WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-fifth Report
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WHO EXPERT COMMITTEE ON SPECIFICATIONS
FOR PHARMACEUTICAL PREPARATIONS

Geneva, 4-9 November 1974

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WHO EXPERT COMMITTEE ON
SPECIFICATIONS FOR PHARMACEUTICAL
PREPARATIONS

Twenty-fifth Report

The WHO Expert Committee on Specifications for Pharmaceutical
Preparations met in Geneva from 4 to 9 November 1974. Dr A. S. Pavlov,
Assistant Director-General, opened the meeting on behalf of the Director-
General.

I. REVISED TEXTS OF DOCUMENTS RELATING TO QUALITY
CONTROL AND CERTIFICATION OF PHARMACEUTICAL
PRODUCTS

The Twenty-second World Health Assembly recommended that Member
States adopt and apply the requirements entitled Good Practices in the
Manufacture and Quality Control of Drugs, as formulated in the report of the
Director-General, a and the Certification Scheme on the Quality of Pharma-
ceutical Products moving in International Commerce, as formulated in the
report of the Director-General. b

The Twenty-third World Health Assembly requested the Director-
General to continue to review, in the light of information obtained, the
requirements embodied in Good Practices in the Manufacture and Quality
Control of Drugs and the Certification Scheme and to report to the Twenty-
fourth World Health Assembly.

The Expert Committee on Specifications for Pharmaceutical Prepara-
tions, in its twenty-fourth report, c undertook a review of comments received
in respect of both documents from a number of Member States, and on the
basis of these comments, proposed revised texts, which were, in turn, sent
to all Member States for further comments in January 1974. At this stage
comments were received from some 40 Member States, including the
majority of countries that manufacture drugs for export.

The Committee noted that although the comments raised no new points of principle, there were several recommendations for changes in the texts. In some cases, the comments were aimed at bringing the text more closely into line with a particular national practice or legislation; however, because this could well conflict with other national practices, it was not always possible to adopt the recommendations made. In other cases, proposals were made for elaborating in more detail on some of the requirements, but it was thought that, unless the whole text were similarly amended, this might lead to an unbalanced document.

Several comments concerned the terms listed under “Definitions” and, although it was agreed that some of the suggested alternatives were in keeping with current practice, it was thought that any advantages gained by adopting them would be more than outweighed by the numerous problems created elsewhere by the introduction of new terms at this stage. This related particularly to the term “drug”. It was considered that a definition of “purity” was unnecessary because this term has no significant use in the text.

Due note was taken of comments that revealed ambiguities or vagueness in the text and might lead to misunderstandings. Suitable corrections were made. Several changes were made in the order of paragraphs within sections, so as to present the requirements in a more logical sequence.

The role of the quality control laboratory has been more clearly defined. The release of batches, which was previously linked solely to the analytical report, has now been changed to require a formal act of release by the quality control department.

In the Certification Scheme, substantial changes have been made in order to distinguish more clearly between the general Certification of Pharmaceutical Products and the issue of batch certificates.

Legislation in effect in some Member States might lead them to have reservations regarding their participation in the scheme. This fact has now been recognized by suitable additions to “Part III — Participation of Member States”. The responsibilities of exporting Member States have been extended by the introduction of a reference to the provision of authority to enforce standards.

The specimen certificate has been revised to recognize that “authorization” is not necessarily accompanied by the issue of permits. It now also provides for the situation in which the person responsible for placing the product on the market is not the manufacturer.

The Twenty-fifth World Health Assembly adopted a resolution requesting the Director-General “to undertake a study of the most feasible means of indicating by a uniform system of marking the limits of shelf life of pharmaceutical products under the conditions of their storage, as well as the date
of manufacture and batch number, and the maintenance of records which facilitate tracing of distribution, and to report thereon to a future World Health Assembly ".".

Accordingly means were sought to incorporate the elements set out in the above resolution both in the Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce and in the revised text of Good Practices in the Manufacture and Quality Control of Drugs, in such a way that the implementation of the Certification Scheme would constitute an important step to achieving the objectives of the resolution.

As part of the revision of Good Practices in the Manufacture and Quality Control of Drugs, it was agreed that the establishment of expiry dates and shelf life specifications, on the basis of stability tests performed by the quality control department of the manufacturer, be no longer optional. In the revised Certification Scheme expiry dates are required on the batch certificates. The inclusion of expiry dates on the labelling of finished products would provide a uniform system of indicating the shelf life under specified conditions of storage, if appropriate legislation existed in the importing countries.

The resolution also refers to information that could be used in tracing distribution when it is necessary to recall batches of finished products. In cases where the protection of public health is at stake, the prompt and complete recall of specific batches of finished drugs would be facilitated if appropriate legislation existed in the importing countries relating to the maintenance of records by importers and wholesalers.

Revised texts of Good Practices in the Manufacture and Quality Control of Drugs and Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, incorporating the recommendations of the Committee, are included as Annex 1 to this report.

2. SPECIFICATIONS FOR RADIOPHARMACEUTICALS

The Committee undertook the revision of Appendix 13, "Radioactivity", and Appendix 13a, "Table of physical characteristics of radio-nuclides" of the International Pharmacopoeia, and the revision of existing monographs on radiopharmaceuticals. It also considered a number of new draft monographs for radiopharmaceuticals.

2.1 Revision of appendices

The Committee undertook the revision of the texts, based on drafts prepared by consultants, which had taken into account developments in the field. The revision concerned especially the procedures used in the detection and measurement of radiation, including the newer techniques of radiation spectrometry employing semiconductor devices, and difficulties arising in the determination of radionuclidic and radiochemical purities. The "Table of physical characteristics of radionuclides" was expanded to include all radionuclides mentioned in the monographs, including radionuclidic impurities.

The revised texts of Appendices 13 and 13a are contained in Annex 2.

2.2 Revision of existing specifications

The Committee considered a number of proposals by consultants for revision of the existing monographs, together with certain amendments made necessary by changes in Appendix 13, "Radioactivity". The amendments accepted included requirements for the radiochemical purity of Cyanocobalamin (57Co) and of Cyanocobalamin (58Co) at expiry, more explicit instructions for the assay of iodine-125 and mercury-197, and more appropriate directives for pyrogen testing of Iodinated (131I) Human Serum Albumin Injection and Iodinated (131I) Human Serum Albumin Injection. Of special note was the distinction made in the monograph on Sodium Pertechnetate (99mTc) Injection between molybdenum-99 prepared by neutron irradiation of molybdenum and molybdenum-99 derived from uranium fission.

The texts of the revised monographs on radiopharmaceuticals are reproduced in full in Annex 2, so that the proposed international requirements are readily available in a single document.

2.3 Proposed specifications for new radiopharmaceuticals

The Committee considered several new draft monographs that had been developed as a result of collaboration between a number of institutions engaged in studies on radiopharmaceuticals and of consultations with the appropriate experts and with the International Atomic Energy Agency.

Provisional specifications were adopted for the following radiopharmaceuticals:

- Indium (113mIn) Chloride Injection
- Indium (113mIn) Pentetate Complex Injection
Macrosolv (99mTc) Injection
Technetium (99mTc) Labeled Human Serum Albumin Injection
Xenon (133Xe) Injection

A monograph on Technetium (99mTc) Pentetate Complex Injection was also considered, but it was decided to defer adoption until a test could be devised to indicate with more certainty the presence of pentetic acid.

2.4 Future work

The Committee discussed the main directions of future work to be carried out in the field of specifications for radiopharmaceuticals.

It was recommended that consideration be given to the addition of further sections to the general requirements for the radiopharmaceuticals contained in Appendix 13, “Radioactivity”, dealing with the following topics:

— operation of generator systems for production of radiopharmaceuticals;
— requirements for application of the Limulus test for endotoxin, especially for short-lived radiopharmaceuticals; and
— requirements concerning volumes of injection in single-dose containers of radiopharmaceuticals.

The Committee also recommended that in the course of further work on monographs for new radiopharmaceuticals, priority should be given to the following products:

— Indium (111In) pentetate complex injection for application in cisternography;
— Technetium (99mTc) sulfur colloid injection;
— Technetium (99mTc) tin pyrophosphate injection for use as a bone-imaging agent.

3. FURTHER WORK ON QUALITY CONTROL SPECIFICATIONS

In a resolution of the World Health Assembly,* the Director-General was requested to continue work on analytical control specifications for international acceptance, to be published as they are completed. Hitherto

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this work has been accomplished by members of the Secretariat working with consultants to produce drafts, which have then been examined and approved by the Expert Committee.

This procedure is demanding in time and resources and makes the above resolution difficult to implement. Specifications cannot be provided as quickly as needed because of the intervals between successive meetings of the Committee. Moreover, it would seem more profitable for the Committee to deliberate on matters of general importance in quality control than to spend time in discussing the details of specifications.

To comply with the above resolution the Committee recommended that the Secretariat initiate certain procedures designed to produce an increased flow of specifications. These procedures would ensure the establishment by the Secretariat, working with members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and with other specialists, of:

- specifications for raw materials, comprising active and inactive ingredients, in pharmaceutical products;
- general methods and tests necessary to support such specifications;
- chemical reference substances necessary to support such specifications.

When specifications have been developed in this way, in accordance with the principles and priorities established by the Committee, and when adequate consultations have been carried out amongst members of the Expert Advisory Panel, established pharmacopoeia commissions, and other appropriate interested parties, the specifications should be published in accordance with the resolution quoted above. When the necessary reference substances have been prepared they should be established after appropriate consultations.

In certain other categories, namely general requirements for dosage forms, and questions of broader general application, such as, for example, the overall control of sterility, the Secretariat is encouraged to elaborate proposals for discussion, and approval, by the Committee.

Work on specifications for individual preparations would be initiated by the Secretariat only when specifically recommended by the Committee.

The selection of drugs for which internationally recommended quality control specifications are to be established should be carried out by the Secretariat in consultation with members of the Expert Advisory Panel, and other specialists. It was recommended that priority should be given to drugs that are widely used throughout the world, and that adequate weight should be given to the therapeutic value of the selected drugs. High priority would be accorded to drugs that are important in WHO health programmes.
Priority should also be given to drugs that are likely to contain impurities arising from degradation or because of difficulties in manufacture.

4. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

4.1 Reports from the WHO Centre

Reports \[^a\] from the WHO Centre for Chemical Reference Substances were reviewed by the Committee.

4.1.1 Establishment of new reference substances

The Committee noted that in accordance with the authorization given in its previous reports the following new International Chemical Reference Substances had been established:

- Aesculine Salicylate
- Allopurinol
- 3-Aminopyrazole-4-carboxamide
- Hemisulfate
- Asathioprine
- Bendazol Hydrochloride
- Benzoarbarbital
- Benzylamine Sulfate
- Benzylpenicillin Sodium
- Betanidine Sulfate
- Bupivaçaine Hydrochloride
- 5-Chloro-2-methylaminobenzophenone
- Diazepam
- Dicoflinium Iodide
- N,N’-Di-(2,3-xylyl)antranilamide
- Etasynic Acid
- Etodaride
- Haloperidol
- Imipramine Hydrochloride
- Levodopa
- Mefenamic Acid
- Metazide
- Methaqualone
- Rose Bengal Sodium
- Trimethylguanidine Sulfate

4.1.2 Replacement of current reference substances

The Committee also noted that the following International Chemical Reference Substances had been replaced by new batches:

- Ampicillin
- Ampicillin Sodium
- Ampicillin Trihydrate
- Chloramphenicol
- Cloxacillin Sodium
- Estrone
- Meticillin Sodium
- Nafillin Sodium
- Propicillin Potassium
- Tubocurarine Chloride
- Vitamin A Acetate

4.1.3 *Future work*

The Committee was informed that work had been initiated to establish the following reference substances in accordance with the authorization given in its twenty-fourth report:

- Chloracyzine Hydrochloride
- Chloromerdin
- Ectothiopate Iodide
- Fluphenazine Hydrochloride
- Idoxuridine
- Metformin Hydrochloride
- Tolnaftate

The Committee noted that the WHO Expert Committee on Biological Standardization had requested the WHO Secretariat to investigate the possibilities of providing chemical reference substances for a number of materials for which International Biological Standards and Reference Preparations had been discontinued or were considered unnecessary. It had been suggested that these materials could now be adequately characterized by physical and chemical methods alone.

After discussing the problems involved, the Committee authorized the establishment of the following chemical reference substances when needed for physical or chemical tests in forthcoming new or revised specifications:

- Anhydrotetracycline
- Colecalciferol
- Cyanocobalamin
- 4-Epianhydrotetracycline
- 4-Epitiotetracycline
- Ergocalciferol
- Tetracycline

In reviewing a report on pecilocin, the Committee concluded that, although the chemical structure had been elucidated and a relatively pure material had been prepared, the composition of the commercially available material was such that adequate quality control of the material was unlikely to be achieved by chemical and physical means alone at the present time. It was also noted that highly purified pecilocin appeared to be unstable. Accordingly it was recommended that no International Chemical Reference Substance be prepared.

The Committee noted that work carried out on reference substances of phenoxymethylpenicillins and of ergotamine tartrate had revealed that the monographs for these substances in the International Pharmacopoeia were in need of revision. It also noted the importance of limiting the amount of an inactive polymorphic form in certain preparations of chloramphenicol palmitate and recommended the establishment of reference substances for this purpose.

It was noted that the substantial increase in the rate at which new specifications were to be produced (see item 3), and the need to establish
further reference substances, would result in a considerable increase in the work-load of the WHO Centre for Chemical Reference Substances.

4.2 General guidelines

General guidelines for the establishment, maintenance, and distribution of chemical reference substances were considered by the Committee and its recommendations appear in Annex 3 to this report. During the discussion it was noted that some specialists considered that comparison with standardized reference spectra might replace the use of chemical reference substances for identification tests based on infrared spectroscopy. For such comparisons to be valid, it would be necessary to prescribe minimum requirements for the calibration of spectrophotometers and it was noted that certain national and international Organizations had made recommendations for this purpose. The Committee asked that the feasibility of such use of reference spectra be investigated and that due note be taken of established recommendations for the calibration of infrared spectrophotometers. Similar considerations might apply to other instrumental techniques.

It was noted that informal arrangements existed on a limited basis for exchange of information relating to the establishment of reference substances by various national and regional authorities. It was recommended that the possibility of a more formal and worldwide exchange of such information should be explored. In this connexion, it would be useful to compile a list of substances available from various authorities, the purposes for which such substances were offered, and the names of the issuing authorities. The Secretariat was asked to investigate the possibility of producing and maintaining an up-to-date list.

In concluding its discussion of this subject, the Committee recognized the importance of WHO activity in work on the provision of chemical reference substances and in fostering greater collaboration and unification among various national and regional authorities responsible for issuing reference substances. It urged that high priority be accorded to these activities.

5. MICROBIAL CONTAMINATION
OF NON-STERILE DRUGS

The Committee examined a joint report* by the Committee of Laboratories and Official Drug Control Services and the Industrial Pharmacists

* *Journal mondial de la pharmacie, 15 : 88 (1972); unpublished document WHO/PHARM/74.477.
Section of the International Pharmaceutical Federation on the subject of microbial purity of non-sterile drugs. It noted with satisfaction the continuing effort being applied to studies of this complex problem.

It was recognized that many variables, such as type of starting material, manufacturing processes, and the type of dosage form, affect the level of microbial contamination of finished products.

The Committee drew attention to the conclusion in the joint report that preparations containing crude products of biological origin present the greatest hazard, and that synthetic raw materials and purified biological substances are generally less of a problem, although exceptions exist even in these categories.

The Committee accepted the recommendations made in the joint report that preparations should be free of pathogenic bacteria, and that counts of microorganisms present in finished products provide the most satisfactory index of hygienic manufacture. In view of the imprecision inherent in such estimates, occasioned both by the techniques utilized and by the non-uniform distribution of microbial contamination, the Committee agreed that, for the present, it was not possible to propose general requirements.

It seems likely that there will be variations in the magnitude of the problems encountered in various regions, although no adequate information was available. A single solution to the overall problem could not, therefore, be advanced. The Committee advocated that this matter be subject to constant vigilance by national control authorities and other interested parties.

6. QUALITY REQUIREMENTS FOR PLASTIC CONTAINERS

It was recommended in the twenty-fourth report * of the WHO Expert Committee on Specifications for Pharmaceutical Preparations that a study be made of information and data available on the suitability of plastics as materials for containers for drugs.

A comprehensive publication † on the subject was reviewed by the Committee. Because of the wide variety of types of container, it was thought necessary to select certain categories for initial attention. The Committee therefore recommended that provisional requirements for plastic containers for pharmaceuticals be published as Annex 4 to this report in order to encourage further work and that comments be invited.

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It contains test methodology and limits for plastic containers used for infusions, injections, and ophthalmics. These items were accorded high priority in the conclusions described in the publication *(page 25).*

7. PHARMACEUTICAL ASPECTS OF DRUG EVALUATION FOR REGISTRATION

A variety of information is required at the time of drug registration, including pharmacological, toxicological, clinical, and pharmaceutical data. The Committee reviewed the pharmaceutical information required. The assembling of information on drugs is a cumulative process, which follows the various phases of development from the primary drug substance into a pharmaceutical preparation. The depth of detail on certain aspects would, therefore, vary with the phase of development of the preparation. The various aspects on which information is required are described in detail in Annex 5.

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Annex 1

A. GOOD PRACTICES IN THE MANUFACTURE AND QUALITY CONTROL OF DRUGS *

1. General considerations

In the manufacture of drugs, overall control is essential to ensure that the consumer receives drugs of high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be necessary to save life or to restore or preserve health.

Difficulties will undoubtedly arise in establishing the necessary criteria for the manufacture of drugs that will meet established specifications and that can, therefore, be used with confidence. Recommended practices for the manufacture of drugs of desired quality are set forth below. Adherence to these practices, complementing the various control tests followed from the beginning to the end of the manufacturing cycle, will contribute substantially to the manufacture of consistently uniform batches of high-quality drugs.

The manufacturer must assume responsibility for the quality of the drugs he produces. He alone can avoid mistakes and prevent mishaps by exercising adequate care in both his manufacturing and control procedures.

The good practices outlined below should be considered as general guides; whenever necessary, they may be adapted to meet individual needs, provided the established standards of drug quality are still achieved.* They are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of drugs in their finished dosage forms.

Sometimes it occurs that several firms cooperate in the production (including packing and labelling) of the finished dosage forms of drugs. It may also occur that a finished, packed, and labelled drug is repacked and/or relabelled, giving it a new designation. It should be pointed out that since such procedures constitute part of a manufacturing operation,

* These requirements are a revised version of those published in WHO Official Records, No. 176, 1969, pp. 99-104 (see this report, p. 5).

* Additional recommendations specifically applicable to biological products are set forth in a number of sets of Requirements for Biological Substances adopted by the WHO Expert Committee on Biological Standardization and other WHO expert groups and published in the WHO Technical Report Series.
they should be subject to the relevant requirements of those proposed below.

The requirements set forth herein are intended to apply primarily to preparations for human administration. However, equal attention should be given to quality in the manufacture of veterinary preparations.

2. Definitions

For the purposes of this document, the following definitions are adopted.

**Drug.** Any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use in (1) the treatment, mitigation, prevention, or diagnosis of disease, an abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction, or modification of organic functions in man or animal.

**Manufacturing.** All operations involved in the production of a drug, including processing, compounding, formulating, filling, packaging, and labelling.

**Starting materials.** All substances, whether active or inactive or whether they remain unchanged or become altered, that are employed in the manufacture of drugs.

**Batch.** A quantity of any drug produced during a given cycle of manufacture. The essence of a manufacturing batch is its homogeneity.

**Batch number.** A designation (in numbers and/or letters) that identifies the batch and that permits the production history of the batch, including all stages of manufacture and control, to be traced and reviewed.

**Quarantine.** The status of a material that is set apart and that is not available for use until released.

**Quality control.** All measures designed to ensure the output of uniform batches of drugs that conform to established specifications of identity, strength, purity, and other characteristics.

**"Half-finished" product.** Any material or mixture of materials that must undergo further manufacture.

3. Personnel

Experts responsible for supervising the manufacture and quality control of drugs should possess the qualifications of scientific education and practical experience required by national legislation. Their education should include
the study of an appropriate combination of (a) chemistry (analytical chemistry, biochemistry, etc.); (b) chemical engineering; (c) microbiology; (d) pharmaceutical sciences and technology; (e) pharmacology and toxicology; (f) physiology and histology; and (g) other related sciences. They should also have adequate practical experience in the manufacture and quality control of drugs. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of drugs.

Such experts should preferably not have any interests outside the manufacturer's organization that (a) prevent or restrict their devoting the necessary time to their assigned responsibilities or (b) may be considered to entail a conflict of financial interest. Finally, they should be given full authority and the facilities necessary to carry out their duties effectively.

In addition to the experts noted above, an adequate number of technically trained personnel should be available to carry out the manufacturing and quality control operations in accordance with established procedures and specifications. All personnel should be motivated towards the establishment and maintenance of high-quality standards.

4. Premises

4.1 General

Drugs should be manufactured, processed, packaged, labelled, and tested in premises that are suitable for these purposes.

In determining the suitability of premises regard should be paid to:

(1) the compatibility of other manufacturing operations that may be carried out in the same or adjacent premises;

(2) the adequacy of the working space, which should allow orderly and logical placement of equipment and materials so as to (a) minimize the risk of confusion between different drugs or their components, (b) control the possibility of cross-contamination by other drugs or substances, and (c) minimize the risk of omission of any manufacturing or control step;

(3) those physical aspects of the premises that could affect the quality and safety of products: buildings should be so designed and constructed as to prevent the entry of animals and insects; interior surfaces (walls, floors and ceilings) should be smooth and free from cracks, should not
shed particulate matter, and should permit easy cleaning and if necessary disinfection;

(4) lighting, heating and ventilation and, if necessary, air conditioning required to maintain a satisfactory temperature and relative humidity that will not adversely affect the drug during manufacture and storage, nor the accuracy and functioning of laboratory instruments.

4.2 Storage areas

The suitability of storage areas cannot be strictly specified in a manner that meets all possible contingencies. However, the following principles should be observed:

(1) storage areas should provide adequate space, suitable lighting, and should be arranged and equipped to allow dry, clean, and orderly placement of stored materials and products, whenever necessary under controlled conditions of temperature and humidity;

(2) such areas should provide for suitable and effective separation of quarantined and other materials and products;

(3) special and segregated areas should be available for storage of
   (a) substances presenting special risks of fire and explosion;
   (b) highly toxic, narcotic, and other dangerous drugs (these areas should be adequately protected against theft);
   (c) rejected and recalled materials and products.

