Quality Control of Radiopharmaceuticals

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The International Pharmacopoeia published by WHO constitutes a collection of recommended specifications for pharmaceutical preparations which are not intended to have legal status in any country, but serve as references so that national specifications can be established on a similar basis in any country.

Like any pharmacopoeia, it contains monographs for the quality control of drugs by means of chemical, physical and simple biological methods, as well as appendices describing general methods.

The work on the International Pharmacopoeia is carried out by WHO with the aid of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists from various countries and the Expert Committee on Specifications for Pharmaceutical Preparations.

SPECIFICATIONS

In the twenty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations it was recommended that WHO expand its work on the preparation of specifications for radioactive pharmaceuticals. Although WHO is responsible for preparing such specifications, it collaborates with the International Atomic Energy Agency. This refers to the agreement reached at the Inter-secretariat meeting between WHO and IAEA in 1968 according to which WHO would continue to take primary responsibility in issuing specifications for radioactive pharmaceuticals, and IAEA cover the methodological part of testing with regard to the tests for radiochemical and radionuclidic purity.

Some tests included in the specifications published in the Supplement 1971 and in Annex 1 to the twenty-fourth report of the Expert Committee were worked out with IAEA laboratory assistance and a representative of the IAEA attends all WHO consultations and meetings dealing with specifications for radioactive pharmaceuticals. The first consultations on specifications for radioactive pharmaceuticals were held in December 1968.

During these consultations the approach to the revision of the parts of the Second Edition of the International Pharmacopoeia concerning radioactive pharmaceuticals was suggested and the list of addenda proposed. The work was continued by correspondence in co-operation with a number of national pharmacopoeia commissions and at consultations which took place in April and October 1969. The results were discussed at the twenty-third Expert Committee meeting and the Expert Committee adopted the specifications for radioactive pharmaceuticals which are included in the 1971 Supplement.

The Second Edition of the International Pharmacopoeia, published in 1967, contains a total number of 555 monographs and 69 appendices, including monographs for radiopharmaceuticals:

Sodium Chromate (^{51}Cr) Injection
Sodium Iodide (^{131}I) Injection
Sodium Iodide (^{131}I) Solution
Sodium Phosphate (^{32}P) Injection

The titles of these monographs originally included the word "Radio", which was later deleted

and an Appendix, "Radioactivity".

The Supplement 1971 to the second edition of the International Pharmacopoeia, which was published in August 1971, contains a total number of 20 monographs and 7 new or revised appendices, including monographs for:

Gold (^{198}Au) Colloidal Injection
Cyanocobalamin (^{57}Co)
Cyanocobalamin (^{58}Co)
Sodium Iodide (^{125}I) Solution
Sodium Iodohippurate (^{131}I) Injection
Rose Bengal (^{131}I) Sodium Injection
Iodinated (^{125}I) Human Serum Albumin Injection
Iodinated (^{131}I) Human Serum Albumin Injection,

a substantially revised Appendix, "Radioactivity", and a new Appendix 13a, "Table of Physical Characteristics of Radionuclides used in Radioactive Pharmaceuticals".

Annex 1 to the twenty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations contains a total number of 33 provisional monographs, including monographs for:

Tritiated Water (^{3}H) Injection
Chlormerodrin (^{197}Hg) Injection
Sodium Pertechnetate (^{99m}Tc) Injection
Selenomethionine (^{75}Se) Injection
Macroaggregated Iodinated (^{131}I) Human Serum Albumin Injection.

RADIONUCLIDE GENERATORS

During the consultations mentioned previously, special consideration was given to radionuclide generators and how to approach the questions connected with the growing use of generators from a pharmacopoeial point of view.

The following generators were considered important:

Molybdenum-99/Technetium-99m
Tin-113/Indium-113m
Yttrium-87/Strontium-87m
Tellurium-132/Iodine-132.

The problems in preparing monographs were similar in each case, and it was decided to deal with the $^{99}Mo/^{99m}Tc$ generator[1] in the first instance. If it proved possible to prepare a monograph or a set of recommendations on this generator, the same principles could be applied to the others, and the steps detailed below could be followed in other analyses.

It was agreed that three items might be the subject of monographs or recommendations:

(a) The generator system itself—that is, for example, the glass device containing alumina on which is adsorbed molybdate ion (^{99}Mo).

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[1] Twenty-fourth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations — Wld Hlth Org. techn. Rep. Ser., 1972, No. 487, p.61

(b) The eluant – that is, for example, the solution of sodium chloride which is employed to elute the daughter radionuclide from the generator.

(c) The eluate – that is, for example, the solution eluted from the generator and containing pertechnetate ion (^{99m}Tc).

