merest traces of reducing agents or readily oxidizable impurities can completely react with the iodinating agent.

Chemical purity has often no relation to radiochemical purity – this is a common pitfall to new users of radiochemicals. Thus the melting point of Hippuran, $^{121}I$, is of no significance in deciding upon the radiochemical purity when the material has been prepared by an exchange reaction with a relatively small amount of inorganic iodine, as it normally is. On the other hand if one prepares D. F. P., $^{32}P$, by normal synthetic procedures from red phosphorus, $^{32}P$, and if one adds no inactive phosphorus-containing compound during the preparation, one can say that, provided the chemical purity is satisfactory, so is the radiochemical purity: in this case the most convenient analytical method is the determination of chemical purity by gas/liquid partition chromatography.

## 5. Conclusions

Lack of purity of a radiopharmaceutical may be objectionable on three grounds:

(a) It may endanger the life or health of a patient.

(b) The product may lack therapeutic efficiency.

(c) The product may lack diagnostic efficiency.

The last case is the one most likely to arise.

What therefore are the standards that must be set? These can be derived only by a detailed consideration of the material – of the impurities that are likely to be present, and whether or not they will interfere with its use. To take some examples:

1. The presence of 1% of $^{134}Cs$ in $^{86}Rb$ may not at first sight seem objectionable. However, if the product is used over a period of 3 months, then at the end of that period the amount of $^{134}Cs$ is 26%.
2. Rose Bengal, $^{131}I$, commonly contains some incompletely iodinated tetrachlorofluoresceins. These behave closely similarly to Rose Bengal as regards uptake by healthy liver cells, and hence do not interfere with the usefulness of the product.
3. High specific activity D.F.P., $^{32}P$, undergoes a significant amount of radiation decomposition. The decomposition product, however, does not label blood cells, and does not interfere in their labelling by D.F.P. A moderate amount of radiation decomposition is therefore not harmful.
4. $^{198}Au$ contains a small amount of $^{199}Au$ from the reaction $^{198}Au$ (n, $\gamma$) $^{199}Au$. As higher fluxes are employed, the proportion of $^{199}Au$ becomes higher. However, the presence of $^{199}Au$ deos not interfere with the use of colloidal gold, $^{198}Au$, either therapeutically or

diagnostically. A relatively large proportion of $^{199}Au$ can therefore be accepted providing the amount is known. Similarly the particle size of colloidal gold is not critical in therapy, but it is in determination of liver blood flow: much more narrow limits must be set for material to be used for the latter application.

It must be emphasized finally that no specification of purity for a radiopharmaceutical can be complete: there are far too many possibilities. The experience and integrity of the manufacturer must therefore always be an important factor.

# 3. New Challenges in Clinical Counting*

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In the field of nuclear medicine the value of the pulse-height spectrometer is now well recognized. Given an alert and informed operator, it can reduce the obscuring effects of background; it can at least partially suppress unwanted scattered radiation; it can provide better stability (other things being equal) than is available in a "threshold" counter; it can check the radiochemical purity of a questionable drug; and often it can measure separately two radioactive components in the same sample. The persistent demand for still lower radiation doses to the patients, and the development of new, low-energy emitters, have created new difficulties for the counting equipment, and skillful operation is more important than ever. Good counting efficiency is hard to obtain, and the factors that determine it should be well understood if weak samples are to be counted. The selection of the spectrometer's energy band depends on resolution, as well as on other things. The counting of large, weak samples, and of whole patients, brings up a number of difficult problems, and calls for an all-out attack on background. The low-energy radionuclides are focussing renewed attention on the problems resulting from absorption and scattering, and special techniques may be needed. Recent arrivals in the moderate- and low-energy fields are: gold-199 and iodine-123 (159 kev), cerium-141 (145), technetium-99m (140), cobalt-57 (122), xenon-133 (81), mercury-197 (67-78), cesium-131 (30), and iodine-125 (28 kev).

## New Challenges in Clinical Counting

With the introduction of the so-called "medical spectrometer" into nuclear medicine, the reliability of the measurements has improved considerably, for the counter's attention can now be focussed on the informative components in the radiation while background and other undesirable junk can be greatly reduced. The scattered radaition that is always present when the source lies inside a patient can now be made less troublesome, thus making it easier for us to design a realistic "phantom" in which the standard of comparison will be counted. The spectrometers may also be able to untangle a mixture of two or more radionuclides, they can check the purity of a questionable radioactive drug, and so on. This selective counting of gamma rays was not possible in the Geiger-tube days, and it was difficult even in the early days of scintillation counting, when most of the instruments operated on the integral or "threshold" basis. If the spectrometer's full potential is to be realized, however, the instrument must be operated with intelligence and insight. Our doctors and technicians are learning to do this.

**Stability** – Returning to the threshold counters for a moment, it is not always realized how easily disturbed they are by factors that change the electronic amplification (including that in the photomultiplier

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