4.3 Special

For special purposes, such as the manufacture of drugs that are intended to be sterile but cannot be sterilized in their final containers, separate enclosed areas, specifically designed for the purpose, should be provided. These areas should be entered through an air-lock and should be essentially dust-free and ventilated with an air supply through bacteria-retaining filters giving a pressure higher than in adjacent areas. Such filters should be checked for performance on installation and periodically thereafter. All surfaces in manufacturing areas should be designed to facilitate cleaning and disinfection.

Routine microbe counts of the air in the areas described above should be carried out before and during manufacturing operations. The results of such counts should be checked against established standards, and adequate records of the counts should be maintained.
For the manufacture of drugs that can be sterilized in their final containers, the requirements given above are considered essential, with the exception of mandatory sterilization of air supplies. The design of areas used for this purpose should preclude the possibility that products intended for sterilization could be mixed with, or taken to be, products already sterilized. This may conveniently be effected by the use of double-ended sterilization apparatus opening into separate and non-communicating areas.

5. Equipment

Manufacturing equipment should be designed, placed, and maintained in such a way as to

(1) be suitable for its intended use;
(2) facilitate thorough cleaning wherever necessary;
(3) minimize any contamination of drugs and their containers during manufacture; and
(4) minimize the risk of confusion or the omission of a processing step such as filtration or sterilization.

Operating conditions within an apparatus used to sterilize products should be monitored by means of recording devices, which should be initially calibrated and checked at approved intervals by approved methods. Suitable standardized microbiological indicators may be used to demonstrate the adequacy of the sterilization process.

Manufacturing equipment and utensils should be thoroughly cleaned and, when necessary, sterilized, and should be maintained in accordance with specific written directions. When indicated, all equipment should be disassembled and thoroughly cleaned, to preclude the carry-over of drug residues from previous operations. Adequate records of such procedures should be maintained.

Equipment used for aseptic filling should be checked at suitable intervals by microbiological methods.\(^\text{*}\) Weighing and measuring equipment used in production and quality control should be calibrated and checked at suitable intervals by appropriate methods. Adequate records of such tests should be maintained.

\(^\text{*}\) This may be accomplished by conducting normal filling operations using suitable sterile liquid bacteriological media or other media suitable for dry powder filling, as the case may be, taking into consideration the risks of microbiological contamination of the equipment.

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6. Sanitation

Manufacturing premises should be maintained in accordance with the sanitary standards issued by the appropriate health authority. They should be clean and free from accumulated waste, orderly, and free from vermin. A written sanitation programme should be available, indicating:

(1) areas to be cleaned, and cleaning intervals;
(2) cleaning procedures to be followed and, if necessary, equipment and materials to be used for cleaning; and
(3) personnel assigned to and responsible for cleaning operations.

Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

Sufficient clean, well-ventilated toilet facilities, including facilities for hand washing and rooms for changing clothes, should be available near working areas for the use of manufacturing personnel.

7. Starting materials

An inventory should be made of all starting materials to be used at any stage in the manufacture of drugs, and records should be kept of the supplier, the origin (if possible), date of receipt, date of analysis, date of release by the quality control department, and their subsequent use in manufacture.

All such materials must be:

(1) identified, and their containers examined for damage;
(2) properly stored in quarantine;
(3) properly sampled by the quality control department;
(4) tested for compliance with requirements (all materials should be marked to indicate that they are undergoing testing); and
(5) released from quarantine by the quality control department by means of written instructions.

Starting materials that are accepted or approved should be properly and conspicuously labelled as such, and should then be transferred, if necessary, to areas designated for the storage of such materials.

All rejected starting materials should be conspicuously identified as such, and should be destroyed or returned to the supplier as soon as possible.
8. Manufacturing operations

Manufacturing operations and controls should be carried out under the supervision of experts, as specified in section 3.

8.1 Cleanliness

Before any manufacturing operation is begun, a check should be made to ensure that all apparatus and equipment to be used in the operation has been cleaned and/or sterilized (see section 5).

8.2 Equipment and containers

The contents of all vessels and containers used in manufacture and storage between manufacturing stages must be identified by conspicuously placed and clearly legible labels, bearing the name and/or identification code of the processed materials and the necessary batch identification data. Similar labels should be attached to mechanical manufacturing equipment during its operation.

8.3 Precautions against contamination and confusion (mix-up)

All manufacturing operations should be confined to separate areas intended for such purposes, with complete equipment used exclusively in those areas, or measures should be taken to ensure that neither cross-contamination nor confusion (mix-up) can occur.∗

In manufacturing areas, clean working garments should be worn over, or in place of, street clothing.

The manufacture of drugs intended to be sterile should be performed in areas specially designed and constructed, as indicated in section 4.3. Whenever the different operations are not physically separated, and there is a possibility that unsterilized and sterilized products might be confused, all containers of batches of products for sterilization should bear a clear indication of whether or not their contents have been sterilized.

Products that undergo sterile operations should be protected from contamination by using methods such as laminar-flow techniques, and by ensuring that personnel wear clean, sterile gowns, head coverings, masks, rubber gloves, and shoe coverings. Before dressing and entering sterile areas, personnel must wash their hands with a suitable disinfectant.

All dust-producing operations involving highly potent substances, particularly antibiotics, should be conducted in confined areas that are

∗ The simultaneous manufacture, in adjacent areas that are not physically separated, of drugs that are similar in appearance should be avoided.
provided with adequate exhaust systems or that are maintained under appropriate pressure, so as to prevent cross-contamination. Adequate precautions should be taken to prevent the recirculation of contaminated air.

8.4 Manufacturing personnel

No person known to be affected with a disease in a communicable form, or to be the carrier of such a disease, and no person with open lesions on the exposed surface of the body, should be engaged in the manufacture of drugs. Manufacturing personnel should undergo periodic health checks. In order to prevent any impairment of health caused by the handling of hazardous or potent materials, manufacturing personnel should, whenever necessary, wear protective clothing, shoes, headgear, dust masks, etc., and such protective clothing should remain in the area in which it is used. In some instances, it may be necessary to have restrictions on the movement of personnel to and/or from special working areas.

8.5 Documents relating to manufacturing procedures

Documents relating to manufacturing procedures should be prepared for each drug under the direct supervision of experts (see section 3) who have the necessary authority. They should contain at least the following information for each drug:

1. its name and dosage form;
2. a description or identification of the final container(s), packaging material(s), and labels and, where applicable, of the closure(s) to be used;
3. the identity, quantity, and quality of each starting material to be used, irrespective of whether or not it appears in the finished drug (the permissible excess ("overage") that may be included in a formulated batch should be indicated);
4. the theoretical yields to be expected from the formulation at different stages of manufacture and the permissible yield limits;
5. detailed instructions for, and precautions to be taken in, manufacture and storage of the drug and of "half-finished" products; and

* Such documents should not be handwritten nor contain handwritten amendments or comments. When necessary they should be rewritten and all outdated instructions withdrawn, to avoid the possibility of re-use. They should be suitable for copying in a manner that avoids any possibility of a transcription error.
(6) a description of all necessary quality control tests and analyses to be carried out during each stage of manufacture, including the designation of persons or departments responsible for or charged with the execution of such tests and analyses.

8.6 Batch manufacturing records

Manufacturing records must provide a complete account of the manufacturing history of each batch of a drug, showing that it has been manufactured, tested, and analysed in accordance with the manufacturing procedures and written instructions described in section 8.5. A separate batch manufacturing record should be prepared for each batch of drug produced, and should include the following information:

(1) name and dosage form;
(2) date of manufacture;
(3) batch identification;
(4) complete formulation of the batch (see section 8.5, point 3);
(5) the batch number (or analytical control number) of each component used in the formulation;
(6) the actual yield obtained at different stages of manufacture of the batch as compared with the theoretical yield (see section 8.5, point 4);
(7) a duly signed record of each step followed, precautions taken, and special observations made throughout the manufacture of the batch;
(8) a record of all in-process controls followed and of the results obtained;
(9) a specimen of the actual coded label used;
(10) identification of packaging materials, containers, and, where applicable, closures used;
(11) signature of the expert responsible for the manufacturing operations, and the date of his signature;
(12) an analytical report showing whether the batch complies with the prescribed specifications for the drug, dated and duly signed by the responsible expert;
(13) a record of the decision regarding the release or rejection of the batch by the quality control department (see section 10.1(5)); and
(14) if the batch is rejected, a record of its disposal or utilization.

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8.7 Maintenance of batch manufacturing records

For reference purposes, all batch manufacturing records should be retained for a specified period.

9. Labelling and packaging

Labelling and packaging materials, including leaflets, should be stored and handled in such a way as to ensure that labels, packaging materials and leaflets relating to different products do not become intermixed. Access to such materials should be restricted to authorized personnel.

Prior to packaging and labelling of a given batch of a drug, the manufacturing and control records specified in section 8.6 should show that the batch has been duly tested, approved, and released by the responsible quality control expert. Prior to being issued, all labels for containers, cartons, and boxes and all circulars, inserts, leaflets, etc., should be examined and released as satisfactory for use by the designated person(s) (see section 10.1(4)).

To prevent packaging and labelling errors, a known number of labelling and packaging units should be issued and, if required, coded. Such issuance should be made against a written, signed request that indicates the quantity and types required.

Upon completion of the packaging and labelling operation, a comparison should be made between the number of labelling and packaging units issued and the number of items labelled and packaged plus the number of units not used. All coded unused units should be destroyed. Any significant or unusual discrepancy in the numbers should be carefully investigated.

All finished drugs should be identified by labelling that should bear, clearly indicated, at least the following information:

(1) the name of the drug;
(2) a list of the active ingredients, showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight or volume;
(3) the batch number assigned by the manufacturer;
(4) the expiry date, if required (see 10.1(8));
(5) any special storage conditions or handling precautions that may be necessary;
(6) directions for use, and warnings and precautions that may be necessary; and

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(7) the name and address of the manufacturer or the person responsible for placing the drug on the market.

10. The quality control system

10.1 Quality control department

Every manufacturing establishment must have a quality control department supervised by a suitably qualified expert directly responsible to management but independent of other departments. The quality control department should control all starting materials, monitor the quality aspects of manufacturing operations, and control the quality and stability of drugs.

The quality control department should have the following principal duties:

(1) to prepare detailed instructions, in writing, for carrying out each test and analysis;

(2) to release or reject each batch of starting material;

(3) to release or reject "half-finished" products, if necessary;

(4) to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;

(5) to release or reject each batch of finished drug that is ready for distribution;

(6) to evaluate the adequacy of the conditions under which starting materials, "half-finished" products, and finished drugs are stored;

(7) to evaluate the quality and stability of finished drugs and, when necessary, of starting materials and "half-finished" products;

(8) to establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions;

(9) to establish, and when necessary revise, control procedures and specifications; and

(10) to be responsible for the examination of returned drugs, to determine whether such drugs should be released, reprocessed, or destroyed. Adequate records of the disposition of such drugs should be maintained.

In order to fulfil its responsibilities, the quality control department should take samples (e.g., of starting materials and finished drugs), accord-
ing to established procedures. The samples should be properly labelled, and portions should be kept for future reference.

The quality control department should maintain adequate analytical records concerning the examination of all samples taken. Such records should include:

(a) the result of every test performed, including observations and calculations, relating to compliance with the established specifications;
(b) the source of the specifications used;
(c) the signature(s) of the person(s) who performed the quality control procedures; and
(d) a final review, the decision taken, and a dated endorsement by a duly authorized expert.

10.2 Quality control laboratory

The quality control department should have a laboratory available to it. The laboratory should:

(1) be adequately staffed and fully equipped for performing all quality control tests and analyses required during and after manufacture; *
(2) be supervised by a qualified expert (see section 3).

11. Self-inspection

In order to maintain strict adherence to all manufacturing procedures and prescribed controls, it may be advisable for a firm to designate an expert or a team of experts to conduct regularly scheduled inspections of its overall manufacturing and control operations. However, this should not be taken to mean that any firm that exercises self-inspection should be exempt from the official inspections required by the laws and regulations of the country in which it is located.

12. Distribution records

Adequate records should be maintained of the distribution of a finished batch of a drug in order to facilitate prompt and complete recall of the batch if necessary.

* If animal tests are necessary, the animals should be given adequate quarters and care (for further information, see WHO Technical Report Series, No. 323, 1966, pp. 14, 16). The use of outside independent laboratories may be advisable for specialized and complex analytical and biological procedures that require the use of costly equipment and that can be performed only by technicians with specialized training. Such laboratories should be adequately staffed and fully equipped to perform such analyses.
13. Complaints and reports of adverse reactions

Reports of injuries or adverse reactions resulting from the use of a drug should be forwarded to the appropriate authorities. Complaints regarding the quality of a drug, including any change in its physical characteristics, must be thoroughly investigated. If they prove well-founded, appropriate measures must be taken as soon as possible. The measures taken should be recorded and filed with the original complaint.

B. CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE *

Part I — Certification of Pharmaceutical Products

1. For the purpose of this Certification Scheme "pharmaceutical product" means any medicine in its finished dosage form, intended for human use, that is subject to control by legislation in the exporting Member State and in the importing Member State.

2. A pharmaceutical product exported or imported under this Certification Scheme would be certified by the competent authority of the exporting Member State on a Certificate of Pharmaceutical Products, issued at the request of the interested party, to be sent to the competent authority of the importing Member State, which would decide to grant or to refuse the authorization for sale or distribution of the certified product, or to make the authorization conditional on the submission of supplementary data.

3. The issue of the Certificate of Pharmaceutical Products would be subject to the conditions required by the competent authority of the exporting Member State in order to certify that:

   (a) the product is authorized for sale or distribution within the exporting Member State (if not, the reasons therefore would be stated on the certificate); and
   (b) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals to show that the manufacturer

* This Certification Scheme is a revised and expanded version of that published in WHO Official Records, No. 176, 1969, pp. 104-105 (see this report, p. 5).
conforms to requirements for good practices in manufacture and quality
control, as recommended by the World Health Organization, in respect
of products to be sold or distributed within the country of origin or to
be exported.

A suggested layout of a Certificate of Pharmaceutical Products, with
explanatory notes, is attached.

4. If certificates of individual batches of products covered by a Certif-
icate of Pharmaceutical Products are required, such certificates could be
issued either by the manufacturer or by the competent authority of the
exporting Member State, according to the nature of the product and the
requirements of the exporting Member State or of the importing Member
State. The batch certificate would indicate the name and dosage form of
the product, the batch number, the expiry date and storage conditions,
a reference to the Certificate of Pharmaceutical Products, and a statement
that the batch conforms either to the requirements of the competent author-
ity for sale or distribution within the exporting Member State (with reference
to the authorization) or, as the case may be, to published specifications,
or to established specifications to be provided by the manufacturer. The
certificate could also include data on packaging, labelling, nature of
the container, the date of manufacture, results of analysis, and other
data.

Part II — Exchange of Information

1. Upon the request of the competent authority of the Member State
into which a pharmaceutical product covered by this Certification Scheme
is to be or has been imported, the competent authority of the exporting
Member State should provide:

(a) information on the implementation of the Requirements for Good
Practices in the Manufacture and Quality Control of Drugs as recom-
manded by the World Health Organization; *

(b) information on controls of the product as exercised by the compe-
tent authority of the exporting Member State;

(c) the names and functions of the persons designated to sign certificates
of individual batches of the product to be exported.

Information on general and specific standards of quality control of the
product to be exported, in so far as they are required to comply with legis-

* It is realized that in some countries this may require the consent of the manufacturer.
relative provisions of the importing Member State, could also be supplied with the consent of the manufacturer.

2. In the case of quality defects of products imported under this Certification Scheme that are considered to be of a serious nature by the importing country, not attributable to local conditions and circumstances, and appearing after the introduction of a particular batch into the importing Member State, the competent authority should notify the occurrence, together with the relevant facts, to the competent authority of the exporting Member State that had issued the Certificate for the product concerned, with a request to institute inquiries. Conversely, if the competent authority of the exporting Member State ascertains serious quality control defects, that competent authority should notify the competent authority of the importing Member State.

Part III — Participating Member States

1. Each Member State agreeing to participate in the Certification Scheme should communicate (a) the name and address of its principal authority to be considered as competent within the meaning of the Certification Scheme, and (b) any significant reservations relating to its participation, to the Director-General of the World Health Organization, who would notify all other Member States.

2. Exporting Member States participating in the Certification Scheme shall ensure that:
   (a) authorization for sale or distribution of pharmaceutical products is subject to appropriate testing measures, by the competent authority, designed to ensure their quality, and that adequate laboratory facilities are available for this purpose;
   (b) the pharmaceutical industry is obliged to conform to requirements for good practices in the manufacture and quality control of drugs as recommended by the World Health Organization;
   (c) the competent authority is empowered to conduct appropriate investigations to ensure that manufacturers conform to the requirements referred to in (b), including, for example, the examination of records and the taking of samples;
   (d) the inspectors of the services of its competent authority have appropriate qualifications and experience.

3. Exporting Member States participating in the Certification Scheme should, whenever possible, ensure that the international nonproprietary
names, whenever available, are used in the description of the composition of the product on the Certificates and, as far as possible, appear on the labelling of pharmaceutical products to be exported under the Certification Scheme.

CERTIFICATE OF PHARMACEUTICAL PRODUCT(S)*

Name and dosage form of product: .................................................................
Name and amount of each active ingredient: *

.............................................................................................................
Manufacturer, and/or when applicable, the person responsible for placing the product on the market:

.............................................................................................................
Address(es):
.............................................................................................................

It is certified that:

☐ This product has been authorized to be placed on the market for use in this country.
  Number of permit and date of issue (if applicable):
  .............................................................................................................

☐ This product has not been authorized to be placed on the market for use in this country for the following reasons:
  .............................................................................................................

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspection at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported (see Explanatory Notes overleaf).

.............................................................................................................
(place and date)
.............................................................................................................
(signature of designated authority)

* This form may be adapted to cover several products of the same manufacturer.
* Use, whenever possible, international nonproprietary names (INN) or national nonproprietary names.
Explanatory Notes

Certificate of pharmaceutical product(s)

This certificate is intended to define the status of the pharmaceutical product and its manufacturer in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required.

The requirements for good practices in the manufacture and quality control of drugs mentioned in the certificate refer to the text* recommended by the Twenty-second World Health Assembly in its resolution WHA22.50, together with any modifications later adopted by the World Health Assembly.

Batch certificates

If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products and a statement that the batch conforms to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, where appropriate, to published specifications or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.

Annex 2

SPECIFICATIONS FOR RADIOPHARMACEUTICALS *

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* Attention is drawn to the provisional nature of these appendices and monographs. It should also be noted that they are intended to be used in conjunction with the second edition of the International Pharmacopoeia (World Health Organization, Geneva, 1967), the Supplement 1971, and the Specifications for Reagents mentioned in the Pharmacopoeia (World Health Organization, Geneva, 1963).
AQUAE TRITIATAE (H) INJECTIO

Tritiated Water (H) Injection

1974 Revision

Tritiated Water (H) Injection is a sterile solution of tritiated water (H) in Water for Injection, which may be made isotonic with blood by the addition of Sodium Chloride.

Tritium (H) is a radioactive isotope of hydrogen and may be prepared by neutron irradiation of lithium.

The content of tritium is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of tritium stated on the label, at the reference date stated on the label.

Not more than 0.1 per cent. of the total radioactivity shall be due to radionuclides other than tritium at the reference date stated on the label.

The solution is sterilized by Method 1 — Heating in an autoclave described under “Injectiones” in Ph. Int. II.

The radioactive half-life of tritium (H) is 12.35 years.

Description. A clear, colourless solution.

Identification. The sample is examined in a suitable liquid scintillation counter, and the counts are determined for various settings of the discriminator. The counts at each discriminator setting suitably corrected for background are then plotted against the discriminator setting as an arbitrary abscissa. The shape of the curve so obtained is identical with that obtained using a standardized tritium solution. Tritium is a pure beta emitter, with maximum energy of 0.0186 MeV.

Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, “Radioactivity” (1974 revision), except that the radionuclidic purity shall be not less than 99.9 per cent.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized tritium solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized tritium solutions are available from national standardizing laboratories.

Storage. Complies with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Labelling. Tritiated Water (H) Injection should be labelled as specified under “Labelling” in Appendix 13 “Radioactivity” (1974 revision).
Gold (198Au) Colloidal Injection

Gold (198Au) Colloidal Injection is a sterile colloidal solution of gold-198 stabilized with gelatin. It may be prepared by reducing a salt of gold-198 with a suitable reducing agent, such as dextrose in alkaline solution, in the presence of gelatin.

Gold-198 is a radioactive isotope of gold and may be prepared by the neutron irradiation of gold under such conditions that not more than 5 per cent. of the total radioactivity is due to gold-199 at the reference date and hour stated on the label.

The content of gold-198 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of gold-198 stated on the label, at the reference date and hour stated on the label.

The solution is sterilized by Method I — Heating in an autoclave described under “Injectiones” in Ph. Int. II.

The radioactive half-life of gold-198 is 2.70 days.

**Description.** A deep red, colloidal solution. About 80 per cent. of the radioactivity is present in particles between 5 and 50 nm diameter, although narrower ranges, within these limits (e.g., 5-10 nm or 20-40 nm), may be specified.

**Identification.** The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized gold-198 solution. The most prominent gamma photon of gold-198 has an energy of 0.412 MeV. Allowance must be made for the possible presence of gold-199 whose most prominent gamma photon has an energy of 0.158 MeV and which decays with a half-life of 3.13 days.

**Reaction.** pH 4.0 to 8.0.

**Radionuclidian purity.** Complies with the general requirements for radionuclidian purity given in Appendix 13, “Radioactivity” (1974 revision).

**Radiochemical purity.** Carry out ascending paper chromatography as described in Appendix 14, “Chromatography”. Apply 10 µl of the sample to the paper and develop for one hour with a mixture of 70 parts of acetone R, 20 parts of water and 10 parts of saturated hydrochloric acid R. The colloid remains at the starting-point and any soluble gold migrates with the solvent front. Allow the chromatogram to dry in air and determine the areas of radioactivity by a suitable method. The spot of soluble gold may
be located by spraying with a mixture containing a 20 per cent. solution of stannous chloride R, a 10 per cent. solution of potassium iodide R and water in the proportion 10:2:88; this reagent gives a black colour with soluble gold. Not less than 98 per cent. of the total radioactivity is in the spot corresponding to colloidal gold.

**Pyrogens.** Complies with the Test for Pyrogens (Appendix 43), using a quantity equivalent to 5 mCi at the reference date and hour stated on the label per kg of the rabbit’s weight, but allowing the radioactivity to decay to less than 50 μCi per kg of the rabbit’s weight before injection.