As the eluate is the solution which is administered directly, or after further treatment, to the patient, it was suggested that the eluate should be the subject of a monograph. It was agreed that the points that would require specifications include:

- *Content of ^{99m}Tc, and the accuracy to which this should be measured.*
- *Content of ^{99}Mo, for which an upper limit would have to be set.*
- *Chemical form of the ^{99m}Tc (i.e. pertechnetate ion) and its radiochemical purity.*
- *Items pertaining to the suitability of the product for injection, e.g. chemical composition, pH, sterility and freedom from pyrogens.*

As the generator can be considered as a device from which a drug is derived, it was decided not to include specifications for the generator itself.

It is the object of a manufacturer to prepare a generator which would yield a product conforming to the specifications of the monograph on the eluate. He might employ a variety of means of achieving this end. He could use different forms of physical construction, different adsorbents, different chemical forms of the parent radionuclide, and so on. The variety of possibilities might be too great to be covered in a conventional monograph.

In the introductory paragraph to the monograph, the Sodium Pertechnetate (^{99m}Tc) Injection is defined as a sterile solution containing technetium-99m in the form of pertechnetate ion.

The paper chromatographic test included in the monograph under radiochemical purity indicates that not less than 95 per cent of the total radioactivity is in the spot corresponding to pertechnetate ion (Rf value for the recommended solvent system is indicated).

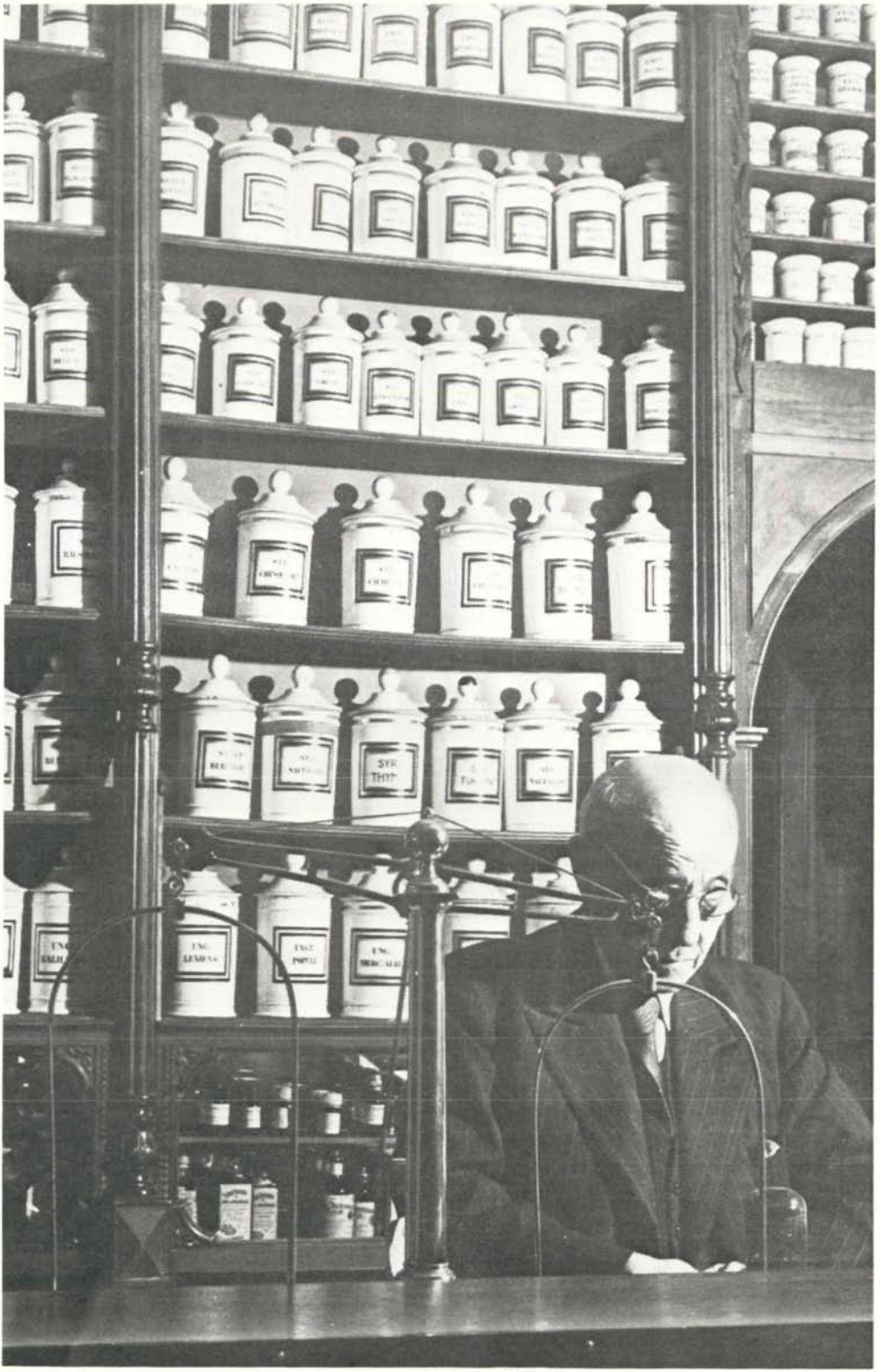
The activity of technetium-99m is limited to not less than 90 per cent and not more than 110 per cent of the content stated on the label at the date and hour stated on the label.