**Assay.** Determine the radioactivity in suitable counting equipment by comparison with a standardized gold-198 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized gold-198 and gold-199 solutions are available from national standardizing laboratories.

**Storage.** Complies with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

**Labelling.** Gold (198Au) Colloidal Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also stating the range of diameters, in nm, of the particles in which about 80 per cent. of the radioactivity is present.

**Caution.** Do not use Gold (198Au) Colloidal Injection after eight days from the date of standardization or if the colour is no longer deep red.

---

**CHLORMERODRIN (197Hg) INJECTIO**

**Chlomerodrin (197Hg) Injection**

1974 Revision

\[ \text{Cl}^{197}\text{Hg} - \text{CH}_2 - \text{CH} - \text{CH}_2 - \text{NH} - \text{CO} - \text{NH}_2 \]
\[ \text{OCH}_3 \]

\[ \text{C}_9\text{H}_2\text{ClHgN}_2\text{O}_2 \]  
Mol. Wt. 367.23

Chlomerodrin (197Hg) Injection is a sterile solution of 3-chloromercuri-2-methoxypropylurea (197Hg), made isotonic with blood by the addition of Sodium Chloride.

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Mercury-197 is a radioactive isotope of mercury and may be prepared by neutron irradiation of mercury-196 sufficiently low in mercury-202 to ensure that the final content of mercury-203 is not more than 0.2 per cent. of the total radioactivity at the reference date and hour stated on the label. Mercury-197m may also be present.

The content of mercury-197 is not less than 85 per cent. and not more than 115 per cent. of the content of mercury-197 stated on the label, at the reference date and hour stated on the label.

The specific activity is not less than 200 mCi per g of chloromerodrin at the reference date and hour stated on the label.

The solution is sterilized by Method 1 — Heating in an autoclave or by Method 3 — Filtration described under "Injectiones" in Ph. Int. II.

The radioactive half-life of mercury-197 is 64.4 hours.

**Description.** A clear, colourless solution.

**Identification**

A. The gamma-ray and X-ray spectra, measured in a suitable instrument, are identical with that of a standardized mercury-197 solution apart from any difference attributable to the presence of mercury-197m; the most prominent photon of mercury-197 has an energy of 0.069 MeV (corresponding to the K X-ray of gold). The presence of a small amount of mercury-197m may be revealed by its major gamma photon of 0.134 MeV; mercury-197m decays with a half-life of 24 hours.

B. The test for radiochemical purity described below serves also to identify the product.

**Reaction.** pH 6.0 to 8.0.

**Radionuclidic purity.** Determine the radionuclidic purity after the decay of mercury-197m and partial decay of mercury-197. The presence of mercury-203 is shown in the gamma-ray spectrum by photons of 0.279 MeV. Mercury-203 decays with a half-life of 46.6 days. The content of mercury-203 is determined by comparison with a standardized mercury-203 solution.

Standardized mercury-203 solutions are available from national standardizing laboratories.

**Radiochemical purity.** Dilute the Chloromerodrin (\(^{197}\text{Hg}\)) Injection with water to give a concentration of about 0.2 mCi in 1 ml and apply 5 µl to a strip of chromatographic paper. Dissolve 0.001 g of chloromerodrin \(\text{R}\) in 1 ml of cold Sodium Chloride Injection and apply immediately 5 µl as a second spot to the same strip of paper. Dissolve 0.001 g of mercuric chloride \(\text{R}\) in 2 ml of Sodium Chloride Injection and apply 5 µl as a third spot to the same strip of paper. Allow to dry and develop the chromatogram.
by descending paper chromatography as described in Appendix 14, "Chromatography", for about 3 hours, using a mixture of 80 volumes of ethanol (95 per cent.) R, 18.5 volumes of water, 1.5 volumes of strong ammonia R and 1 g of sodium chloride R. Allow to dry and locate the spots due to chloromerodrin and inorganic mercury on the strips by lightly spraying the paper with a solution prepared by dissolving 0.2 g of dithizone R in 100 ml of ethanol (95 per cent.) R containing 2 v/v per cent. of acetic acid R. Allow to dry and identify the spots corresponding to chloromerodrin (A) and inorganic mercury (B). Determine the radioactivity of both spots and of the rest of the paper strip by a suitable method. Not less than 90 per cent. of the total radioactivity is in the spot A, not more than 2 per cent. of the total radioactivity is in the spot B.

**Assay.** Determine the radioactivity using suitable counting equipment by comparison with a standardized mercury-197 solution or by measurement in an instrument calibrated with the aid of such a solution. If an ionization chamber is used it should have a thin wall.

Standardized mercury-197 solutions are available from national standardizing laboratories.

**Storage.** Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

**Stability.** Chloromerodrin (\(^{197}\text{Hg}\)) Injection decomposes gradually with an accompanying decrease of radiochemical purity. It is particularly liable to undergo decomposition during the heating in an autoclave.

**Labelling.** Chloromerodrin (\(^{197}\text{Hg}\)) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision), together with the information on the weight of chloromerodrin.

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**CYANOCOBALAMINUM (\(^{60}\text{Co}\))**

**Cyanocobalamin (\(^{60}\text{Co}\))**

**1974 Revision**

Cyanocobalamin (\(^{60}\text{Co}\)) is vitamin \(B_{12}\) containing cobalt-57. It may be produced by the growth of certain micro-organisms on a medium containing cobaltous ion (\(^{60}\text{Co}\)).

Cobalt-57 is a radioactive isotope of cobalt and may be produced by irradiation of nickel with protons of suitable energy.
The content of cobalt-57 is not less than 85.0 per cent. and not more than 115.0 per cent. of the content of cobalt-57 stated on the label, at the reference date stated on the label.

The specific radioactivity is not less than 0.5 μCi per μg of cyanocobalamin at the reference date stated on the label.

Not less than 90.0 per cent. of the cobalt-57 is in the form of cyanocobalamin at the reference date stated on the label, and not more than 1.0 per cent. of the total radioactivity is due to cobalt-60 at the reference date stated on the label.

The radioactive half-life of cobalt-57 is 270 days.

**Description.** A pink solid, supplied in sealed glass containers or in capsules, or a clear, colourless to pink solution.

**Identification.** The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized cobalt-57 solution; the most prominent gamma photon has an energy of 0.122 MeV.

**Reaction.** For Cyanocobalamin (85Co) supplied as a solution, pH 4.0 to 5.5.

**Radionuclidic purity.** Measure the gamma-ray spectrum in a suitable instrument calibrated against standardized solutions of cobalt-57 and cobalt-60 and determine the relative amounts of cobalt-57 and cobalt-60 present. The presence of cobalt-60 is shown by gamma photons of 1.173 and 1.333 MeV. Cobalt-60 decays with a half-life of 5.27 years.

**Radiochemical purity.** To a quantity equivalent to 0.5 μCi at the reference date stated on the label add 0.008 g of cyanocobalamin and sufficient water to produce 25 ml. Reserve 12 ml of the solution at a temperature between 2° and 10°, protected from light (solution A).

Slurry a suitable carboxymethylcellulose (Whatman CM 23 carboxymethylcellulose is suitable) with 0.5 N hydrochloric acid, dilute with water, allow to settle, reject the supernatant liquid, and wash the residue with water until free from acid. Prepare a column of the adsorbant about 1 cm in diameter and 4 cm long, pass the remainder of the cyanocobalamin solution down the column, elute with water, and collect between 15 and 20 ml of the effluent. Extract the effluent with 2 ml of a mixture of 2 volumes of carbon tetrachloride R and 1 volume of cresol R, wash the extract with 2 quantities, each of 5 ml, of water, place in a centrifuge tube, add dropwise a mixture of equal volumes of acetone R and ether R until precipitation begins, and allow to stand for about fifteen minutes. Centrifuge, wash the precipitate with 2 quantities, each of 2 ml, of a mixture of equal
volumes of acetone R and ether R and with 2 quantities, each of 2 ml, of acetone R, and dissolve in 0.1 ml of water. With this solution prepare a chromatogram by descending paper chromatography as described in Appendix 14, "Chromatography", using as the stationary and mobile phases a mixture of 750 volumes of sec-butanol R, 270 volumes of water, and 1 volume of glacial acetic acid R. Use a piece of thick filter-paper 15 cm wide and streak the solution along the pencil line for 9 cm. Allow elution to proceed for eighteen hours, protecting the apparatus from light. Cut out the pink zone of the paper, reject the edges, and elute the coloured material by descending chromatography, using the smallest possible volume of water and protecting the apparatus from light. Dilute the eluate to 12 ml with water (solution B).

For each solution, determine the radioactivity, using suitable counting equipment, and the content of cyanocobalamin in the following manner: dilute 6 ml to 50 ml with water, measure the absorbance of a 1-cm layer at the maximum at about 361 nm and calculate the content of cyanocobalamin, \(\text{C}_{\text{n}}\text{H}_{\text{m}}\text{CoN}_{\text{w}}\text{O}_{\text{y}}\text{P}\), taking 20.7 as the value of the absorptivity at the maximum at about 361 nm.

The radioactivity per mg of cyanocobalamin for solution B is not less than 90 per cent. of that for solution A.

**Assay.** Prepare a solution of the solid if necessary and determine the radioactivity in suitable counting equipment by comparison with a standardized cobalt-57 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized cobalt-57 and cobalt-60 solutions are available from national standardizing laboratories.

**Storage.** Cyanocobalamin (\(^{57}\text{Co}\)) should be stored at a temperature not exceeding 10° and protected from light. Other conditions of storage should comply with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

**Expiry date.** Cyanocobalamin (\(^{57}\text{Co}\)) decomposes gradually with an accompanying decrease of radiochemical purity. The expiry date is not later than 3 months after the reference date stated on the label and the radiochemical purity at expiry should be not less than 80 per cent.

**Labelling.** Cyanocobalamin (\(^{57}\text{Co}\)) should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision), the label also giving the information on storage temperature.
Cyanocobalamin (^{68}Co) 

1974 Revision

Cyanocobalamin (^{68}Co) is vitamin B_{12} containing cobalt-58. It may be produced by the growth of certain micro-organisms on a medium containing cobaltous ion (^{60}Co).

Cobalt-58 is a radioactive isotope of cobalt and may be produced by neutron irradiation of nickel.

The content of cobalt-58 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of cobalt-58 stated on the label, at the reference date stated on the label.

Not less than 90.0 per cent. of the cobalt-58 is in the form of cyanocobalamin at the reference date stated on the label, and not more than 1.0 per cent. of the total radioactivity is due to cobalt-60 at the reference date stated on the label.

The radioactive half-life of cobalt-58 is 70.8 days.

Description. A pink solid, supplied in sealed glass containers or in capsules, or a clear, colourless to pink solution.

Identification. The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized cobalt-58 solution; the most prominent gamma photons have energies of 0.511 and 0.811 MeV.

Reaction. For Cyanocobalamin (^{68}Co) supplied as a solution, pH 4.0 to 5.5.

Radiochemical purity. Measure the gamma-ray spectrum using an instrument of adequate resolving power, calibrated against standardized solutions of cobalt-58 and cobalt-60 and determine the relative amounts of cobalt-58 and cobalt-60 present. The presence of cobalt-60 is shown by gamma photons of 1.173 and 1.333 MeV. Cobalt-60 decays with a half-life of 5.27 years.

Radiochemical purity. Carry out the test for radiochemical purity described under "Cyanocobalamin (^{68}Co) ".

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized cobalt-58 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized cobalt-58 and cobalt-60 solutions are available from national standardizing laboratories.
Storage. Cyanocobalamin (\(^{58}\text{Co}\)) should be stored at a temperature not exceeding 10° and protected from light. Other conditions of storage should comply with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Expiration. Cyanocobalamin (\(^{58}\text{Co}\)) decomposes gradually with an accompanying decrease of radiochemical purity. The expiration date is not later than 3 months after the reference date stated on the label and the radiochemical purity at expiry should be not less than 80 per cent.

Labelling. Cyanocobalamin (\(^{58}\text{Co}\)) should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also giving the information on storage temperature.

**FERRI (\(^{59}\text{Fe}\)) CITRATIS INJECTIO**

**Ferric Citrate (\(^{59}\text{Fe}\)) Injection**

1974 Revision

Ferric Citrate (\(^{59}\text{Fe}\)) Injection is a sterile solution containing iron-59 in the ferric state, 1 per cent. w/v of Sodium Citrate, and sufficient Sodium Chloride to make the solution isotonic with blood.

Iron-59 is a radioactive isotope of iron and may be prepared by neutron irradiation of iron-58 sufficiently low in iron-54 to ensure that the final content of iron-55 is not more than 2 per cent. of the total radioactivity at the reference date stated on the label.

The content of iron-59 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of iron-59 stated on the label, at the reference date stated on the label.

The specific radioactivity is not less than 1 mCi per 0.001 g of iron at the reference date stated on the label.

The solution is sterilized by Method 1 — *Heating in an autoclave* described under “Injections” in Ph. Int. II. The addition of a bacteriostatic agent to this preparation is not recommended.

The radioactive half-life of iron-59 is 44.6 days.

**Description.** A clear, colourless or faintly orange-brown solution.

**Identification**

A. The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized iron-59 solution; the most prominent
gamma photons have energies of 1.099 and 1.292 MeV. Although iron-55 may be present, it emits only an X-ray of 0.006 MeV and this will not normally be detected. The radioactive half-life of iron-55 is 2.7 years.

B. Yields reaction B characteristic of citrates (see Appendix 4).

Reaction. pH 6.0 to 8.0.

Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity" (1974 revision).

Total iron. Complies with the Limit Test for Iron (Appendix 27), a volume equivalent to 40 μCi of iron-59 at the reference date stated on the label being used.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized iron-59 solution or by measurement in an instrument calibrated with the aid of such a solution. Standardized iron-59 solutions are available from national standardizing laboratories.

Storage. Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labelling. Ferric Citrate (59Fe) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

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INDII (113mIn) CHLORIDE INJECTION

Indium (113mIn) Chloride Injection is a sterile solution of indium-113m in the form of complexes of trivalent indium in 0.04 N aqueous hydrochloric acid. It may be injected intravenously using appropriate precautions.

Indium-113m is a radioactive isotope of indium formed by radioactive decay of tin-113. Tin-113 is a radioactive isotope of tin and may be produced by the neutron irradiation of tin enriched in tin-112.

The content of indium-113m is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of indium-113m stated on the label, at the reference date and hour stated on the label.

Not more than 0.01 per cent. of the total radioactivity shall be due to radionuclides other than indium-113m, except that tin-113 may be present.
to the extent of 0.05 per cent., all calculated to the time of administration.

The Indium (\(^{113m}\) In) Chloride Injection may be prepared from a generator containing tin-113. Such generators are commonly designed to operate under aseptic conditions to give a sterile product. If the solution is prepared by other means it may be sterilized by Method 1 — Heating in an autoclave, or by Method 3 — Filtration, described under "Injectiones" in Ph. Int. II.

A suitable bacteriostatic agent, such as Chlorocresol 0.1 per cent., may be present.

The radioactive half-life of indium-113m is 99.5 minutes.

**Description.** A clear, colourless or faintly yellow solution.

**Identification.** The gamma-ray spectrum measured with a suitable instrument is identical with that of a standardized indium-113m solution. The gamma photon of indium-113m has an energy of 0.392 MeV. Alternatively a standardized solution of tin-113 in equilibrium with indium-113m may be employed, making appropriate allowance for the photons due to the tin-113.

**Reaction.** pH 1.3 to 1.5.

**Radionuclidic purity.** Retain a sample of the injection for a sufficient length of time to allow indium-113m to decay to a sufficiently low level to permit the detection of radionuclidic impurities. All measurements of radionuclidic impurities are to be expressed at the time of administration of the injection.

**Tin-113.** The presence of tin-113 is revealed by its gamma-ray and X-ray spectrum. Tin-113 emits a gamma photon with an energy of 0.255 MeV (emitted in only 2.1 per cent. of disintegrations), but the most prominent photon is the K X-ray of indium of 0.024 MeV. The radioactive half-life of tin-113 is 115 days. Not more than 0.05 per cent. of the radioactivity shall be due to tin-113.

**Other radionuclidic impurities.** 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. The total radioactivity due to these other radionuclidic impurities should not exceed 0.01 per cent. of the total radioactivity of the sample.

**Assay.** Determine the radioactivity with suitable counting equipment by comparison with a standardized indium-113m solution or by measurement in an instrument calibrated with the aid of such a solution. A good approximation may be obtained using an ionization chamber and employing a standardized solution of tin-113 in equilibrium with indium-113m, provided
that the ionization chamber has a lining thick enough to absorb the 0.024 MeV X-ray (1 mm thickness of brass is sufficient). Standardized solutions of indium-113m and of tin-113 are available from national standardizing laboratories.

**Storage.** Complies with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

**Labelling.** Indium (\(^{113m}\)In) Chloride Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision).

**Caution.** Indium (\(^{113m}\)In) Chloride Injection should be administered by slow intravenous injection.

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**INDII (\(^{113m}\)In) PENTETATIS COMPLEXIONIS INJECTIO**

**Indium (\(^{113m}\)In) Pentetate Complex Injection**

Indium (\(^{113m}\)In) Pentetate Complex Injection is a sterile solution of indium-113m complexed with pentetic acid [\(N,N\)-bis[2-[bis(carboxymethyl)-amino]ethyl]-glycine], which is present in excess.

The content of indium-113m is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of indium-113m stated on the label, at the reference date and hour stated on the label.

Not less than 95 per cent. of the total indium-113m is present as indium (\(^{113m}\)In) pentetate complex.

The injection may be prepared from sterile starting materials under aseptic conditions or may be sterilized by Method 3 - Filtration, described under “Injectiones” in Ph. Int. II.

The radioactive half-life of indium-113m is 99.5 minutes.

**Description.** A clear, colourless or faintly yellow solution.

**Identification**

A. Complies with the test for identification described under “Indii (\(^{113m}\)In) Chloridi Injectio”.

B. The test described below under the heading “Radiochemical purity” serves to indicate the chemical nature of the product.

**Reaction.** pH 4.0 to 8.0.

**Radiochemical purity.** Complies with the requirements for radionuclidic purity described under “Indii (\(^{113m}\)In) Chloridi Injectio”.

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Radiochemical purity. Carry out ascending paper chromatography as described in Appendix 14, "Chromatography". Apply 5 µl of the sample to the paper and develop for two hours with a mixture of 50 ml of ethanol (95 per cent.) R, 125 ml of water, and 0.1 ml of strong ammonia R. The cationic indium remains at the starting point and the indium (113mIn) pentetate complex has an Rf of about 0.9. Allow to dry and determine the areas of radioactivity by a suitable method. Not less than 95 per cent. of the total radioactivity is in the spot corresponding to the indium (113mIn) pentetate complex.

Assay. Carry out the "Assay" as described under "Indii (113mIn) Chloridi Injectio".

Storage. Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labeling. Indium (113mIn) Pentetate Complex Injection should be labelled as specified under Appendix 13, "Radioactivity" (1974 revision).

MACROALBUM (131I) INJECTIO
Macrosalb (131I) Injection
1974 Revision

SYNONYM: Seroalbumini Humani Iodinati (131I) Macroaggregati Injectio

Macrosalb (131I) Injection is a sterile suspension of human serum albumin that has been iodinated with iodine-131 and has been denatured in such a manner as to form insoluble aggregates. The aggregates are suspended in a saline solution isotonic with blood. It is suitable for intravenous administration.

The human serum albumin employed shall contain not more than 5 per cent. of globulins and shall comply with the national regulations of the country in which the Macrosalb (131I) Injection is employed. The human serum albumin used for this preparation should have been suitably treated to prevent the transmission of serum hepatitis (e.g., by heating in an aqueous solution for 10 hours at 59.5° to 60.5°).

The content of iodine-131 is not less than 90.0 per cent., and not more than 110.0 per cent., of that stated on the label, at the reference date and hour stated on the label.
The content of iodine-131 is usually within the range 0.15 to 1.5 mCi/ml and the specific activity is usually in the range 0.1 to 2.0 mCi/mg of iodinated albumin.

The radioactivity is virtually all present in particles with mean dimensions in the range 10 to 100 microns, and no particle shall have a dimension greater than 150 microns.

The product is prepared under strict aseptic conditions because terminal sterilization is not practicable. A suitable bacteriostatic agent, such as benzyl alcohol R 0.9 per cent. v/v, shall be present.

The radioactive half-life of iodine-131 is 8.06 days.

**Description.** A dilute suspension of white or faintly yellow particles, which may settle on standing.

**Identification**
A. Complies with the test for identification described under "Natrii Iodidi (¹³¹I) Solutio".

B. The test for soluble radioactivity below serves to characterize the physical nature of the product.

**Reaction.** pH 5.0 to 8.5.

**Radionuclidic purity.** Complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity" (1974 revision).

**Soluble radioactivity.** Place a measured volume of Macrosalb (¹³¹I) Injection in a centrifuge tube, and determine the net radioactivity in a suitable counting assembly. Centrifuge at 1000 g or more for a minimum of 5 minutes. Separate the supernatant liquid by aspiration, and determine its net radioactivity in a suitable counting assembly. Not more than 5 per cent. of the radioactivity in the original sample is found in the supernatant liquid after centrifugation.

**Microscopic examination.** Observe the size distribution of a representative sample contained in a suitable chamber by optical microscopy using a micrometer attachment, or by reference to a haemocytometer grid. No particle shall have a dimension greater than 150 μm.

**Biological distribution.** Inject a suitable volume into the tail vein of each of 3 rats, using a hypodermic needle of a minimum of 0.32 mm internal bore size. After a period of 5 minutes observe the distribution of radioactivity in the animals by any suitable means, such as dissection and measurement of radioactivity in the organs, or by an external measurement technique. In no animal shall there be less than 90 per cent. of the administered dose in the lungs.
Pyrogens. Complies with the Test for Pyrogens (Appendix 43), using a quantity corresponding, at the reference date and hour stated on the label, to not less than 25 μCi per kg of the rabbit’s weight.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-131 solution or by measurement in an instrument calibrated with the aid of such a solution. The method chosen should take cognizance of the fact that the product is a suspension.

Standardized iodine-131 solutions are available from national standardizing laboratories.

Storage. Macrosalb (¹³¹I) Injection should be stored at a temperature between 2° and 10°. Other conditions of storage should comply with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Labelling. Macrosalb (¹³¹I) Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also giving the information on storage temperature.

MACROALBUMIN (⁹⁹ᵐTc) INJECTION

Macrosalb (⁹⁹ᵐTc) Injection is a sterile suspension of human serum albumin that has been labelled with technetium-99m and has been denatured in such a manner as to form insoluble aggregates. It is suitable for intravenous administration.

The human serum albumin employed shall contain not more than 5 per cent. of globulins and shall comply with the national regulations of the country in which the Macrosalb (⁹⁹ᵐTc) Injection is employed. The human serum albumin used for this preparation should have been suitably treated to prevent the transmission of serum hepatitis (e.g., by heating in an aqueous solution for 10 hours at 59.5° to 60.5°).

The content of technetium-99m is not less than 90.0 per cent. and not more than 110.0 per cent. of that stated on the label, at the reference date and hour stated on the label.

The specific activity of the preparation is not less than 1.0 mCi of technetium-99m per mg of macroaggregated human serum albumin at the time of administration.

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The radioactivity is virtually all present in particles with mean dimensions in the range of 10 to 100 μm, and no particle shall have a dimension greater than 150 μm.

The product is prepared under strict aseptic conditions because terminal sterilization is not practicable. It may contain antimicrobial, reducing, chelating, and stabilizing agents, buffers, and nonaggregated human serum albumin.

The radioactive half-life of technetium-99m is 6.02 hours.

**Description.** A dilute suspension of white or faintly yellow particles, which may settle on standing.

**Identification**

A. Complies with the test for identification described under "Natrii Pertechnetatis (99mTc) Injectio".

B. The test for soluble radioactivity below serves to characterize the physical nature of the product.

**Reaction.** pH 4.0 to 7.0.

**Radionuclidic purity.** Complies with the requirements for radionuclidic purity described under "Natrii Pertechnetatis (99mTc) Injectio".

**Soluble radioactivity.** Place a measured volume of Macrosalb (99mTc) Injection in a centrifuge tube and determine the net radioactivity in a suitable counting assembly. Centrifuge at 1000 g or more for a minimum of 5 minutes. Separate the supernatant liquid by aspiration, and determine its net radioactivity in a suitable counting assembly. Not more than 10 per cent. of the radioactivity in the original sample is found in the supernatant liquid after centrifugation.

**Microscopic examination.** Observe the size distribution of a representative sample contained in a suitable chamber by optical microscopy using a micrometer attachment, or by reference to a haemocytometer grid. No particle shall have a dimension greater than 150 μm.

**Biological distribution.** Inject a suitable volume into the tail vein of each of 3 rats using a hypodermic needle of a minimum of 0.32 mm internal bore size. After a period of 5 minutes, observe the distribution of radioactivity in the animals by any suitable means, such as dissection and measurement of radioactivity in the organs, or any external measurement technique. In no animal shall there be less than 80 per cent. of the administered dose in the lungs.
**Pyrogens.** Complies with the Test for Pyrogens (Appendix 43), using a quantity corresponding, at the reference date and hour stated on the label, to not less than 250 μCi per kg of the rabbit's weight.

**Assay.** Determine the radioactivity in suitable counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution. The method chosen should take cognizance of the fact that the product is a suspension.

Standardized solutions of technetium-99m are available from national standardizing laboratories.

**Storage.** Macrosalb (99mTc) Injection should be stored at a temperature between 2° and 10°. Other conditions of storage should comply with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

**Labelling.** Macrosalb (99mTc) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision), the label also giving the information on storage temperature.

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**NATRII CHROMATIS (65Cr) INJECTIO**

**Sodium Chromate (65Cr) Injection**

1974 Revision

Sodium Chromate (65Cr) Injection is a sterile solution of sodium chromate (65Cr) made isotonic with blood by the addition of Sodium Chloride. Chromium-51 is a radioactive isotope of chromium and may be prepared by the neutron irradiation of chromium, either of natural isotopic composition or enriched in chromium-50.

The content of chromium-51 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of chromium-51 stated on the label, at the reference date and hour stated on the label.

The specific activity is not less than 20 mCi per mg of chromium at the reference date and hour stated on the label.

The solution is sterilized by Method I - *Heating in an autoclave described under "Injectiones" in Ph. Int. II.*

The radioactive half-life of chromium-51 is 27.7 days.

**Description.** A clear, colourless or faintly yellow solution.
Identification. The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized chromium-51 solution; the most prominent gamma photon has an energy of 0.320 MeV.

Reaction. pH 5.0 to 8.0.

Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity" (1974 revision).

Radiochemical purity. Carry out ascending paper chromatography as described in Appendix 14, "Chromatography". Apply about 10 μl of the sample to the paper and immediately develop for one hour with a mixture of 5 parts of water, 2 parts of ethanol (95 per cent.) R and 1 part of strong ammonia R. The cationic chromium remains at the starting-point and the chromate ion has an Rf of about 0.9. Allow the chromatogram to dry in air and determine the areas of radioactivity by a suitable method. Not less than 90 per cent. of the total radioactivity is in the spot corresponding to the chromate ion.

Total chromate. Not more than 100 μg per mCi of chromate ion at the reference date and hour stated on the label.

Determine the content of chromium by measuring the absorbance of a 1-cm layer of the solution at 370 nm and calculating the result from the absorbance of a 0.00017 per cent. w/v solution of potassium chromate R adjusted to pH 8.0 by the addition of sodium bicarbonate R.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized chromium-51 solution or by measurement in an instrument calibrated with the aid of such a solution. Standardized chromium-51 solutions are available from national standardizing laboratories.

Storage. Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labelling. Sodium Chromate (¹⁹⁵Cr) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

NATRIUM IODIDI (¹²⁴I) SOLUTIO
Sodium Iodide (¹²⁴I) Solution
1974 Revision

Sodium Iodide (¹²⁴I) Solution is a solution suitable for oral administration containing sodium iodide (¹²⁴I). It also contains sodium thiosulfate or other suitable reducing agent.
Iodine-125 is a radioactive isotope of iodine and may be prepared by the neutron irradiation of xenon.

The content of iodine-125 is not less than 85.0 per cent., and not more than 115.0 per cent., of the content of iodine-125 stated on the label, at the reference date stated on the label.

The specific radioactivity is not less than 2 mCi per μg of iodine at the reference date stated on the label. Not more than 1.0 per cent. of the total radioactivity is due to iodine-126 at the reference date stated on the label.

The radioactive half-life of iodine-125 is 60.0 days.

**Description.** A clear, colourless solution.

**Identification.** The gamma-ray and X-ray spectra measured in a suitable instrument are identical with those of a standardized iodine-125 solution, apart from any differences attributable to the presence of iodine-126. The most prominent photon of iodine-125 has an energy of 0.028 MeV (corresponding to the K X-ray of tellurium). The presence of iodine-126 is shown by major gamma photons with energies of 0.389 and 0.666 MeV; iodine-126 decays with a half-life of 13 days.

**Reaction.** pH 7.0 to 10.0.

**Iodine-126.** Standardized solutions of iodine-126 are not available, and a standardized solution of caesium-137, which has a gamma photon of closely similar energy, is employed. Measure the gamma-ray and X-ray spectra in a suitable instrument in comparison with standardized solutions of iodine-125 and caesium-137. Determine the relative amounts of iodine-125 and iodine-126 present on the assumption that the 0.666 MeV gamma photon of iodine-126 is emitted in 30 per cent. of disintegrations, and that the 0.662 MeV gamma photon of barium-137m in equilibrium with caesium-137 is emitted in 85.1 per cent. of disintegrations.

**Radionuclidic purity.** In addition to the above requirements for iodine-126, complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity." (1974 revision).

**Radiochemical purity.** Carry out the test for radiochemical purity described under "Natrii Iodidi (35I) Solutio".

**Assay.** Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-125 solution or by measurement in an instrument calibrated with the aid of such a solution. An instrument incorporating a scintillation detector, such as a thin sodium iodide crystal, should be employed, and the instrument should be set so that the contribution from iodine-126 is minimized. Additionally, the sample container
and the protective covering of the crystal must be of such material and of such thickness as to minimize absorption of the photons iodine-125. A thin-walled ionization chamber may be employed, but the iodine-126 content must then be known accurately to permit an appropriate correction to be made.

Standardized iodine-125 and caesium-137 solutions are available from national standardizing laboratories.

**Storage.** Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

**Labelling.** Sodium Iodide (I\(^{131}\)) Solution should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

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**NATRII IODIDI (I\(^{131}\)) INJECTIO**

**Sodium Iodide (I\(^{131}\)) Injection**

**1974 Revision**

Sodium Iodide (I\(^{131}\)) Injection is a sterile solution containing sodium iodide (I\(^{131}\)). It also contains sodium thiosulphate or other suitable reducing agent.

Iodine-131 is a radioactive isotope of iodine and may be prepared by neutron irradiation of tellurium. It is produced in the form of sodium iodide in such a manner that it is carrier-free.

The content of iodine-131 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of iodine-131 stated on the label, at the reference date and hour stated on the label.

The specific activity is not less than 5 mCi per µg of iodine at the reference date and hour stated on the label.

The solution is sterilized by Method 1 - Heating in an autoclave described under "Injectiones" in Ph. Int. II.

The radioactive half-life of iodine-131 is 8.06 days.

**Description.** A clear, colourless solution.

**Identification.** Complies with the test for Identification under "Natrii Iodidi (I\(^{131}\)) Solutio".

**Reaction.** pH 7.0 to 8.0.
Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity" (1974 revision).

Radiochemical purity. Carry out the test for radiochemical purity under "Natrii Iodidi (I\textsuperscript{131}) Solutio".

Assay. Carry out the Assay as described under "Natrii Iodidi (I\textsuperscript{131}) Solutio".

Storage. Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labelling. Sodium Iodide(I\textsuperscript{131}) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

NATRII IODIDI (I\textsuperscript{131}) SOLUTIO

Sodium Iodide (I\textsuperscript{131}) Solution

1974 Revision

Sodium Iodide (I\textsuperscript{131}) Solution is a solution suitable for oral administration containing sodium iodide (I\textsuperscript{131}). It also contains sodium thiosulfate or other suitable reducing agent.

Iodine-131 is a radioactive isotope of iodine and may be prepared by neutron irradiation of tellurium. It is produced in the form of sodium iodide in such a manner that it is carrier-free.

The content of iodine-131 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of iodine-131 stated on the label, at the reference date and hour stated on the label.

The specific activity is not less than 5 mCi per μg of iodine at the reference date and hour stated on the label.

The radioactive half-life of Iodine-131 is 8.06 days.

Description. A clear, colourless solution.

Identification. The gamma-ray spectrum, measured in a suitable instrument, is identical with that of a standardized iodine-131 solution; the most prominent gamma photon has an energy of 0.364 MeV.

Reaction. pH 7.0 to 10.0.

Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, "Radioactivity" (1974 revision).
Radiochemical purity. If necessary, dilute the solution to give an appropriate counting rate on the chromatogram. Add an equal volume of a solution containing 0.1 per cent. of potassium iodide R, 0.2 per cent. of potassium iodate R, and 1 per cent. of sodium bicarbonate R, mix, place 10 μl of the mixture on a strip of chromatographic paper, and allow to dry. On the same paper, place 10 μl of a 1 per cent. solution of potassium iodide R and 10 μl of a 2 per cent. solution of potassium iodate R, and allow to dry. Develop the chromatogram by ascending chromatography, using a mixture of 3 volumes of methanol R and 1 volume of water. Allow to dry and determine the positions of the inactive potassium iodide and potassium iodate by the application of filter-paper impregnated with acetic acid R and potassium iodate R, and acetic acid R and potassium iodide R, respectively. Determine the radioactive distribution by scanning with a suitable instrument. The radioactivity of the iodide band is not less than 95 per cent. of the total radioactivity. The Rf value for the iodide band falls within 5 per cent. of the value found for an iodine-131 sample of known purity when determined under parallel conditions.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-131 solution or by measurement in an instrument calibrated with the aid of such a solution. Standardized iodine-131 solutions are available from national standardizing laboratories.

Storage. Complies with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labelling. Sodium Iodide (131I) Solution should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

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**NATRII IODOHIPPURATIS (131I) INJECTIO**

**Sodium Iodohippurate (131I) Injection**

1974 Revision

\[
\text{CO} - \text{NH} - \text{CH}_2 - \text{COONa}
\]

\[
\text{C}_7\text{H}_7\text{IINaO}_3
\]
Sodium Iodohippurate (I\textsuperscript{31}I) Injection is a sterile solution containing sodium \(\text{o-iodohippurate} (I\text{\textsuperscript{31}}I)\).

The content of iodine-131 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of iodine-131 stated on the label, at the reference date and hour stated on the label.

Not less than 95.0 per cent. of the iodine-131 is in the form of sodium \(\text{o-iodohippurate}\) at the reference date and hour stated on the label.

The solution is sterilized by Method 1 - Heating in an autoclave described under “Injectiones” in Ph. Int. II.

The radioactive half-life of iodine-131 is 8.06 days.

**Description.** A clear, colourless solution, which may darken during storage.

**Identification**

A. Complies with the test for Identification described under “\text{Natrii Iodidi} (I\text{\textsuperscript{31}}I) Solutio”.

B. The test for radiochemical purity described below serves also to identify the product.

**Reaction.** pH 7.0 to 8.5.

**Radioactive purity.** Complies with the general requirements for radio-nuclidic purity given in Appendix 13, “Radioactivity” (1974 revision).

**Radiochemical purity.** Dilute the sample with water, when necessary, to give a concentration of about 1 mCi in 1 ml. Carry out ascending paper chromatography as described in Appendix 14, “Chromatography”. Apply 5 µl of the sample to the paper. Dissolve 0.005 g of \(\text{o-iodohippuric acid R}\) in 1 ml of dioxan R and apply 5 µl separately to the same paper. Allow to dry and develop the chromatogram, using a mixture of 120 volumes of \(\pi\)-butanol R, 50 volumes of water, and 30 volumes of glacial acetic acid R. Allow to dry, locate the spots due to \(\text{o-iodohippuric acid}\) by examination under an ultraviolet lamp II. a maximum output at about 365 nm, and determine the areas of radioactivity by a suitable method. Not less than 95 per cent. of the radioactivity is in the spot corresponding to \(\text{o-iodohippuric acid R}\).

**Assay.** Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-131 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized iodine-131 solutions are available from national standardizing laboratories.

**Storage.** Sodium Iodohippurate (I\textsuperscript{31}I) Injection should be stored at a temperature not exceeding 25° and protected from light. Other conditions
of storage should comply with the requirements under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

**Labelling.** Sodium Iodosyrupurait (99mTc) Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also giving the information on storage temperature.

**Caution.** The product is not necessarily suitable for the determination of effective renal plasma flow or for other purposes that require a radiochemical purity in excess of 95 per cent.

**NATRII PERTECHNETATIS (99mTc) INJECTIO**

**Sodium Pertechnetate (99mTc) Injection**

1974 Revision

Sodium Pertechnetate (99mTc) Injection is a sterile solution containing technetium-99m in the form of pertechnetate ion and sufficient Sodium Chloride to make the solution isotonic with blood.

Technetium-99m is a radioactive nuclide formed by the radioactive decay of molybdenum-99. Molybdenum-99 is a radioactive isotope of molybdenum and may be produced by the neutron irradiation of natural molybdenum or of molybdenum enriched in molybdenum-98, or it may be produced by uranium fission. The label must show whether or not the molybdenum-99 was produced by uranium fission.

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

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-99 may be present to the extent of 0.1 per cent. of the total radioactivity, all calculated to the time of administration. When the molybdenum-99 has been produced by uranium fission there is an additional requirement that not more than 10^{-7} per cent. of the total radioactivity shall be due to alpha-emitting radionuclides, and, as a further exception to the requirement that not more than 0.01 per cent. of the total activity shall be due to radionuclides other than technetium-99m, iodine-131 may be present to the extent of 0.005 per cent. of the total radioactivity, all calculated to the time of administration.

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The injection may be prepared from a sterile preparation of molybdenum-99 under aseptic conditions, or it may be sterilized by Method 1 - Heating in an autoclave or by Method 3 - Filtration described under "Injections" in Ph. Int. II.

The radioactive half-life of technetium-99m is 6.02 hours.

**Description.** A clear, colourless solution.

**Identification.** The gamma-ray spectrum measured with a suitable instrument is identical with that of a standardized technetium-99m solution. The most prominent gamma photon of technetium-99m has an energy of 0.141 MeV.

**Reaction.** pH 4.5 to 7.5.

**Radionuclidic purity**

A. **Tests prior to use**

**Molybdenum-99.** Take 1 mCi of the Injection and determine the gamma-ray spectrum 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, when all measurements are calculated to the time of administration. It should be noted that, when the molybdenum-99 has been produced by uranium fission, iodine-132 may be present. Iodine-132 has a high abundance of gamma photons in the 0.7 to 0.8 MeV region and its presence may cause the failure, in this test, of a product that meets the formal requirements for radionuclidic purity. Iodine-132 may be distinguished from molybdenum-99 by its short half-life (2.29 hours).

Standardized solutions of molybdenum-99 are available from national standardizing laboratories.

**Iodine-131.** When the Injection has been prepared from molybdenum-99 produced by uranium fission, the above test should be suitably modified to measure also the iodine-131 content. This should not exceed 0.5 μCi per 1 mCi of technetium-99m at the time of administration.

Standardized solutions of iodine-131 are available from national standardizing laboratories.

B. **Retrospective tests**

Retain a sample of the Injection for a sufficient length of time to allow technetium-99m to decay to a sufficiently low level to permit the detection
of radionuclidic impurities. All measurements of radioactivity are to be expressed at the time of administration of the injection.

Molybdenum-99. The presence of molybdenum-99 is revealed by its characteristic gamma-ray spectrum; the most prominent photons have energies of 0.181, 0.740 and 0.778 MeV. The instrument should be calibrated using a standardized solution of molybdenum-99. The radioactive half-life of molybdenum-99 is 66.2 hours. Not more than 0.1 per cent. of the total radioactivity shall be due to molybdenum-99.

Iodine-131. The presence of iodine-131 is revealed by its characteristic gamma-ray spectrum; the most prominent photons have energies of 0.284, 0.364 and 0.637 MeV. The instrument should be calibrated using a standardized solution of iodine-131. The radioactive half-life of iodine-131 is 8.06 days. Not more than 0.05 per cent. of the total radioactivity shall be due to iodine-131.

Other radionuclidic impurities. 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. The total radioactivity due to these other radionuclidic impurities shall not exceed 0.01 per cent. of the total radioactivity of the sample. When the Injection has been prepared from molybdenum-99 produced by uranium fission it may also be appropriate to examine the sample of the Injection for the presence of beta-emitting and alpha-emitting impurities. The total radioactivity due to alpha-emitting impurities shall not exceed 10^-4 per cent. of the total radioactivity of the sample.

Radiochemical purity. Dilute the Injection with water to a suitable radioactive concentration. Carry out ascending paper chromatography as described in Appendix 14, "Chromatography". Apply 5 µl of the sample to the paper. Allow to dry and develop the chromatogram for 2 hours, using a mixture of 80 volumes of acetone R and 20 volumes of 2 N hydrochloric acid. Allow the chromatogram to dry and determine the areas of radioactivity by a suitable method. Not less than 95 per cent. of the total radioactivity is in the spot corresponding to pertechnetate ion and having an Rf value of about 0.9.

Chemical purity—aluminium.

Transfer 10 ml of standard aluminium solution (containing 2 µg of aluminium in 1 ml) to two 50-ml volumetric flasks. Add 3 drops of methyl orange TS to each flask and 1 to 2 drops of dilute ammonia TS, and then add dropwise 0.5 N hydrochloric acid until the indicator turns red. To one flask, add 25 ml of sodium thioglycolate TS and to the other 1 ml of
disodium edetate TS. To both flasks add 5 ml of eriochrome cyanine TS and 5 ml of acetate buffer solution and dilute with water to 50 ml. Determine immediately the absorbance \( A_s \) of the solution containing thioglycolate at 535 nm using the solution containing disodium edetate as a blank.

Carry out the same procedure using two 1-ml aliquots of sodium pertechnetate \(^{99m}\text{Tc}\) Injection (absorbance \( A_d \)).

Calculate the content of aluminium in \( \mu g/ml \) of the injection by the formula:

\[
\frac{A_d}{A_s} 
\]

Not more than 20 \( \mu g \) of aluminium in 1 ml should be present.

**Assay.** Determine the radioactivity with suitable counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized solutions of technetium-99m, molybdenum-99, and iodine-131 are available from national standardizing laboratories.

**Storage.** Complies with the requirements under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

**Labelling.** Sodium Pertechnetate \(^{99m}\text{Tc}\) Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision). If the injection has been prepared from molybdenum-99 produced from uranium fission, this shall be stated on the label.

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**NATRII PHOSPHATIS \(^{32}\text{P}\) INJECTIO**

*Sodium Phosphate \(^{32}\text{P}\) Injection*

*1974 Revision*

Sodium Phosphate \(^{32}\text{P}\) Injection is a sterile solution of sodium phosphate \(^{32}\text{P}\) in saline TS. The solution contains added phosphate.

Phosphorus-32 is a radioactive isotope of phosphorus and may be prepared by the neutron bombardment of sulfur. It is produced in the form of sodium phosphate.

The content of phosphorus-32 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of phosphorus-32 stated on the label, at the reference date and hour stated on the label.
The specific activity is not less than 1 mCi per mg of phosphate ion at the reference date and hour stated on the label.

The solution is sterilized by Method 1 - Heating in an autoclave described under "Injectiones" in Ph. Int. II.

The radioactive half-life of phosphorus-32 is 14.3 days.

**Description.** A clear, colourless solution.

**Identification.** The beta-ray absorption coefficient, calculated from the absorption curve obtained by measurement in a suitable instrument, is identical with that obtained using a standardized phosphorus-32 solution. For the determination, evaporate the sample on an aluminium plate, mount rigidly under a Geiger-Müller counter with a thin end-window, interpose a series of aluminium foils between the source and the counting tube, and determine the counting rate for each foil. Use at least 6 foils, ranging in thickness from 10 to 200 mg/cm², and a single absorber of not less than 800 mg/cm², and proceed as described in Appendix 13, "Radioactivity" (1974 revision).

**Reaction.** pH 6.0 to 7.0.

**Radioisotopic purity.** Complies with the general requirements for radioisotopic purity given in Appendix 13, "Radioactivity" (1974 revision).

**Radiochemical purity.** Dilute the injection with water until its activity is about 20,000 counts per minute, add an equal volume of a 10 per cent. v/v solution of phosphoric acid R, mix, and place 10 µl of the mixture on a strip of chromatographic paper. Develop the chromatogram by descending chromatography, using a mixture of 40 volumes of tertiary butanol R, 20 volumes of water, and 5 volumes of formic acid R. Allow to dry, and determine the position of the inactive phosphoric acid by spraying the paper with a solution prepared in the following way: Dissolve 5 g of ammonium molybdate R in 100 ml of water and pour, with constant stirring, into a mixture of 12 ml of nitric acid R and 24 ml of water. Determine the position of the radioactive distribution by scanning with a collimated Geiger-Müller counter; the radioactivity appears in one band only, corresponding in Rf value to the phosphoric acid.