The radionuclidic purity is specified as follows: Not more than 0.01 per cent of the total radioactivity shall be due to radionuclides other than technetium-99m, except that technetium-99 resulting from the decay of technetium-99m may be present, and except that molybdenum-99m may be present to the extent of 0.1 per cent and iodine-131 to the extent of 0.05 per cent of the total radioactivity, all calculated at the time of administration.

With regard to sterility and sterilization, three ways are admitted: the injection may be prepared from a sterile preparation of molybdenum-99 under aseptic conditions, or it may be sterilized by heating in an autoclave, or by filtration.

A special caution has been added warning that this injection cannot be tested before administration for sterility and pyrogens and therefore it must be prepared and handled under aseptic conditions.

This tranquil chemist, surrounded by his hundreds of jars of powders which he mixes himself, is rarely seen nowadays. Today the pharmacist is faced with continually increasing responsibilities in a world which every week produces more and more specialized and powerful pharmaceutical drugs – WHO ▶



The injection is identified by its gamma-ray spectrum. The specified pH is 4.5 - 7.

Tests for radionuclidic purity are split into two groups: tests prior to use and retrospective tests. Under the **tests prior to use** *tests for molybdenum-99 and iodine-131 are specified as follows:*

Molybdenum-99. *In 1 mCi of the injection the gamma-ray spectrum is determined using a sodium iodide detector with a shield of lead, of thickness 6 millimetres, interposed between the sample and the detector. The response in the region corresponding to the 0.740 MeV photon of molybdenum-99 does not exceed that obtained using 1 µCi of a standardized solution of molybdenum-99 measured under the same conditions.*

Iodine-131. *When the injection has been prepared from molybdenum-99 produced by uranium fission the above test should be suitably modified to measure the iodine-131 content. As indicated in the introductory paragraph, this should not exceed 0.05 per cent (0.5 µCi per 1 mCi) of technetium-99m.*

For the retrospective tests — *a sample of the injection is retained for a sufficient length of time in order to allow technetium-99m to decay to a sufficiently low level to permit the detection of radionuclidic impurities. The presence of molybdenum-99 and iodine-131 are revealed by their gamma-ray spectra (the most prominent photons have energies of 0.181, 0.740, 0.780 and 0.284, 0.364, 0.637 MeV respectively). All measurements of radioactivity are expressed at the time of administration of the injection.*

The gamma-ray spectrum of the retained sample of the injection should be examined for the presence of other radionuclidic impurities which should, where possible, be identified and quantified. When the injection has been prepared from molybdenum-99 produced by uranium fission it may be appropriate to examine the sample of injection for the presence of beta-emitting and alpha-emitting impurities. The total radioactivity due to these radionuclidic impurities shall not exceed 0.01 per cent of the total radioactivity of the sample.

In addition to these tests, the monograph for Sodium Pertechnetate Injection includes a test for Aluminium, which may be present as a chemical impurity. Its content is limited to not more than 20 µg of aluminium in 1 ml of the solution. For the assay of aluminium a colorimetric assay using the colour complex with eriochromcyanine is described.

An assay test is also provided for the determination of radioactivity by comparison with a standardized technetium-99m solution.

FUTURE WORK

A discussion was held in WHO concerning the number and kind of monographs that might be required in the future. With the introduction of Sodium Pertechnetate (^{99}mTc) in the International WHO Pharmacopoeia the way is now open to consider other short-lived generators-produced radionuclides such as ^{113}mIN and ^{87m}SR. It was also considered that preparations of ^{99}m Tc other than sodium pertechnetate, such as serum albumin or macroaggregated serum albumin, could be profitably studied.

Special problems were presented by such preparations as iodinated fats and fatty acids [(^{131}I) and (^{125}I)], which required further study before monographs on them could be prepared. The production of short-lived accelerator-produced radionuclides, e.g. ^{18}F and ^{123}I will need future consideration.