**Total phosphate.** Dilute the injection with water to produce a solution containing 10 µCi of phosphorus (³²P) per ml. To 1 ml add 0.5 ml of a 0.25 per cent. solution of ammonium vanadate R, 0.5 ml of ammonium molybdate TS, 1 ml of perchloric acid (70 per cent. w/w) R and 2 ml of water, mixing after each addition, and allow to stand for thirty minutes; the colour produced is not deeper than that produced by treating in the same manner 1 ml of a solution containing 47.3 mg of sodium phosphate, anhydrous, R per litre.

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Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized phosphorus-32 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized phosphorus-32 solutions are available from national standardizing laboratories.

Storage. Complies with the requirements under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Labelling. Sodium Phosphate (32P) Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision).

ROSEI BENGALENSIS (131I) NATRICI INJECTIO
Rose Bengal (131I) Sodium Injection
1974 Revision

\[\text{C}_{28}\text{H}_{38}\text{Cl}_{4}^{131}\text{I}\text{Na}_{2}\text{O}_{5}\]

Rose Bengal (131I) Sodium Injection is a sterile solution of the disodium salt of 4,5,6,7-tetrachloro-2',4',5',7'-tetrainodofluorescein (131I).

The content of iodine-131 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of iodine-131 stated on the label, at the reference date and hour stated on the label.

Not less than 90 per cent. of the total iodine-131 is present as iodinated 4,5,6,7-tetrachlorofluoresceins, and in addition not less than 70 per cent. of the total iodine-131 is present as 4,5,6,7-tetrachloro-2',4',5',7'-tetrainodofluorescein.

The solution is sterilized by Method 1 - Heating in an autoclave or by Method 3 - Filtration described under “Injections” in Ph. Int. II.

The radioactive half-life of iodine-131 is 8.06 days.
Description. A clear, purplish-red solution.

Identification
A. Complies with the test for Identification described under "Natril Iodidi (I\(^{131}\)) Solutio".
B. The test for radiochemical purity and the assay for rose bengal sodium described below serve also to identify the product.

Reaction. pH 6.0 to 8.5.

Radioactive purity. Complies with the general requirements for radioactive purity given in Appendix 13, "Radioactivity" (1974 revision).

Radiochemical purity
A. Separation of iodide ion from iodinated chlorofluoresceins: Take a sample, dilute it if necessary, to contain not more than 5 \(\mu\)g of Rose Bengal (I\(^{131}\)) Sodium per \(\mu\)l of solution. Carry out ascending paper chromatography as described in Appendix 14, "Chromatography", using Whatman No. 3 paper or equivalent. Apply 5 \(\mu\)l of the sample to the paper and apply also, as a separate spot, 5 \(\mu\)l of a solution containing about 25 \(\mu\)g of Rose Bengal Sodium R. Develop with water containing 1 per cent. \(v/v\) of strong ammonia R and saturated with amyl alcohol R until the solvent front has travelled 30 cm. Allow the chromatogram to dry in air, observe the location of coloured spots on it, and determine the areas of radioactivity by a suitable method. Iodide ion has an Rf value of about 0.9, whereas the iodinated chlorofluoresceins have Rf values in the region 0.5 to 0.6 and form spots that may be incompletely separated from each other (these spots may be apparent by their colour, but, if the weight of the Rose Bengal (I\(^{131}\)) Sodium applied to the chromatogram is small, they may be revealed only by their radioactivity, e.g., by autoradiography). Not less than 90 per cent. of the total iodine-131 is present in the coloured spots or band corresponding to the iodinated chlorofluoresceins.
B. Separation of individual iodinated chlorofluoresceins: Carry out the method for thin-layer chromatography described in Appendix 14, using a suitable silica gel as the absorbant. Prepare the chromatoplates of layer thickness 250-300 \(\mu\) and dry them at 130° for thirty minutes.
Apply 5 \(\mu\)l of the sample solution, containing not more than 25 \(\mu\)g of Rose Bengal (I\(^{131}\)) Sodium (see A above), to the plate, and apply to the same plate 5 \(\mu\)l of the solution containing 25 \(\mu\)g of Rose Bengal Sodium R. Allow the plate to dry for fifteen minutes and develop with a mixture of 87 parts of chloroform R and 13 parts of formic acid R until the mobile
phase has reached a height of 10 cm. Allow the plate to dry in air and
determine the areas of radioactivity by a suitable method.

Not less than 70 per cent. of the total iodine-131 is present as 4,5,6,7-
tetrachloro-2',4',5',7'-tetraiodofluorescein.

Note. Method B gives better separation of the iodinated tetrachlorofluores-
ceins, but is not so suitable for the determination of iodide ion as method A.

Rose bengal sodium. Determine the absorbance of a sample of the injection,
appropriately diluted, in a 1-cm cell at 550 nm, with a suitable spectro-
photometer, using water as the blank. Calculate the quantity, in mg, of
rose bengal sodium per ml of the injection by the formula 0.004 D (A_s/A_o),
in which D is the dilution factor, A_o is the absorbance of the sample solution,
and A_s is the absorbance, similarly determined, of a solution of Rose
Bengal Sodium R adjusted to pH 8.0 by the addition of sodium bicarbonate
R and containing 4 μg of rose bengal sodium per ml. The content of rose
bengal sodium is not less than 50.0 per cent. and not more than 150.0 per
cent. of the amount stated on the label.

Assay. Determine the radioactivity in suitable counting equipment by
comparison with a standardized iodine-131 solution or by measurement
in an instrument calibrated with the aid of such a solution.

Standardized iodine-131 solutions are available from national standard-
izing laboratories.

Storage. Rose Bengal (¹³¹I) Sodium Injection should be stored at a tem-
perature not exceeding 25° and protected from light. Other conditions of
storage should comply with the requirements under “ Storage ” in Appen-

Stability. Rose Bengal (¹³¹I) Sodium Injection decomposes gradually
with an accompanying decrease in radiochemical purity.

Labelling. Rose Bengal (¹³¹I) Sodium Injection should be labelled as
specified under “ Labelling ” in Appendix 13, “ Radioactivity ” (1974
revision), the label also giving the information on storage temperature and
the weight of rose bengal sodium per ml.

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L-SELENOMETHIONINE (³⁵Se) INJECTIO

-Selenomethionine (³⁵Se) Injection

1974 Revision

\[ \text{C}_2\text{H}_2\text{Se} = \text{CH}_2\text{-CH}_2\text{-CH-COOH} \]
\[ \text{NH}_2 \]

Mol. Wt. 196.10

L-Selenomethionine (³⁵Se) Injection is a sterile solution of L-selenomethionine (³⁵Se). It may be produced either by chemical synthesis or by the growth of certain micro-organisms in a medium containing selenite (³⁵Se).

Selenium-75 is a radioactive isotope of selenium and may be produced by neutron irradiation of natural selenium or of selenium enriched in selenium-74.

The content of selenium-75 is not less than 90.0 per cent. and not more than 110.0 per cent. of the content of selenium-75 stated on the label, at the reference date stated on the label.

Not less than 90 per cent. of selenium-75 is in the form of selenomethionine at the reference date stated on the label.

The solution is sterilized by Method 1 – Heating in an autoclave described under “Injectiones” in Ph. Int. II.

The radioactive half-life of selenium-75 is 120 days.

Description. A clear, colourless or faintly yellow solution.

Identification

A. The gamma-ray spectrum, measured with a suitable instrument, is identical with that of standardized selenium-75. The most prominent gamma photons have energies of 0.136 MeV and 0.265 MeV.

B. The test for radiochemical purity described below serves also to identify the product.

Reaction. pH 6.0 to 8.0.

Radiochemical purity. Complies with the general requirements for radiochemical purity given in Appendix 13, "Radioactivity" (1974 revision).

Radiochemical purity. Dilute the Injection with water to a suitable radioactive concentration and add L-methionine to obtain the concentration of 1 µg of L-methionine per 1 µl in the final solution. Apply 5 µl of this solution to a suitable chromatographic paper and carry out descending
chromatography as described in Appendix 14, "Chromatography", using a mixture of 60 volumes of n-butanol R, 15 volumes of glacial acetic acid R, and 25 volumes of water. Develop the chromatogram for about 6 hours. Allow the chromatogram to dry in air and determine the areas of radioactivity by a suitable method. Not less than 90 per cent. of the total radioactivity is in the spot that has an RF value of about 0.6, which corresponds to selenomethionine.

**Pyrogens.** Complies with the Test for Pyrogens (Appendix 43), using a quantity equivalent, at the reference date stated on the label, to 20 μCi per kg of the rabbit's weight.

**Assay.** Determine the radioactivity in suitable counting equipment by comparison with a standardized selenium-75 solution or by measurement in an instrument calibrated with the aid of such a solution. Standardized selenium-75 solutions are available from national standardizing laboratories.

**Storage.** L-Selenomethionine (75Se) Injection should be stored at a temperature not exceeding 10° and protected from light. Other conditions of storage should comply with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

**Labelling.** L-Selenomethionine (75Se) Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision).

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**SEROALBUMINI HUMANI IODINATI (125I) INJECTIO**

**Iodinated (125I) Human Serum Albumin Injection**

**1974 Revision**

Iodinated (125I) Human Serum Albumin Injection is a sterile solution of human serum albumin, which has been iodinated with iodine-125, in a saline solution isotonic with blood.

The human serum albumin used for iodination shall contain not more than 5 per cent. of globulins and shall comply with the national regulations of the country in which the iodinated (125I) Human Serum Albumin Injection is employed. The human serum albumin used for iodination should have been suitably treated to prevent the transmission of serum hepatitis (e.g., by heating in an aqueous solution for 10 hours at 59.5° to 60.5°).
The content of iodine-125 is not less than 85.0 per cent. and not more than 115.0 per cent. of that stated on the label, at the reference date stated on the label. The iodination should be carried out so that not more than one gram-atom of iodine is introduced for each gram-molecule of albumin. Further albumin may be added after the iodination. The concentration of protein in the final product shall be not less than 1 per cent. w/v.

A suitable bacteriostatic agent, such as benzyl alcohol R 0.9 per cent. v/v, shall be present. The product is sterilized by Method 3 - Filtration described under “Injectiones” in Ph. Int. II.

The radioactive half-life of iodine-125 is 60.0 days.

Description. A clear, colourless or faintly yellow solution.

Identification
A. Complies with the test for Identification described under “Natrii Iodidi (\(^{125}\)I) Solutio”.
B. The tests described below under the headings “Radiochemical purity” and “Protein” serve to identify the product as a radioactively labelled albumin.
C. By precipitation with specific antisera or by immunoelectrophoresis contains only human serum proteins.

Reaction. pH 6.5 to 8.5.

Radionuclidic purity. Complies with the requirements for radionuclidic purity described under “Natrii Iodidi (\(^{125}\)I) Solutio”.

Radiochemical purity. Carry out the test for radiochemical purity described under “Seroalbumini Humani Iodinati (\(^{131}\)I) Injectio”, using a volume containing not less than 0.0005 g of iodinated (\(^{131}\)I) human serum albumin. Not less than 95 per cent. of the radioactivity on the paper occurs in a position corresponding to human serum albumin.

Protein
A. When a volume containing between 0.0002 g and 0.0005 g of iodinated (\(^{131}\)I) human serum albumin is used, complies with the test A for protein described under “Seroalbumini Humani Iodinati (\(^{131}\)I) Injectio”.
B. Complies with the tests B and C for protein described under “Seroalbumini Humani Iodinati (\(^{131}\)I) Injectio”.

Pyrogens. Complies with the Test for Pyrogens (Appendix 43), using a quantity corresponding, at the reference date stated on the label, to 10 μCi or 0.1 ml, whichever is less, per kg of the rabbit’s weight.
Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-125 solution or by measurement in an instrument calibrated with the aid of such a solution. An instrument incorporating a scintillation detector, such as a thin sodium iodide crystal of such thickness as to minimize absorption of the photons of iodine-125, should be employed, and the instrument should be set so that the contribution from iodine-126 is minimized. A thin-walled ionization chamber may be employed, but the iodine-126 content must then be known accurately to permit an appropriate correction to be made.

Standardized iodine-125 and caesium-137 solutions are available from national standardizing laboratories.

Storage. Iodinated (\(^{131}\)I) Human Serum Albumin Injection should be stored at a temperature between 2° and 10°. Other conditions of storage should comply with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Labelling. Iodinated (\(^{131}\)I) Human Serum Albumin Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also giving the information on storage temperature.

Caution. This product is not suitable for metabolic studies, nor for intrathecal, intraventricular, or intracisternal injection unless it is labelled specifically as suitable for these purposes.

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SEROALBUMINI HUMANI IODINATI (\(^{131}\)I) INJECITO

Iodinated (\(^{131}\)I) Human Serum Albumin Injection

1974 Revision

Iodinated (\(^{131}\)I) Human Serum Albumin Injection is a sterile solution of human serum albumin, which has been iodinated with iodine-131, in a saline solution isotonic with blood.

The human serum albumin used for iodination shall contain not more than 5 per cent. of globulins and shall comply with the national regulations of the country in which the iodinated (\(^{131}\)I) human serum albumin injection is employed. The human serum albumin used for iodination should have been suitably treated to prevent the transmission of serum hepatitis (e.g., by heating in an aqueous solution for 10 hours at 59.5° to 60.5°).
The content of iodine-131 is not less than 90.0 per cent., and not more than 110.0 per cent., of that stated on the label, at the reference date and hour stated on the label. The iodination should be carried out so that not more than one gram-atom of iodine is introduced for each gram-molecule of albumin. Further albumin may be added after the iodination. The concentration of protein in the final product shall be not less than 1 per cent. w/v.

A suitable bacteriostatic agent, such as benzyl alcohol R 0.9 per cent. v/v, shall be present. The product is sterilized by *Method 3 - Filtration* described under "Injections" in Ph. Int. II.

The radioactive half-life of iodine-131 is 8.06 days.

**Description.** A clear, colourless or faintly yellow solution.

**Identification**

A. Complies with the test for identification described under "Natrii Iodidi (II) Solutio".

B. The tests described below under the headings "Radiochemical purity" and "Protein" serve to identify the product as a radioactively labelled albumin.

C. By precipitation with specific antisera or by immunoelectrophoresis contains only human serum proteins.

**Reaction.** pH 6.5 to 8.5.

**Radiochemical purity.** Complies with the general requirements for radio-nuclide purity given in Appendix 13, "Radioactivity" (1974 revision).

**Radiochemical purity.** Submit a volume containing not less than 0.0005 g of iodinated (I¹³¹) human serum albumin to electrophoresis on a strip of filter-paper 30 cm long and 5 cm wide at 500 volts for one hour in a solution containing 5 g of barbital sodium R, 3.25 g of sodium acetate R, 4 g of sodium octanoate R, and 34.2 ml of 0.1 N hydrochloric acid in sufficient water to produce 1000 ml. Allow the paper to dry and determine the area of radioactivity by a suitable method. Not less than 95 per cent. of the radioactivity on the paper occurs in a position corresponding to human serum albumin.

**Protein**

A. Carry out the test for radiochemical purity using a volume containing between 0.0002 and 0.0005 g of iodinated (I¹³¹) human serum albumin and a strip of cellulose acetate about 20 cm long and 2.5 cm wide instead of the paper. Dry the strip at about 80° to 100° for fifteen minutes and stain

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for fifteen minutes in a solution of 0.2 g of naphthalene black 12B R in a mixture of 10 ml of glacial acetic acid R and 90 ml of methanol R. Wash the strip in a mixture of 12 ml of glacial acetic acid R and 88 ml of methanol R until the background is white, for ten minutes in dilute acetic acid R, and finally in water, and dry between blotting-paper pressed between glass plates. The distribution of the stained protein does not deviate significantly from that obtained by simultaneously treating human serum albumin in the same manner.

B. The ultraviolet spectrum of the sample solution in water in the range 250 nm to 330 nm exhibits one maximum only at 280 nm corresponding to serum proteins.

C. Microdetermination of nitrogen:

_Caution._ During the procedure care must be taken to absorb the liberated iodine-131.

Place 1.0 ml of the _injection_ in a round-bottomed centrifuge tube, add 5 ml of water, mix, add 0.2 ml of a 7.5 per cent. solution of sodium molybdate R and 0.2 ml of a mixture of 1 part of nitrogen-free sulfuric acid R with 30 parts of water, shake, and centrifuge for five minutes. Decant the supernatant liquid and allow the inverted tube to drain on a filter-paper. To the residue in the tube, add 3 drops of a 30 per cent. solution of copper sulfate R and 1 ml of nitrogen-free sulfuric acid R and boil gently for ten minutes; cool; add 1 g of anhydrous sodium sulfate R and 0.01 g of selenium R, boil gently for one hour and cool. Transfer to an ammonia distillation apparatus, add 6 ml of a saturated solution of sodium hydroxide R and pass steam through the flask; distil for seven minutes, collecting the distillate in a mixture of 5 ml of a saturated solution of boric acid R, 5 ml of water, and 1 drop of a saturated solution of methyl red R in ethanol (95 per cent.) R containing 0.1 per cent. of methylthioninium chloride R, and titrate with 0.015 N hydrochloric acid. Not less than 8 ml of 0.015 N hydrochloric acid is required.

_Pyrogens._ Complies with the Test for Pyrogens (Appendix 43), using a quantity corresponding, at the reference date and hour stated on the label, to 50 μCi or 0.1 ml, whichever is less, per kg of the rabbit's weight.

_Assay._ Determine the radioactivity in suitable counting equipment by comparison with a standardized iodine-131 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized iodine-131 solutions are available from national standardizing laboratories.
Storage. Iodinated ($^{131}$I) Human Serum Albumin Injection should be stored at a temperature between 2° and 10°. Other conditions of storage should comply with the requirements stated under "Storage" in Appendix 13, "Radioactivity" (1974 revision).

Labelling. Iodinated ($^{131}$I) Human Serum Albumin Injection should be labelled as specified under "Labelling" in Appendix 13, "Radioactivity" (1974 revision), the label also giving the information on storage temperature.

Caution. This product is not suitable for metabolic studies, nor for intrathecal, intraventricular or intracisternal injection, unless it is labelled specifically as suitable for these purposes.

SEROALBUMINI HUMANI TECHNETIO ($^{99m}$Tc) SIGNATI

INJECTIO

Technetium ($^{99m}$Tc) Labelled Human Serum Albumin Injection

Technetium ($^{99m}$Tc) Labelled Human Serum Albumin Injection is a sterile solution of human serum albumin that has been labelled with technetium-99m. It is made isotonic with blood by the addition of Sodium Chloride.

The human serum albumin used in the preparation shall contain not more than 5 per cent. of globulins and shall comply with the national regulations of the country in which the Technetium ($^{99m}$Tc) Labelled Human Serum Albumin Injection is employed. The human serum albumin injection used in the preparation should have been suitably treated to prevent the transmission of serum hepatitis (e.g., by heating in an aqueous solution for 10 hours at 59.5° to 60.5°).

The content of technetium-99m is not less than 90.0 per cent. and not more than 110.0 per cent. of that stated on the label, at the reference date and hour stated on the label.

The product may contain antimicrobial, reducing, chelating, and stabilizing agents, as well as buffers. The product is sterilized by Method 3 - Filtration, described under "Injectiones" in Ph. Int. II.

The radioactive half-life of technetium-99m is 6.02 hours.

Description. A clear, colourless or faintly yellow solution.
Identification
A. Complies with the test for identification described under “Natrii Pertechnetatatis (99mTc) Injectio”.
B. The tests described under the headings “Radiochemical purity” and “Protein” serve to identify the product as a radioactively labelled albumin.
C. By precipitation with specific antisera or by immunoelectrophoresis contains only human serum proteins.

Reaction. pH 4.0 to 7.0.

Radiochemical purity. Complies with the requirements for radionuclidic purity described under “Natrii Pertechnetatatis (99mTc) Injectio”.

Radiochemical purity. Carry out ascending paper chromatography as described in Appendix 14, “Chromatography”. Apply 5 μl of the sample to the paper. Allow to dry and develop the chromatogram for 1 hour, using a mixture of 80 volumes of methanol R and 20 volumes of water. Allow the chromatogram to dry and determine the areas of radioactivity by a suitable method. Not less than 95 per cent. of the total radioactivity is in the spot corresponding to human serum albumin at the point of application.

Protein. Complies with the test for protein described under “Seroalbumini Humani Iodinati (131I) Injectio”.

Pyrogens. Complies with the Test for Pyrogens (Appendix 43), using a quantity corresponding, at the reference date and hour stated on the label, to not less than 500 μCi per kg of the rabbit’s weight.

Assay. Determine the radioactivity in suitable counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized solutions of technetium-99m are available from national standardizing laboratories.

Storage. Technetium (99mTc) Labelled Human Serum Albumin Injection should be stored at a temperature between 2° and 10°. Other conditions of storage should comply with the requirements stated under “Storage” in Appendix 13, “Radioactivity” (1974 revision).

Labelling. Technetium (99mTc) Labelled Human Serum Albumin Injection should be labelled as specified under “Labelling” in Appendix 13, “Radioactivity” (1974 revision), the label also giving the information on storage temperature.
XENONIS (133Xe) INJECTIO

Xenon (133Xe) Injection is a sterile solution of xenon-133 made isotonic with blood by the addition of Sodium Chloride.

Xenon-133 is a radioactive isotope of xenon and may be prepared from the products of uranium fission. The total content of xenon-133 in the container, or the radioactive concentration of xenon-133 per ml of the injection, is not less than 80.0 per cent. and not more than 130.0 per cent. of the content or radioactive concentration stated on the label, at the reference date and hour stated on the label. Preferably, the container should be of a form from which the injection can be extracted without creation of a free space above the injection, e.g., an injection cartridge.

The radioactive half-life of xenon-133 is 5.29 days.

Description. A clear, colourless solution.

Identification. The gamma-ray and X-ray spectrum measured with a suitable instrument is identical with that of a standardized solution of xenon-133 in isotonic saline, apart from any differences attributable to the presence of xenon-131m and xenon-133m. The most prominent gamma photon of xenon-133 has an energy of 0.081 MeV and there is an X-ray emission (resulting from internal conversion) of 0.031 MeV. The presence of xenon-131m may be revealed by its major gamma photon of 0.164 MeV. Xenon-131m decays with a half-life of 12.0 days. The presence of xenon-133m may be revealed by a gamma photon of 0.233 MeV. Xenon-133m decays with a half-life of 2.26 days.

Reaction. pH 5.0 and 8.0.

Radionuclidic purity. Complies with the general requirements for radionuclidic purity given in Appendix 13, “Radioactivity” (1974 revision), except that xenon-131m and xenon-133m may be present.

Assay

A. If there is a free space above the solution: In this case, a significant amount of xenon-133 will be present in the free space. The method serves only to measure the total amount of xenon-133 present in the container and does not indicate the radioactive concentration of the Xenon (133Xe) Injection. After withdrawal of a portion of the solution the radioactive concentration will decrease because of the increase of the free space relative to the volume of injection. The total activity in the container is determined
by measurement in a well-type ionization chamber by comparison with a
standardized xenon-133 solution or by measurement in such a chamber
calibrated with the aid of a standardized xenon-133 solution under effectively
identical conditions. Correct for the activity in the rubber stopper of the
vial or the rubber parts of a cartridge, determined by removing them,
rapidly washing with water, sealing in a suitable container, and measuring
the activity.

B. *If the solution completely fills a cartridge*: The radioactive concentration
is measured by the following method. Determine the total activity in the
container as above, and weigh the container. Expel a portion of the solu-
tion, re-weigh the container, and determine the total activity remaining
in the container as before. From these data, the radioactive concentration
of the injection may be calculated.

**Storage.** Complies with the requirements stated under "Storage" in
Appendix 13, "Radioactivity" (1974 revision).

**Labelling.** Xenon (¹³³Xe) Injection should be labelled as specified under
Appendix 13, "Radioactivity" (1974 revision).
Radioactive pharmaceuticals require specialized techniques in their handling and testing in order that correct results may be obtained and hazards to personnel be minimized. All operations should be carried out or supervised by personnel who have received expert training in handling radioactive materials.

**DEFINITIONS**

*Nuclide*

A species of atom characterized by its mass number, atomic number and nuclear energy state, provided that the mean life in that state is long enough to be observable.

*Radioactivity*

The property of certain nuclides of emitting radiation by the spontaneous transformation of their nuclei into those of other nuclides.

**Explanatory Note.** The term "disintegration" is widely used as an alternative to the term "transformation". Transformation is preferred as it includes, without semantic difficulties, those processes in which no particles are emitted from the nucleus.

*Radioisotope*

A nuclide that is radioactive.

*Curie*

The unit of radioactivity. This is defined in terms of the number of nuclear transformations that occur in a quantity of radioactive material in unit time. One curie (Ci) is $3.7 	imes 10^{10}$ nuclear transformations per second. Convenient subunits are the milli-curie (mCi) and the micro-curie (μCi).

*Half-life*

The time in which the radioactivity decreases to one-half the original value.

**Explanatory Note.** The rate of radioactive decay is constant and characteristic for each individual radionuclide. The exponential decay curve is described mathematically by the equation

$$N = N_0 e^{-\lambda t}$$
where \( N \) is the number of atoms at elapsed time \( t \), \( N_0 \) is the number of atoms when \( t = 0 \), and \( \lambda \) is the disintegration constant characteristic of each individual radionuclide. The half-life period is related to the disintegration constant by the equation

\[
T_{\frac{1}{2}} = \frac{0.693}{\lambda}
\]

Radioactive decay corrections are calculated from the exponential equation, or from decay tables, or are obtained from a decay curve plotted for the particular radionuclide involved (see figure below).

**Radioactive concentration**

The radioactive concentration of a solution refers to the radioactivity in a unit volume of the solution. As with all statements involving radioactivity, it is necessary to include a reference date of the standardization. For radionuclides with a half-life of less than 30 days, the time of standardization should be expressed to the nearest hour. For radionuclides with a half-life of less than one day, a more precise statement of the reference time is required.

**Specific radioactivity (or specific activity)**

The specific activity of a preparation of a radioactive material is the radioactivity per unit mass of the element or of the compound concerned.
EXPLANATORY NOTE. It is usual to specify the radionuclide concerned and also it is necessary to express the time thus: "1 mCi of iodine-131 per mg of o-iodophippuric acid R at 12.00 hours UT on 1 January 1975", or "1 mCi of selenium-75 per mg of selenomethionine on 1 January 1975".

Specific radioactivity is often not determined directly but is calculated from a knowledge of the radioactive concentration of the solution and of the chemical concentration of the radioactive compound. Thus, if a solution contains $x$ mCi of $^{131}$I per ml, and if the $^{131}$I is entirely in the chemical form of sodium iodohippurate of which the concentration is $y$ mg per ml, then at that time the specific activity is:

$$\frac{x}{y}$$ mCi of iodine-131 per mg of o-iodophippuric acid.

Where necessary, the radiochemical purity of the preparation (see below) must be taken into account.

The term employed in radiochemical work is "specific activity". As the word "activity" has other connotations in a pharmacopoeia, the term should, where necessary, be modified to "specific radioactivity" to avoid ambiguity.

Radiochemical purity

The radionuclidic purity of a preparation is that percentage of the total radioactivity which is present in the form of the stated radionuclide.

EXPLANATORY NOTE. Some radionuclides decay into nuclides that are themselves radioactive: these are referred to as mother (or parent) and daughter radionuclides respectively. Such daughter radionuclides are often excluded when calculating the radionuclidic purity; for example, iodine-131 will always contain its daughter xenon-131, but this would not be considered an impurity because its presence is unavoidable.

In employing the definition, the radioactivity must be measured in appropriate units; that is, in the number of nuclear transformations that occur in unit time, for example, in terms of curies, millicuries or microcuries. If, for example, a preparation stated to be iodine-125 is known to contain 99 mCi of iodine-125 and 1 mCi of iodine-126, and no other radionuclide, then the preparation is said to be of 99 per cent. radionuclidic purity. It will be noted that the relative amounts of iodine-125 and iodine-126, and hence the radionuclidic purity, will change with time. An expression of radionuclidic purity must therefore contain a statement of the time, such as: "Not more than 1 per cent. of the total radioactivity is due to iodine-126 at the reference date stated on the label". In case of radionuclides with a half-life of less than 30 days the reference hour should also be included.

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It is clear that, in order to give a statement of the radionuclidic purity of a preparation, the activities (and hence the identities) of every radionuclide present must be known. There are no simple and certain means of identifying and measuring all the radionuclidic impurities that might be present in a preparation. An expression of radionuclidic purity must either depend upon the judgement of the person concerned, or it must be qualified by reference to the method employed, for example: "No radionuclidic impurities were detected by gamma scintillation spectrometry using a sodium iodide detector ".

Radiochemical purity

The radiochemical purity of a preparation is that percentage of the stated radionuclide that is present in the stated chemical form.

EXPLANATORY NOTE. If, for example, a preparation of cyanocobalamin (\(^{60}\text{Co}\)) is stated to be 99 per cent. radiochemically pure, then 99 per cent. of the cobalt-57 is present in the form of cyanocobalamin. Radiochemical impurities might include such substances as cobaltous (\(^{60}\text{Co}\)) ion or hydroxy-cobalamin (\(^{60}\text{Co}\)).

The possible presence of radionuclidic impurities is not taken into account in the definition. If the radionuclidic impurity is not isotopic with the stated radionuclide, then it cannot possibly be in the identical chemical form. If the radionuclidic impurity is isotopic with the stated radionuclide, it could be, and indeed is likely to be, in the same chemical form.

Radiochemical impurities may arise during the preparation of the material or during storage, because of ordinary chemical decomposition or, what is often more important, because of radiation decomposition (that is, because of the physical and chemical effects of the radiation).

PRODUCTION AND HANDLING OF RADIOACTIVE PHARMACEUTICALS

The following paragraphs concern special considerations applying to the monographs on radioactive drugs. The facilities for the production, use, and storage of radioactive pharmaceuticals are generally subject to licensing by national authorities. They often have to comply with two sets of regulations, those concerned with pharmaceuticals and those concerned with radioactive materials. Each producer or user must be thoroughly cognizant of the national requirements pertaining to the articles concerned.
Carriers

The mass of radioactive material usually encountered in radioactive pharmaceuticals is often too small to be measured by ordinary chemical or physical methods. Since such small amounts may not be subject to the usual methods of separation and purification, a carrier, in the form of inactive material isotopic with the radionuclide, may be added during processing and dispensing to permit ready handling. The amount of carrier added must be sufficiently small for it not to cause undesirable physiological effects. The mass of an element formed in a nuclear reaction may be exceeded by that of the inactive isotope present in the target material or in the reagents used in the separation procedures.

Radioactive preparations in which no carrier is intentionally added during the manufacture or processing are often loosely referred to as carrier-free.

DETECTION AND MEASUREMENT

Radioactive transformations may involve the emission of charged particles, the process of electron capture, or the process of isomeric transition. The charged particles emitted from the nucleus may be alpha particles (helium nuclei of mass number 4) or beta particles (electrons of negative or positive charge, \( \beta^- \) or \( \beta^+ \) respectively, the latter known as positrons). The emission of charged particles from the nucleus may be accompanied by gamma rays, which are of the same physical nature as X-rays. Gamma rays are also emitted in the process of isomeric transition (IT). X-rays, which may be accompanied by gamma rays, are emitted in the process of electron capture (EC). Positrons are annihilated on contact with matter, the process being accompanied by the emission of gamma rays with an energy of 511 keV.

The methods employed for the detection and measurement of radioactivity are dependent upon the nature and energy of the radiation emitted. Radioactivity may be detected and/or measured by a number of different instruments based upon the action of radiation in causing the ionization of gases, or the fluorescence of certain solids and liquids, or by the effect of radiation on a photographic emulsion.

In general, a counting assembly consists of a sensing unit and an electronic scaling device. The sensing unit may be a Geiger-Müller tube, a proportional counter, or a scintillation detector in which a photomultiplier tube is employed in conjunction with a scintillator.

Geiger-Müller counters and proportional counters are generally used for the measurement of the beta emitters. Scintillation counters employing
liquid or solid phosphors may be used for the measurement of beta and gamma emitters. The electronic circuitry associated with a detector system usually consists of a high-voltage supply, an amplifier, a pulse-height selector, and a scaler, a ratemeter, or other readout device. When the electronic scaling device or the scaler in a counting assembly is replaced by an electronic integrating device, the resultant assembly is a ratemeter. Ratemeters are used for the purpose of monitoring and surveying radioactivity and are somewhat less precise as measuring instruments than the counters. Ionization chambers are often used for measuring gamma-ray activities and, provided they are thin-walled, for measuring X-rays.

Radiation from a radioactive source is emitted in all directions. Procedures for the standardization and measurement of beta emitters by means of a count of the emissions in all directions are known as \(4\pi\)-counting; those based on a count of the emissions in a solid angle of \(2\pi\) steradians (180°) are known as \(2\pi\)-counting; and those based on a fraction of the emissions defined by the solid angle subtended from the detector to the source are known as counting by fixed geometry. It is customary to assay the radioactivity of a preparation by comparison with a standardized preparation. The validity of such an assay is critically dependent upon the reproducibility of the spatial relationships of the source to the detector and its surroundings. In the primary standardization of radionuclides coincidence techniques are employed in preference to simple \(4\pi\)-counting whenever the decay scheme of the radionuclide permits. The most commonly employed coincidence technique is \(4\pi\)-beta/gamma coincidence counting, which is used for nuclides in which some or all of the disintegrations are followed by prompt photon emission. An additional adjacent detector, sensitive only to photons, is used to measure the efficiency in the \(4\pi\)-counter of those disintegrations with which the photons are coincident.

The construction and performance of instruments and accessory apparatus vary. The preparation of samples must be modified to obtain satisfactory results with a particular instrument. The operator must follow carefully the manufacturer's instructions for optimum instrument performance and substantiate results by careful examination of known samples.

Radioactivity due to materials of construction, to cosmic rays, and to spontaneous discharges in the atmosphere contributes what is known as the background activity. All sample radioactivity measurements must be corrected by subtracting background activity.

In the counting of samples at high activity levels, corrections must be made also for loss of counts due to inability of the equipment to resolve pulses arriving in close succession. Such coincidence-loss corrections must be made prior to the subtraction of background correction.
The corrected count rate, \( R \), is given by the formula

\[
R = \frac{r}{1 - r\tau}
\]

\( r \) is the observed count rate
\( \tau \) is the resolving time

A radioactivity count is a statistical value — i.e., it is a measure of nuclear decay probabilities — and is not exactly constant over any given time interval. The magnitude of the standard deviation is approximately equal to the square root of the number of counts. In general, at least 10,000 counts are necessary to obtain a standard deviation of 1 per cent.

*Absorption*

Ionizing radiation is absorbed in the material surrounding the source of the radiation. Such absorption occurs in air, in sample coverings, in the window of the detection device, and in any special absorbers placed between the sample and the detector. Since alpha particles have a short range of penetration in matter, beta particles have a somewhat greater range, and gamma rays are deeply penetrating, identification of the type and energy of radiation emitted from a particular radionuclide may be determined by the use of absorbers of varying thickness. In practice this method is little used, and then only in connexion with beta emitters. However, variations in counting rate due to variations in thickness and density of sample containers can be a major problem with beta emitters and with X-ray emitters, such as iodine-125. Plastic tubes, in which variations of density and thickness are minimal, are therefore often employed.

The absorption coefficient (\( \mu \)), which is the reciprocal of the "thickness" expressed in mg/cm\(^2\), is commonly determined to characterize the beta radiation emitted by a radionuclide.

*Method*

The following procedure is used for the identification test in "Natrri Phosphatis (\(^{32}\)P) Injectio" for the measurement of beta activity and for calculation of the absorption coefficient:

Place the radioactive substance, suitably mounted for counting, under a suitable counter. Make activity determinations individually and successively, using at least 6 different thicknesses of aluminium chosen from a range of 10 to 200 mg/cm\(^2\) and a single absorber with a thickness of at least 800 mg/cm\(^2\). Obtain the net beta activity at the various absorbers used by subtracting the activity found with the 800 mg/cm\(^2\) or greater absorber.
Plot the logarithm of the net beta activity as a function of the total absorber thickness. The total absorber thickness is the thickness of the aluminium plus the thickness of the counter window (as stated by the manufacturer), plus the air-equivalent thickness (the distance, expressed in cm, of the sample from the counter window multiplied by 1.205), all expressed in mg/cm². An approximately straight line results.

Choose two of the absorber thicknesses that are 20 mg/cm² or more apart and that fall on the plot, and calculate the absorption coefficient by the equation

\[ \mu = \frac{1}{t_2 - t_1} \ln \left( \frac{A_{t_1}}{A_{t_2}} \right) \]

where \( t_1 \) and \( t_2 \) represent the total absorber thickness greater than 10 mg/cm², and differing by at least 20 mg/cm², \( t_2 \) being the thicker absorber, and \( A_{t_1} \) and \( A_{t_2} \) represent the net beta activity with \( t_1 \) and \( t_2 \) absorbers, respectively.

The choice of absorber thickness depends on the source. For sources other than phosphorus-32, which have higher or lower beta energy, greater or lesser absorber thicknesses are necessary.

For characterization of the radionuclide, the absorption coefficient should be within ±5 per cent. of that found for a sample of the same radionuclide of known purity when determined in parallel.

Radioactivity at zero total absorber thickness may be determined by plotting a curve identical with the one described for determination of the absorption coefficient and extrapolating the straight line plot to zero absorber thickness, taking into consideration the thickness, expressed in mg/cm², of sample coverings, the air, and the counter window.

Radiation spectrometry

Crystal scintillation spectrometry

When the energy of beta or gamma radiation is dissipated within materials known as scintillators, light is produced in an amount proportional to the energy dissipated. This quantity of light may be measured by suitable means, and is proportional to the energy absorbed in the scintillator. The scintillators most commonly used for this purpose are single crystals of thallium-activated sodium iodide. The light emitted under the impact of a gamma photon or a beta particle is converted into an electric output pulse by a photomultiplier. Scanning of the output pulses with a suitable pulse height analyser results in an energy spectrum of the source. Gamma-ray

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scintillation spectra show one or more sharp, characteristic photoelectric peaks, corresponding to the energies of the gamma radiation of the source. They are thus useful for identification purposes and also for the detection of gamma-emitting impurities in a preparation. These peaks are accompanied by other peaks due to secondary effects of radiation on the scintillator and its surroundings, such as backscatter, positron annihilation, coincidence summing, and fluorescent X-rays. In addition, broad bands known as the Compton continua arise from the scattering of the gamma photons in the scintillator and in surrounding materials. Calibration of the instrument is achieved with the use of known samples of radionuclides whose energy spectra have been characterized. The shape of the spectrum produced will vary with the instrument used, owing to such factors as differences in the shape and size of the crystal, in the shielding materials used, and in the types of discriminator employed in the pulse height analysers. When using the spectrum for identification of radionuclides it is therefore necessary to compare the spectrum with that of a known sample of the radionuclide obtained in the same instrument under identical conditions.

Certain radionuclides, e.g., iodine-125, emit characteristic X-rays of well-defined energies which will produce photoelectric peaks in a suitable gamma spectrometer. Beta radiation also interacts with the scintillators, but the spectra are continuous and diffuse and generally of no use for identification of the radionuclide or for the detection of beta-emitting impurities in a preparation.

*Semiconductor detector spectrometry*

Gamma-ray and beta-ray spectra may be obtained using solid-state detectors. The peaks obtained do not suffer to the same extent the broadening shown in crystal scintillation spectrometry, and the resolution of gamma photons of similar energies is very much improved.

The energy required to create an electron-hole pair or to promote an electron from the valence band to the conduction band in a semiconductor is far less than the energy required to produce a photon in a scintillation crystal. In gamma-ray spectrometry a lithium-drifted germanium detector can provide an energy resolution of 0.33 per cent. for the 1.33 MeV photon of cobalt-60, as compared with 5.9 per cent. with a 7.6 cm × 7.6 cm thallium-activated sodium iodide crystal.

Solid state spectrometers are available only in the more specialized laboratories.

*Liquid scintillation counting*

For weak beta-emitters like $^{38}$S, $^{34}$C and $^3$H, where self-absorption of the low-energy beta particles is significant, the preferred counting method is
by liquid scintillation, which can occasionally be employed also for emitters of X-rays, alpha-rays and gamma-rays. If the sample to be counted is dissolved in, or mixed with, a solution of an appropriate scintillator material, the decay energy from the sample is converted into light photons. These are sensed by a photomultiplier, which converts them into an electric pulse, whose intensity is proportional to the energy of the initial radiation. Thus simultaneous counting of several radionuclides differing in the energy of emitted radiation can be effected with suitable discriminators (pulse height analysers), providing the energy separation is sufficient. Detection efficiencies approaching 95 per cent. for $^{14}$C and 60 per cent. for $^3$H are reached because self-absorption is minimized.

The scintillator solute usually consists of a polycyclic aromatic compound, such as $p$-terphenyl or 2,5-diphenyloxazole (primary solute), together with a secondary solute, such as 1,4-di[2-(4-methyl-5-phenyloxazole)]benzene (dimethyl POPOP), that shifts the wavelength of the light emitted to match the highest sensitivity of the photomultiplier tube. Water-immiscible solvents, such as toluene, or water-miscible solvents, such as dioxan, can be used. To facilitate the counting of aqueous solutions, special solvents have been developed. Alternatively, samples may be counted as suspensions in scintillator gels. As a means of attaining compatibility and miscibility with aqueous specimens to be assayed, many additives, such as surfactants and solubilizing agents, are also incorporated into the scintillator. For accurate determination of sample radioactivity, care must be exercised to prepare a sample that is truly homogeneous. The presence of impurities and colour in solution causes a decrease in photon output of the scintillator; such a decrease is known as quenching. Accurate radioactivity measurement requires correcting for count-rate loss due to quenching. Solutions containing organic scintillators are prone to photo-excitation and samples may need to be prepared in subdued light and kept in darkness before counting.

**RADIATION SHIELDING**

Adequate shielding must be used to protect laboratory personnel from ionizing radiation, and measuring instruments must be suitably shielded from background radiation.

Alpha and beta radiations are readily shielded because of their limited range of penetration, although the production of Bremsstrahlung by the latter must be taken into account (see below). The range of alpha and beta particles varies inherently with their kinetic energy. The alpha particles are mono-energetic and have a range of a few centimetres in air. The absorption of beta particles, owing to their continuous energy spectrum and
scattering, follows an approximately exponential function. The range of beta particles in air varies from centimetres to metres.

The secondary radiation produced by beta radiation upon absorption by shielding materials is known as Bremsstrahlung and resembles soft X-rays in its property of penetration. The higher the atomic number or density of the absorbing material, the greater the intensity of the Bremsstrahlung produced. Elements of low atomic number produce low-energy Bremsstrahlung, which is readily absorbed; therefore, materials of low atomic number or of low density, such as aluminium, glass, or transparent plastic, are used to shield sources of beta radiation.

Gamma-ray radiation is deeply penetrating. Attenuation of gamma-ray radiation in matter is exponential and is given in terms of half-value layers. The half-value layer is the thickness of shielding material necessary to decrease the intensity of radiation to half its initial value. A shield of 7 half-value layers is of a thickness that will reduce the intensity of radiation to less than 1 per cent. of its unshielded intensity of activity. Gamma-ray radiation is commonly shielded with lead.

Intensity of gamma-ray radiation is diminished according to the inverse square of the intervening distance between the source and the point of reference. Radioactive materials of millimillierie strength can be handled safely in the laboratory by using proper shielding and/or by arranging for the maximum practicable distance between the source and the operator by means of remote-handling devices.

DETERMINATION OF RADIONUCLIDIC PURITY

For gamma emitters the most useful method of examination for radionuclidic purity is that of gamma scintillation spectrometry. It is not, however, a completely certain method, because:

(a) beta-emitting impurities are, in general, not detected;
(b) when sodium iodide detectors are employed, the photoelectric peaks due to impurities may be obscured by those due to the major radionuclide, or, in other words, the degree of resolution of the instrument is insufficient;
(c) unless the instrument has been calibrated with a standard source of known radionuclidic purity under identical conditions of geometry, it is difficult to determine whether additional peaks are due to impurities or whether they result from such secondary effects as backscatter, coincidence summation, or fluorescent X-rays.
The range of gamma scintillation spectrometry may be extended in two ways: first, by observing changes in the spectrum of a preparation with time (this is especially useful in detecting the presence of long-lived impurities in a preparation of a short-lived radionuclide); secondly, by the use of chemical separations, whereby the major radionuclide may be removed by chemical means and the residue examined for impurities, or whereby specific impurities may be separated chemically and then quantified. It is evident that chemical means will not separate an impurity that is isotopic with the major radionuclide.

**Requirements for Radionuclidic Purity**

Requirements for radionuclidic purity are specified in two ways:

(a) By expression of a minimum level of radionuclidic purity. Unless otherwise stated in the individual monograph, the radionuclidic purity, as determined by simple gamma spectrometry employing a sodium iodide detector, shall not fall below 99 per cent. before the expiry date is reached. When a limit is specified in the monograph for a specific radionuclidic impurity (see below), that impurity shall be excluded from the calculation of the minimum level of radionuclidic purity referred to above.

(b) By expression of maximum levels of specific radionuclidic impurities in the individual monographs. In general, such impurities are those that are known to be likely to arise during the production of the material—for example, mercury-203 in a preparation of mercury-197.

It is evident that while the above requirements are necessary, they are not in themselves sufficient to ensure that the radionuclidic purity of a preparation is sufficient for human use. A duty must remain with the manufacturer to examine his products in detail, and especially to examine preparations of short-lived radionuclides for long-lived impurities after a suitable period of decay. In this way the manufacturer may satisfy himself that the manufacturing processes employed are producing materials of appropriate purity. In particular, the radionuclidic composition of certain preparations is determined by the chemical and isotopic composition of the target material, which is irradiated with neutrons, and trial preparations are advisable when new batches of target material are employed.

**DETERMINATION OF RADIOCHEMICAL PURITY**

Radiochemical purity can be studied by a variety of techniques, but paper chromatography, thin-layer chromatography, and electrophoresis
are of particular importance. After completion of the separation, the
distribution of radioactivity on the chromatogram is determined. The
weight of substance applied to the chromatogram is often extremely small
(because of the great sensitivity of detection of the radioactivity) and partic-
ular care has to be taken in interpretation with regard to the formation
of artefacts. As mentioned above, the addition of carriers (i.e., the corre-
sponding non-radioactive compounds) is sometimes helpful. There is,
however, a danger that when an inactive carrier of the radioactive pharma-
ceutical is added it may interact with the radiochemical impurity, leading
to underestimation of these impurities.

DETERMINATION OF CHEMICAL PURITY

Chemical purity refers to the proportion of the preparation that is in
the specified chemical form regardless of the presence of radioactivity; it
may be determined by normal methods of analysis.

The chemical purity of a preparation is often no guide to its radio-
chemical purity. Preparations, especially those resulting from exchange
reactions (in which, for example, some of the iodine atoms in o-iodohippuric
acid are replaced by atoms of iodine-131), may be of high chemical purity
but may contain large amounts of impurities of high specific activity (that
is, a tiny weight of the impurity may be associated with a large amount of
the radionuclide).

In general, chemical impurities in preparations of radiopharmaceuticals
are objectionable only if they are toxic or if they modify the physiological
processes that are under study.

TESTS FOR STERILITY AND PYROGENS

The half-life of some radiopharmaceutical products is so short that
they must be released by the manufacturer before tests for sterility and
pyrogens can be completed.

Sterility tests

In such instances the manufacturer should begin the sterility test as soon
as possible and read the results after release.

A particular responsibility falls upon the manufacturer of such products
to validate the sterilization process by all suitable measures, which may
include careful and frequent calibration of sterilizers and the use of biological
and chemical indicators of the efficiency of the sterilization process.
Pyrogen tests

The manufacturer also bears a particular responsibility to ensure that all substances used in the preparation of such products are handled in a manner that ensures their freedom from pyrogens. Pyrogen tests are specified in certain monographs where there are special dangers.

ADDITION OF BACTERIOSTATIC AGENTS

Injections of radioactive pharmaceuticals are commonly supplied in containers that are sealed to permit the withdrawal of successive doses on different occasions. The International Pharmacopoeia normally requires that such injections should contain a suitable bacteriostatic agent in a suitable concentration.

Many common bacteriostatic agents—for example, benzyl alcohol—are gradually destroyed by the effect of radiation in aqueous solutions. The rate of destruction is dependent upon a number of factors, including the nature of the radionuclide and the radioactive concentration of the solution. It is therefore not always possible to prescribe an effective bacteriostatic agent for an injection of a radiopharmaceutical and for certain preparations the addition of an agent is undesirable; for this reason the inclusion of bacteriostatic agents is not mandatory. The nature of the bacteriostatic agent, if present, must be stated on the label; if no bacteriostatic agent is present, this must also be stated.

OTHER REQUIREMENTS

Radiopharmaceuticals administered parenterally comply with the requirements stated under "Injections", except that they are not subject to the requirements concerning the "Volume of Injection in a single-dose container".

EXPIRY DATE

The special nature of a radiopharmaceutical requires that it be assigned an expiry date, beyond which its continued use is not recommended. The expiry period so designated begins with the date at which the radioactivity is expressed on the label, and may be stated in terms of days, weeks or months. Alternatively, the expiry date itself may be stated. For radionuclides with a half-life of sixty days or less, the expiry period is at most three half-lives. For longer-lived radionuclides, the expiry period does not
exceed six months. The expiry period depends on the chemical and radiochemical stability of the preparation under consideration. At the end of the expiry period, the radioactivity will have decreased to the extent where insufficient radioactivity remains to serve the intended purpose or where the dose of active ingredient must be increased so much that undesirable physiological responses occur. In addition, chemical or radiation decomposition may have reduced the radiochemical purity to an unacceptable extent. The use of products beyond their expiry periods is therefore inadvisable.

LABELLING

The following information must appear on the immediate container (e.g., vial):

(1) The name of the preparation.
(2) A statement that the product is radioactive.
(3) The name and location of the manufacturer.
(4) The total radioactivity present at a stated date and hour. Whenever the half-life is more than 30 days only the date should be stated.
(5) The expiry date or the expiry period.
(6) A number or other indication by which the history of the product may be traced—for example, batch or lot number.
(7) In the case of solutions, the total volume of the solution.

Note. — In the case of a solution, instead of a statement of the total radioactivity, a statement of the radioactive concentration (e.g., in mCi per ml of the solution) may be given.

The shipment of radioactive substances is subject to special national and international regulations as regards their packaging and outer labelling.

STORAGE

Radiopharmaceuticals should be kept in well-closed containers and stored in an area assigned for the purpose. The storage conditions should be such that the maximum radiation dose rate to which persons may be exposed is reduced to an acceptable level. Care should be taken to comply with national regulations for protection against ionizing radiation. Glass containers may darken under the effect of radiation.
### Appendix 13a

**TABLE OF PHYSICAL CHARACTERISTICS OF RADIONUCLIDES**

**1974 Revision**

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half life</th>
<th>Type of decay</th>
<th>Transition probabilities</th>
<th>Electromagnetic transitions</th>
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<td></td>
<td>Photon energy (MeV)</td>
<td>Photon energy (MeV)</td>
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<td></td>
<td>Probability (%)</td>
<td>Probability (%)</td>
</tr>
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<td>Caesium-137</td>
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<td>β−</td>
<td>0.512 1.114</td>
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<tr>
<td>Chromium-51</td>
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<td>Cobalt-57</td>
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<td>e.c.</td>
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<tr>
<td>Cobalt-58</td>
<td>70.8d</td>
<td>β± e.c.</td>
<td>0.475 0.054</td>
<td>99.0% 0.5%</td>
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<tr>
<td>Cobalt-60</td>
<td>5.27y</td>
<td>β−</td>
<td>0.318 1.491</td>
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<td>Element</td>
<td>Half-Life (d)</td>
<td>Decay Mode</td>
<td>Percentage</td>
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<td>Gold-198</td>
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<tr>
<td>Gold-199</td>
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<td>β−</td>
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<tr>
<td>Indium-115m</td>
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<td>γ−, β−</td>
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<tr>
<td>Iodine-125</td>
<td>60.0d</td>
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<td>93%</td>
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<td>Osmium-126</td>
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<td>β−</td>
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<td>Osmium-131</td>
<td>8.06d</td>
<td>β−</td>
<td>3.8%</td>
<td>3.8%</td>
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<tr>
<td>(Krypton-131m)</td>
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* e.c. = electron capture; i.t. = isomeric transition
<table>
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<th>nuclide</th>
<th>half life</th>
<th>type of decay</th>
<th>particle energies and transition probabilities</th>
<th>electromagnetic transitions</th>
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<td>energy (MeV)</td>
<td>transition probability</td>
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<tr>
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<td>1.986</td>
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<tr>
<td>Decay Product</td>
<td>Half-Life (h)</td>
<td>Mode</td>
<td>Emission</td>
<td>Percentage</td>
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<td>---------------</td>
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<td>Mercury-197</td>
<td>84.4h</td>
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<td>0.177</td>
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<td>a.c.</td>
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<td>f.t.</td>
<td>93.5%</td>
<td>0.363</td>
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<td>Phosphorus-32</td>
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* e.c. — electron capture; f.t. — isomeric transition
## Appendix 13a (continued)

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<th>nuclide</th>
<th>half life</th>
<th>type of decay</th>
<th>particle energies and transition probabilities</th>
<th>electromagnetic transitions</th>
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<td></td>
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<td>energy (MeV)</td>
<td>transition probability</td>
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<td>Selenium-75</td>
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<tr>
<td>Technetium-99m</td>
<td>6.02h</td>
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<td>Tm-113</td>
<td>115d</td>
<td>e.c.</td>
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<tr>
<td>Tl-203</td>
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<tr>
<td>Tritium (H)</td>
<td>12.35y</td>
<td>β-</td>
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<td>Zn-65</td>
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<td>β-</td>
<td>0.0119</td>
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<td>Ba-133</td>
<td>2.66y</td>
<td>β-</td>
<td>0.0083</td>
<td>100%</td>
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<td>Isotope</td>
<td>Decay</td>
<td>Half-Life</td>
<td>Emission</td>
<td>Energy</td>
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<tr>
<td>------------</td>
<td>---------</td>
<td>-----------</td>
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</tr>
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<td>Xenon-131m</td>
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<td>I.T.</td>
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<td>Xenon-133</td>
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<td>Xenon-133m</td>
<td>2.26 d</td>
<td>I.T.</td>
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<td>0.253</td>
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</table>

Daughter: ^131Xe

* e.c. = electron capture; I.T. = isomeric transition
# LIST OF REAGENTS MENTIONED IN THE MONOGRAPHS ON RADIOPHARMACEUTICALS

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Reference *</th>
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<tbody>
<tr>
<td>Acetate buffer solution</td>
<td>EC 24, p. 69</td>
</tr>
<tr>
<td>Acetic acid R</td>
<td>Int. Ph. II, p. 611</td>
</tr>
<tr>
<td>Acetic acid, dilute, R</td>
<td>Int. Ph. II, p. 611</td>
</tr>
<tr>
<td>Acetic acid, glacial, R</td>
<td>SRIP, 1963, p. 25</td>
</tr>
<tr>
<td>Acetone R</td>
<td>SRIP, 1963, p. 27</td>
</tr>
<tr>
<td>Ammonia, dilute, TS</td>
<td>Int. Ph. II, p. 614</td>
</tr>
<tr>
<td>Ammonia, strong, R</td>
<td>SRIP, 1963, p. 31</td>
</tr>
<tr>
<td>Ammonium molybdate R</td>
<td>SRIP, 1963, p. 34</td>
</tr>
<tr>
<td>Ammonium vanadate R</td>
<td>SRIP, 1963, p. 41</td>
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<td>Amyl alcohol R</td>
<td>SRIP, 1963, p. 42</td>
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<tr>
<td>Barbital sodium R</td>
<td>Int. Ph. II, p. 60</td>
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<td>Boric acid R</td>
<td>Int. Ph. II, p. 12</td>
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<tr>
<td>n-Butanol R</td>
<td>SRIP, 1963, p. 54</td>
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<td>Butanol, tertiary, R</td>
<td>Int. Ph. II, p. 619</td>
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<tr>
<td>sec-Butanol R</td>
<td>Suppl. 1971, p. 53</td>
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<td>Carbon tetrachloride R</td>
<td>SRIP, 1963, p. 63</td>
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<tr>
<td>Chloromerdrin R</td>
<td>Int. Chem. Ref. Subst.</td>
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<td>Chloroform R</td>
<td>SRIP, 1963, p. 66</td>
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<td>Copper sulfate R</td>
<td>SRIP, 1963, p. 72</td>
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<td>Cresol R</td>
<td>Int. Ph. II, p. 144</td>
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<td>Dioxan R</td>
<td>SRIP, 1963, p. 80</td>
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<td>Disodium edetate TS</td>
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<td>Dithizone</td>
<td>SRIP, 1963, p. 83</td>
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<td>Eriochromcyanine TS</td>
<td>EC 24, p. 70</td>
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<td>Ethanol (95 per cent.) R</td>
<td>SRIP, 1963, p. 84</td>
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<td>Ether R</td>
<td>SRIP, 1963, p. 85</td>
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<tr>
<td>Formic acid R</td>
<td>SRIP, 1963, p. 92</td>
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* The abbreviations used here have the meanings indicated below:


SRIP, 1963: Specifications for Reagents mentioned in the International Pharmacopoeia, 1963


Reagent

Hydrochloric acid, saturated, R
Hydrochloric acid, 2N
Hydrochloric acid, 0.5N
Hydrochloric acid, 0.1N
Hydrochloric acid, 0.015N
o-Iodohippuric acid R
Mercerio chloride R
Methanol R
Methyl orange TS
Methyl red R
Methylthioninium chloride R
Naphthalene black 12B R
Nitric acid R
Perchloric acid (70 per cent. w/w) R
Phosphoric acid R
Potassium chromate R
Potassium iodate R
Potassium iodide R
Rose Bengal Sodium R
Selenium R
Sodium acetate R
Sodium bicarbonate R
Sodium chloride R
Sodium Chloride Injection
Sodium hydroxide R
Sodium molybdate R
Sodium octanoate R
Sodium phosphate, anhydrous, R
Sodium sulfate, anhydrous, R
Sodium thioglycolate TS
Stannous chloride R
Sulfuric acid, nitrogen-free, R

Reference

SRIP, 1963, p. 96
Int. Ph. II, p. 660
Int. Ph. II, p. 660
Int. Ph. II, p. 660
Suppl. 1971, p. 55

Int. Chem. Ref. Subst.
SRIP, 1963, p. 113
SRIP, 1963, p. 117
Int. Ph. II, p. 637
SRIP, 1963, p. 118
Int. Ph. II, p. 344
Suppl. 1971, p. 54
SRIP, 1963, p. 123
SRIP, 1963, p. 137
SRIP, 1963, p. 141
SRIP, 1963, p. 152
SRIP, 1963, p. 160
SRIP, 1963, p. 161

Int. Chem. Ref. Subst.
Suppl. 1971, p. 54
SRIP, 1963, p. 176
SRIP, 1963, p. 177
SRIP, 1963, p. 181
Int. Ph. II, p. 361
SRIP, 1963, p. 185
Int. Ph. II, p. 649
Suppl. 1971, p. 55
SRIP, 1963, p. 193
SRIP, 1963, p. 193
EC 24, p. 71
SRIP, 1963, p. 198
Int. Ph. II, p. 652
Annex 3

GENERAL GUIDELINES FOR THE ESTABLISHMENT, MAINTENANCE, AND DISTRIBUTION OF CHEMICAL REFERENCE SUBSTANCES

1. Criteria for determining the need for the establishment of chemical reference substances

The production, validation, maintenance, and distribution of chemical reference substances is a costly and time-consuming undertaking. It is therefore of great importance to limit the work involved by determining in a critical way whether a need for a given substance exists. Requests for new reference substances usually arise because a certain approach to the development of a specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a reference substance for use as a comparative standard and the first matter that should be assessed, therefore, is whether some alternative procedure could be adopted that does not require a comparative standard and that might still be equally satisfactory. For example, an analytical procedure based on a stoichiometric relationship might be as valid, in a given context, as one based on ultraviolet absorption spectrophotometry and would obviate a possible need for a reference substance.

The types of analytical procedure at present used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

(a) infrared spectroscopy, whether for identification or quantitative purposes;
(b) quantitative methods based on ultraviolet absorption spectroscopy;
(c) quantitative methods based on the development of a colour and measurement of its intensity, whether by instrumental or visual comparison;
(d) methods based on chromatographic separation for identification or quantitative purposes;
(e) quantitative methods (including automated methods) based on other separative techniques that depend upon partition of the material.

The term chemical reference substance when used in this document refers to an authenticated uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with the properties of a product under examination, and that possesses a degree of purity adequate for its intended use.
to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that vary from time to time and from laboratory to laboratory;

(f) quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;

(g) assay methods based on measurement of optical rotation.

There is a consensus among experts that for certain of the above categories a reference substance is essential. For example, the use of thin-layer chromatography as a means of identification dictates the need for a reference material, because the migration of a substance relative to the solvent front is dependent on the operating conditions; certain of the conditions, such as temperature and composition of mobile phase, are readily controllable; others, such as the precise thickness and the water content of the layer used and the degree of saturation of the tank cannot be exactly reproduced. Other examples are non-stoichiometric procedures, such as the iodimetric titration of penicillins and the determination of ascorbic acid by titration with an indophenol.

In other cases, however, differences of opinion exist as to whether a reference substance is essential. It has been proposed, for example, that a reference sample might not be essential for infrared spectroscopy; instead it might be possible to define certain characteristics of a spectrum or to provide a copy of an "authentic spectrum" that could be used for purposes of comparison. Differences in the mode of presentation of spectra by diverse instruments, differences in resolution between instruments, and problems associated with polymorphism and solvation make such an approach difficult in some instances at the present time. Nevertheless, this approach, implemented where feasible, would significantly reduce the number of reference substances needed and also reduce the extent of use of these substances required for other purposes.

The need for reference substances in ultraviolet absorption spectrophotometry has probably given rise to the greatest controversy. Certain compendia (for example, the International Pharmacopoeia, the Nordic Pharmacopoeia, the United States Pharmacopeia, and the National Formulary of the USA) require comparison of observed spectral characteristics of the substance under examination with those of a reference substance similarly treated, whilst others (for example the British Pharmacopoeia and the European Pharmacopoeia) rely on comparison with quoted extinction values. Both of these methods have advantages, but neither is above criticism. A mere comparison of spectra obtained by an operator using poor technique and inadequately maintained equipment might lead to acceptance of a sample but might not constitute a valid assay. Conversely, the use of
inadequately controlled conditions and a quoted extinction value might lead to rejection of a satisfactory sample. It must also be accepted that, despite considerable improvements in the stability, accuracy, and precision of ultraviolet spectrophotometers during the past decade, variations between instruments still occur and may undermine the validity of using quoted extinction values.

These considerations, which also apply in some measure to other instrumental techniques such as infrared spectroscopy, make it essential that adequate criteria for instrumental performance should be defined. This, in turn, suggests that a further class of reference materials designed to assist in the calibration of instruments and the standardization of procedures may also be necessary. For example, it might be necessary to prescribe the use of standardized didymium or holmium oxide filters for wavelength calibration and standardized potassium dichromate or potassium nitrate for absorbance calibration of ultraviolet spectrophotometers.

2. Chemical and physical methods used in evaluating reference substances

In determining whether a material proposed for use as a reference substance is suitable, it is necessary to consider all the data obtained by examining it in several independent laboratories, employing a wide variety of analytical methods. The complementary data so obtained, when taken as a whole, give confidence that the material is suitable for its intended purpose.

Such sets of data are called “purity profiles”. The methods used to establish these profiles fall into two broad groups, those intended primarily to identify the material and those to establish the purity.

With most methods, the percentage purity of a reference substance cannot be expressed as an absolute value if the impurities have not been identified. In such instances, the quoted purity is an estimate based upon the data obtained by use of the various analytical methods employed to establish the purity of the reference substance.

2.1 Methods useful for verifying the identity of reference substances

The identity of a material that is intended to replace an established reference substance of the same molecular constitution may be verified by means of tests that are capable of demonstrating that the characteristic properties of the two specimens are identical. For this purpose, a comparison of their infrared absorption spectra often suffices. Similarly, where a newly proposed reference substance consists of a compound whose structure has been satisfactorily elucidated, its identity may be confirmed by matching the infrared spectra of the material and of an authentic compound. Other
highly specific techniques, such as nuclear magnetic resonance spectroscopy, mass spectrometry, or X-ray diffraction crystallography, may also be used for such comparisons.

However, where no authentic specimen of the proposed reference substance is available for comparison and definitive data about its properties are lacking, it may be necessary to verify the identity of the material by applying several analytical techniques currently used to characterize new compounds. Such analytical methods may include elemental analyses, crystallographic studies, mass spectrometry, nuclear magnetic resonance spectroscopy, functional group analyses, infrared spectrophotometry, and ultraviolet spectrophotometry, as well as such other supplementary tests as are necessary and sufficient to establish that the proposed reference material is the required substance.

2.2 Purity requirements for reference substances

The purity requirements for a reference substance depend on its intended use. A reference substance proposed for an identification test by infrared spectrophotometry does not require meticulous purification, because the presence of a few per cent. of impurities in the substance often has no noticeable influence on its infrared spectrum. Similarly, reference substances that are applied in low loadings in thin-layer chromatographic tests, need not be highly purified.

On the other hand, reference substances that are to be used in assays should preferably possess a high degree of purity. As a guiding principle, a purity of 99.5 per cent. or better is desirable for such reference substances, although in cases where the precision of the analytical procedure for which the reference substance is required is low, such a degree of purity may not be necessary. In making a decision about the suitability of a reference substance, the most important consideration is the influence of the impurity on the attribute measured in the assay. Impurities with physicochemical characteristics similar to those of the main component will not impair the usefulness of a reference substance, whereas even traces of impurities with significantly different properties may render a substance unsuitable as a reference substance.

2.3 Methods used in determining the purity of chemical reference substances

A consideration of the methods to be employed in examining a chemical reference substance should take account of its method of preparation and its intended purpose. Such analytical methods can be divided into two broad categories — those that require comparison with an external standard, e.g., chromatographic or spectrophotometric methods, and those that depend upon an intrinsic thermodynamic property of the system, e.g.,
phase solubility analysis and differential scanning calorimetry. Methods in the latter group measure the concentration of impurities in the reference substance, but they provide little information regarding the molecular structure of these contaminants.

2.3.1 Phase solubility analysis

Phase solubility analysis may be employed to detect contaminating substances, including isomeric species, and to estimate their concentration. The coefficient of variation that can be achieved using this method is about 0.2 per cent. It is applicable to most reference substances and uses relatively simple apparatus. In some instances, phase solubility techniques may permit recovery of highly purified crystals of the main component as well as a concentrated solution of the contaminating substances from which they may be isolated for identification by other methods. These fractions provide significant data bearing upon the acceptability of the reference substance. Phase solubility analysis is time-consuming and its execution demands painstaking attention to detail. It is therefore often regarded as unsuitable for routine use in control laboratories, but it has proved of great value in laboratories engaged in the assessment of reference substances. Some factors that may make the method inapplicable are degradation of the substance during the course of analysis, formation of a solid solution, and polymorphism in the main component. In the rare instance where the ratio of the impurity to the main component is the same as the ratio of their respective solubilities in the solvent system employed, the results may lead to erroneous interpretation.

2.3.2 Differential scanning calorimetry

Purity estimation by differential scanning calorimetry is based on the determination of the heat of fusion of the sample and the determination of the change in its melting point caused by the impurities present in it. This analytical method can be performed rapidly and is capable of high precision. It is, however, inapplicable if the substance melts with decom- position and this limits its value as a general procedure for purity estimation of reference substances. Like phase solubility analysis it is also inapplicable where solid solutions are formed.

2.3.3 Spectrophotometric methods

Ultraviolet spectrophotometry is a widely used method for determination of purity. Since it depends upon the presence of a characteristic chromo-

phore, it is capable of detecting impurities that contribute excessively to the
absorbance value and may indicate the presence of impurities that have negligible absorbance. However, the utility of the method is limited by the small number of absorption maxima in the ultraviolet range, the large numbers of compounds containing similar characteristic chromophores, and the need for reliance on an external reference standard.

As previously noted, infrared spectrophotometry is of less value for detecting impurities. However, it is sometimes useful, for example in determining the proportion of the geometric isomers. Nuclear magnetic resonance spectroscopy is also useful occasionally for the determination of purity.

2.3.4 Chromatographic methods

Methods of analysis based on chromatographic separation are especially useful for detecting and determining impurities in reference substances. Thin-layer chromatography and gas-liquid chromatography are often used, and high pressure liquid chromatography is finding increasing application.

The individual components separated by chromatographic methods may sometimes be recovered for characterization.

Thin-layer chromatography employs apparatus that is simple and cheap, it is easy to carry out and is readily applicable even in the microgram range. It is frequently capable of separating closely related compounds, such as geometric isomers and the members of a homologous series. All the constituents of the chromatographed reference substance occur somewhere on the chromatogram. However, some constituents may remain on the starting line of the chromatogram, they may move with the solvent front, they may migrate at the same rate as the main component, or they may remain undetected. The usefulness of the method may be greatly enhanced by means of two-dimensional chromatography, and by employing a number of different solvent systems and a variety of methods of detection. It is probably the most widely used method for assessing chemical reference substances. The method is, however, rarely applicable on a quantitative basis but has great value in tests devised to limit the concentration of the amounts of impurities. Variations that may be encountered in material used as stationary phases, particularly when they are obtained from different suppliers, may sometimes cause marked differences in the migration of substances in the thin-layer chromatogram.

The resolving power of gas-liquid chromatography and probably also of high pressure liquid chromatography exceeds that of thin-layer chromatography. Both the first two methods also have the advantage of being readily applicable on a quantitative basis, but require more complex equipment. The great variety and sensitivity of detection-systems used in
gas-liquid chromatography give this method an advantage over high pressure liquid chromatography at the present time, although degradation during chromatography is less likely to occur with the latter method. Especially for examination of reference substances destined for use in connexion with ultraviolet absorption method assays, the use of high pressure liquid chromatography employing a spectrophotometric method of detection is of great value. Gas-liquid chromatography methods have particular value in detecting and determining volatile impurities, including solvent residues in reference substances.

2.3.5 Optical rotation methods

Many reference substances are optically active and the relative proportion of optical isomers is usually determined by an optical rotation method. The quantitative use of this technique is well established and can yield results of high precision, depending on the solvent and the wavelength chosen for measurement.

2.3.6 Other methods

Other methods, such as gravimetric analysis, titrimetry, electrophoresis, atomic absorption spectroscopy, polarography, and combustion procedures, may be valuable in the determination of purity. Several of the foregoing methods, as well as other techniques, may be used to determine functional groups or elements. The concentration of impurity in the reference substance may then be calculated, using an assumed atomic or molecular weight for the impurity.

Conclusions regarding the purity profile of a reference substance and its suitability for its intended use must be based upon the data derived from many or all of the foregoing methods, and must be confirmed by compatible results obtained in independent collaborating laboratories.

3. Handling and distribution of reference substances

The measures employed in handling, distributing, and using established chemical reference substances must provide for assurance that their integrity will be safeguarded and maintained throughout their period of use.

3.1 Packing and storage

Containers for reference substances should afford protection from moisture, light, and oxygen. From the point of view of the stability of the substances, sealed glass ampoules are the best containers, but they suffer from certain disadvantages, notably the risk of contaminating the
substance with glass particles when the ampoules are opened and the
difficulty of re-closure. Sealed ampoules are therefore principally used
for materials that must be kept in an oxygen-free atmosphere. Certain
materials may require even more elaborate protection. Most chemical
reference substances, however, are conveniently supplied in re-closable
containers, which should be uniform in type and size to facilitate distribu-
tion. In determining the suitability of containers for reference substances
it is emphasized that their permeability to moisture is an important factor.

The packing of a batch of a reference substance into containers is a
small-scale operation for which suitable equipment is not always available
to the manufacturer of the substance. Therefore the packing of reference
substances is usually undertaken by the authorities responsible for them.

Vibration spatulas and similar devices are available for dispensing
substances on a small scale, but these should be used with caution because
of the risk of segregation of particles of different size during the filling
operation, which may lead to inhomogeneity. Screw-type feeders have
also been constructed, but as yet are not commercially available, and so
far the packing of reference substances has been done manually.

Several pharmaceutical reference substances have to be packed under
nitrogen or in conditions of controlled humidity. The use of a glove-box
is of great value in this connexion.

The various stages in packing reference substances should be controlled
to avoid contamination of the sample, mis-labelling of containers, and
other factors that might result in an unsatisfactory reference substance.

Information about suitable storage conditions for reference substances
can often be obtained from the manufacturer and should be requested
routinely when a new reference substance is established. Theoretically
the stability of the substances should be enhanced by keeping them at
low temperatures, but, for substances that contain water, storage below
0°C may impair the stability. It should also be remembered that the
relative humidity in normal refrigerators or cold rooms may be high,
and, unless ampoules or other tightly closed containers are used, the
intended improvement in stability by storage in such places may be more
than offset by degradation processes due to absorption of moisture. Storage
at about ±5°C with precautions to prevent such absorption has proved
satisfactory for most chemical reference substances.

3.2 Stability and periodic re-evaluation

It should be recognized that a reference substance is an integral part
of the drug specification. Thus, if the reference substance deteriorates,
this also implies a change in the specification of the drug. It is therefore
of the utmost importance that the stability of reference substances be monitored by regular re-examination and that replacement be made as soon as a significant change in a property is noted.

The definition of what is a "significant change" differs, however, with the intended use of the reference substance. Degradation products in a substance amounting to several per cent. may not impair the usefulness of the material in an infrared identification test. For reference substances that are used in chromatographic tests or in assays, however, even small amounts of impurities may be quite unacceptable. In setting standards for reference substances, consideration must be given to the intended use of the substance and to the performance characteristics of the analytical method for which it is to be used. It must be recognized, however, that the tolerable degree of degradation will be different from case to case.

Laboratories in charge of reference standards collections should have a system for regular re-examination of the materials in stock. When sufficient experience has been gained, the frequency of re-testing may be modified. In this context, however, it is appropriate to bear in mind that the stability of a specially prepared reference substance may not always parallel that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of reference substances depends on the nature of the substance. Thin-layer chromatography is used extensively and often simple tests, such as determination of water or pH, are useful for recognizing the onset of degradation.

When quantitative estimation of the degree of degradation is needed, more complicated techniques, such as phase solubility analysis, differential scanning calorimetry, or chromatography coupled with quantitative determination of the separated components, must be used.

Changing moisture content of reference substances is a phenomenon that is difficult to control. To establish suitable conditions for packing operations and storage that might minimize such changes, it is recommended that for each substance data be obtained relating to moisture content and relative humidity.

3.3 Information to be supplied with reference substances

Some centres for reference materials supply extensive documentation with reference substances, and include directions for use. Other centres supply no information except the name of the substance and of the issuing authority. Such differing practices may result in improper use of the reference substances. It is desirable that recommendation be made concerning the information to be supplied with reference substances and its manner of expression.
It is suggested that labels on chemical reference substances should give the following information:

(a) name of the substance;
(b) type of reference substance (e.g., International Chemical Reference Substance, B.P. Authentic Specimen, etc.);
(c) name and address of issuing authority;
(d) approximate quantity of material in the container;
(e) batch or control number.

The following information should be given as necessary either on the labels or in associated documents:

(i) recommended storage conditions (information about hygroscopicity, etc.);
(ii) expiry date if necessary;
(iii) directions for use (e.g., instructions about drying the material before use and any necessary cautionary statements);
(iv) information about the composition of the reference substance needed for calculation of results of tests for which the substance is intended to be used;
(v) a disclaimer of responsibility when reference substances are used for other purposes than those intended by the issuing authority.

It is advisable to restrict the supplying of analytical data about reference substances to the minimum consistent with proper use of the material.

The question of whether expiry dates should be assigned to reference substances is of great importance both to the users and to the distributors of the substances. The arguments against expiry dating are that it might lead to the unnecessary discarding of satisfactory materials and that considerable experimental work would have to be carried out to make the setting of meaningful expiry dates possible.

At present most reference substances are replaced by new batches only when this has been shown to be necessary by re-evaluation. This procedure minimizes unnecessary waste of valuable materials, but in order to make it completely satisfactory it would be necessary to devise a recall system or other effective means of informing analysts in possession of reference substances about any replacement of batches.

3.4 Distribution problems

Distribution of reference substances within a country usually presents no problems. However, when samples are to be sent to other countries
both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations. At present distributors of reference substances are wasting a considerable portion of their resources in seeking information concerning the different import regulations in various countries and in filling in the required forms. Means should be sought to reduce such difficulties and barriers to the effective distribution of reference substances without compromising their integrity.

4. Means of promoting effective exchange of information and ensuring collaboration between organizations establishing reference substances

During the past few years, there has been an increasing exchange of information between laboratories that evaluate chemical reference substances. However, the collaboration has generally been on a personal and ad hoc basis.

It would be of value if such information could be exchanged on a more formal basis and if timely notification of work to be undertaken could be circulated. In every instance this should be done well before any approach is made to a pharmaceutical manufacturer for supply of material. If this were done, it would be possible for a manufacturer to set aside a portion of a particular batch, so that sufficient of the proposed reference material would be available for all expected needs. The advantages of this procedure would be: first, that the studies carried out might be shared by collaborating laboratories; secondly, that the same reference material would be used by each issuing authority; and thirdly, that if supplies of that material at one laboratory were depleted, appropriate arrangements might be made to share remaining material held by other laboratories. Finally, there would be considerable benefit to industry in that requests for supply or reference materials would be coordinated and would be reduced in frequency.

In such a cooperative effort, it might also be possible for the manufacturer to pack the reference substance into appropriate standardized containers so that the possibility of variation due to storage and transport would be minimized.

From time to time each laboratory will need to replace a certain number of reference substances. It would be advantageous for each laboratory to review its needs well in advance so as to permit a concerted request to be made to a manufacturer, thus achieving the benefits mentioned above.
PROVISIONAL REQUIREMENTS FOR PLASTIC CONTAINERS
FOR PHARMACEUTICALS

The following discussion and test procedures apply to plastic containers intended primarily for use with parenteral and ophthalmic pharmaceutical products. They also apply in general to plastic containers for solid, semi-solid, and other liquid forms. Plastic containers should conform to the definition in the second edition of the *International Pharmacopoeia*, page XXXIII.

Plastic containers for pharmaceutical use are produced from a wide range of solid materials that are largely organic, based upon synthetic resins (polyolefins, polyamides, polyesters, polystyrenes, halogenated vinyls and various copolymers), or upon modified polymers of natural origin (cellulose esters) that possess appreciable mechanical strength and that are capable of being cast, moulded, or polymerized into shape. These characteristics have led to the development of a large variety of rigid bottles, flexible forms for blood and infusions, as well as films and laminates for enclosing many different solid dosage forms.

The mechanical, physicochemical, and biological properties of formed plastic containers depend upon the chemical structure, molecular weight, and class of the polymer, and the type and concentration of additives. Some plastics may contain as impurities, the monomer, catalytic materials, and other residues of ingredients that are used in processing. The concentration of such impurities generally represents only a small fraction of the total polymer weight. Purposeful additives, in greater concentrations, and extractives are frequently highly reactive and thus represent substances potentially incompatible with various ingredients in the pharmaceutical dosage forms. Likewise, they may be undesirable or toxic materials capable of migration into the dosage form.

The selection of a plastic container, combination of plastics, or combination of plastic and other materials, for packaging pharmaceutical products, should be based upon adequate and appropriate testing to establish the processing characteristics and the protective qualities of the container, and the compatibility, safety, and stability of the product.

Since all parenteral and ophthalmic pharmaceutical products are required to be sterile, consideration must be given to the use of suitable methods for cleaning and sterilizing plastic containers for such products. Care needs to be exercised, for example, in selecting detergents or other substances used for washing, so that the surface properties of plastic

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containers are not altered. Similarly, the method of sterilization that is selected must not significantly alter the properties of the plastic container, leave undesirable residues, or form objectionable new impurities. In sufficient concentrations, such residues or impurities may be hazardous. Generally, moist heat, ethylene oxide, or penetrating radiation have been employed successfully for sterilizing empty plastic containers. Moist heat is frequently used for sterilizing blood and infusion bags, either empty or filled with intravenous infusion solution.

While the present tests and specifications apply to the materials at present most widely used for containers and packaging, each new polymeric material may introduce unforeseen problems, which will require new tests and specifications to make it safe and useful for pharmaceutical purposes.

When considering containers for large-volume infusion solutions, specific properties, such as flexibility, collapsibility, clarity, and temperature resistance, are important and should be controlled. The requirements specifically listed should be borne in mind when selecting a plastic material and container. In this respect, materials so far found to be suitable include polyvinyl chloride and polyethylene. Other materials, such as ethylene vinyl acetate, might also be suitable.

It is recommended that at the outset the composition of the plastic material should be known. This will assist in the elaboration of any additional biological and physicochemical tests that seem necessary. This applies particularly in the case of plasticized polyvinyl chloride (PVC), which is itself a complex formulation. The specific tests listed do not necessarily represent a total testing programme. Additional searching tests on concentrated aqueous extracts of the plastic material designed to reveal any undesirable pharmacological effect should be carried out in one or more animal species.

Plastic materials similar to those used for containers for large-volume intravenous infusion solutions have been employed for making containers for blood and blood substitutes. For these applications, a much more detailed testing scheme is required, which should take into account the need to preserve the properties and characteristics of blood and its substitutes, and should include a stringent search for possible adverse haematological effects.

Plastic containers for parenteral dosage forms should be, and should remain, sufficiently transparent so that the appearance and the clarity of the preparations can be examined at any time. The container should not impart an objectionable odour to the contents.

Plastics are also used as containers (or components of containers) for dosage forms other than parenteral and ophthalmic pharmaceutical pro-
ducts. These include preparations for direct application to the skin (ointments, creams, lotions, gels, sprays), nasal drops or sprays, enemas, suppositories, and inhalation aerosols. For these applications it must be ascertained that nothing will be extracted from the plastic by the preparation that will give rise to adverse effects during use, e.g., irritation or sensitization of the skin, irritation of mucous membranes (nasal, bronchial, intestinal, and rectal), or unacceptable taste and/or odour on inhalation. For example, materials known to produce skin sensitization (nickel, chromium), or surface anaesthesia should not be included unless evidence is available that they are not extractable into the product.

Ultimately, the acceptability of a plastic container for a particular dosage form can be assessed by carrying out animal toxicity irritation tests on the preparation stored in the container for an appropriate period of time. In some cases (such as enemas and dialysis solutions) it will be necessary to carry out clinical acceptability trials in patients with the preparations stored as above. These storage tests should also be designed to ascertain whether loss of active ingredient, preservative, or other essential components of the product, where they occur, are attributable to the plastic.

In view of the above, and in order to maintain consistent and uniform quality, it is desirable to agree on mutually acceptable specifications. Any change in composition or processing of the plastic containers or components should be reviewed in advance with the pharmaceutical manufacturer.

To ensure compliance with the agreed specification, routine control tests (biological and/or physicochemical) on incoming batches of containers or components are necessary.

It is proposed that the following tests be carried out on plastic containers intended for use with infusions, injections, and ophthalmics.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Source</th>
<th>Page</th>
</tr>
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<tbody>
<tr>
<td>In vitro biological Haemolytic effect</td>
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<td>65</td>
</tr>
<tr>
<td>In vivo biological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute systemic toxicity (mice)</td>
<td>USP</td>
<td>32</td>
</tr>
<tr>
<td>Intracutaneous activity (rabbit)</td>
<td>USP</td>
<td>32</td>
</tr>
<tr>
<td>Cat toxicity</td>
<td>BP (1973)</td>
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<tr>
<td>Physicochemical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-volatile residue</td>
<td>USP</td>
<td>33</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>USP</td>
<td>33</td>
</tr>
<tr>
<td>Ether-soluble extractive</td>
<td>BP (1973)</td>
<td>74</td>
</tr>
</tbody>
</table>
**INFUSIONS AND INJECTIONS (contd)**

<table>
<thead>
<tr>
<th>Physical chemical (contd)</th>
<th>Source</th>
<th>Page in PCP on which test reproduced</th>
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<tbody>
<tr>
<td>Heavy metals</td>
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</tr>
<tr>
<td>Barium ‡</td>
<td>BP (1973)</td>
<td>74</td>
</tr>
<tr>
<td>Tin ‡</td>
<td>BP (1973)</td>
<td>74</td>
</tr>
<tr>
<td>Buffering capacity</td>
<td>USP</td>
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</tr>
<tr>
<td>Reducing substances</td>
<td>PH</td>
<td>47</td>
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<tr>
<td>Turbidity of solution</td>
<td>NP</td>
<td>63</td>
</tr>
</tbody>
</table>

**OPHTHALMICS**

**In vivo biological**

- Acute systemic toxicity (mice) NF 43
- Eye irritation (rabbit) NF 44

**Chemical**

- Non-volatile residue NF 45
- Heavy metals NF 45

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* BP = British Pharmacopoeia; NF = National Formulary; NP = Nordic Pharmacopoeia; PH = Pharmacopoeia Helvetica; USP = United States Pharmacopoeia.


* Polyethylene glycol extracts are to be excluded.

* The application of the test is tentative.

* Infusions autoclaved in container only.

* Chlorine-containing polymers only.

* Chlorine-containing polymers and urethane only.
Annex 5

PHARMACEUTICAL ASPECTS OF DRUG EVALUATION
FOR REGISTRATION

1. Raw material

By the time that a substance has been synthesized and then recognized as
having a potentially useful pharmacological activity, it is expected that much
information on its structure should be available. Ideally, before clinical
trials are initiated the complete molecular structure and configuration
should have been determined. It is recognized, however, that this may
present difficulties with certain compounds or mixtures, e.g., some anti-
biotics or hormones. Nevertheless, adequate data to assure identity,
consistency, and homogeneity of the material should be available.

Where the material is a synthetically produced substance the complete
structural characterization of the material should be supplemented by
details of the nature and extent of impurities arising from the synthetic
procedures. The possibility that such impurities might possess toxic
or other undesirable properties should be investigated.

Subsequently, before registration of the product is sought, additional
information on the nature and extent of likely impurities should have
been gained during pilot-plant operations and during development of the
full-scale production procedure. Unequivocal purity criteria should be
available at this stage as well as one or more quantitative methods of assay
in order to permit the establishment of a specification for the substance.
Careful comparison should be made between the material used in the
early clinical studies and that subsequently obtained from the chosen
production process, so as to avoid inadvertent changes in chemical or
physical properties that might result from the changed scale of operations.

Characterization of active ingredients can be made using a selection
of such properties as melting point, solubility in various solvents, optical
rotation, infrared characteristics, infrared and ultraviolet absorption, nuclear
magnetic resonance, and X-ray diffraction. The techniques of thin-layer,
gas-liquid, and high-pressure liquid chromatography enable other factors,
notably the degree of contamination by other molecular species, including
solvents used for recrystallization, to be defined. This list is not exhaustive,
nor will all properties necessarily be required on every occasion: the com-

* It is not expected that every item of information referred to in this text will be
needed for the purposes of each registration procedure. Each case should be considered
on its own scientific merit to determine the extent of the data needed.

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bination that is necessary and sufficient to establish unequivocally the identity, physical characteristics (e.g., crystal form), and degree of purity of a chemical substance will suffice.

2. Dosage form

The drug substance will first be administered to animals in a provisional dosage form, but as these animal tests (designed to study the absorption, distribution, metabolism, and excretion of the drug) proceed, a promising dosage form for the human clinical studies will be developed. Specifications for the inactive ingredients to be used in this dosage form should be established, and, if a proposed excipient unexpectedly produces an undesirable change in the effectiveness of the dosage form, the scientific basis underlying the change should be investigated and documented.

The possibility that one or more of the ingredients to be incorporated with the active material might possess undesirable properties should be assessed at this time, particularly where these ingredients have not previously been widely used.

When the clinical studies have proceeded sufficiently to suggest that the dosage form is an acceptable one, a tentative finished product specification should be developed to provide a means of confirming that subsequent batches are consistent in nature and quality. As further experience in manufacture is gained, the tentative specification should be continuously reviewed and updated. The details of specifications and analytical methods should be as simple as possible, consistent with the precision, accuracy, and specificity that is thought to be required in the particular application.

When the final dosage form has been decided, a comparison should be made of the blood levels produced in humans by that form, and of those produced by a solution of the drug administered by the oral or intravenous route (the latter may not always be practicable). In the case of a poorly soluble substance, an oral suspension may be used instead. Urinary excretion data may also be obtained and will be particularly helpful when blood level data are inappropriate or unavailable. The administration of the drug in solution in this way provides baseline data that are independent of the characteristics of the dosage form.

3. Stability studies

Stability studies on the active ingredient should be continued and similar studies on the chosen dosage form should be begun as soon as possible. Accelerated stability tests often yield useful indications in the early stages
of a study, but long-term storage under appropriate conditions must be undertaken to provide data on which to base expiry dates for the product.

Materials and dosage forms that have been stored must be examined by methods capable of differentiating between the active ingredient and its potential degradation products. If degradation products do develop they should be isolated and identified and, where appropriate, they should be examined for toxicity. The extent of this type of testing that might be necessary will depend upon the chemical nature of the impurities and on the amounts present; these should therefore be determined at intervals throughout the study. Maximum limits for the content of toxic or other undesirable impurities arising from degradation should be set and methods should be established for the determination of such contents.

Changes in the physical characteristics of the dosage form should also be followed and the influence of any such changes on the clinical effectiveness of the dosage form should be assessed. Such changes should be taken into account when setting an expiry date.