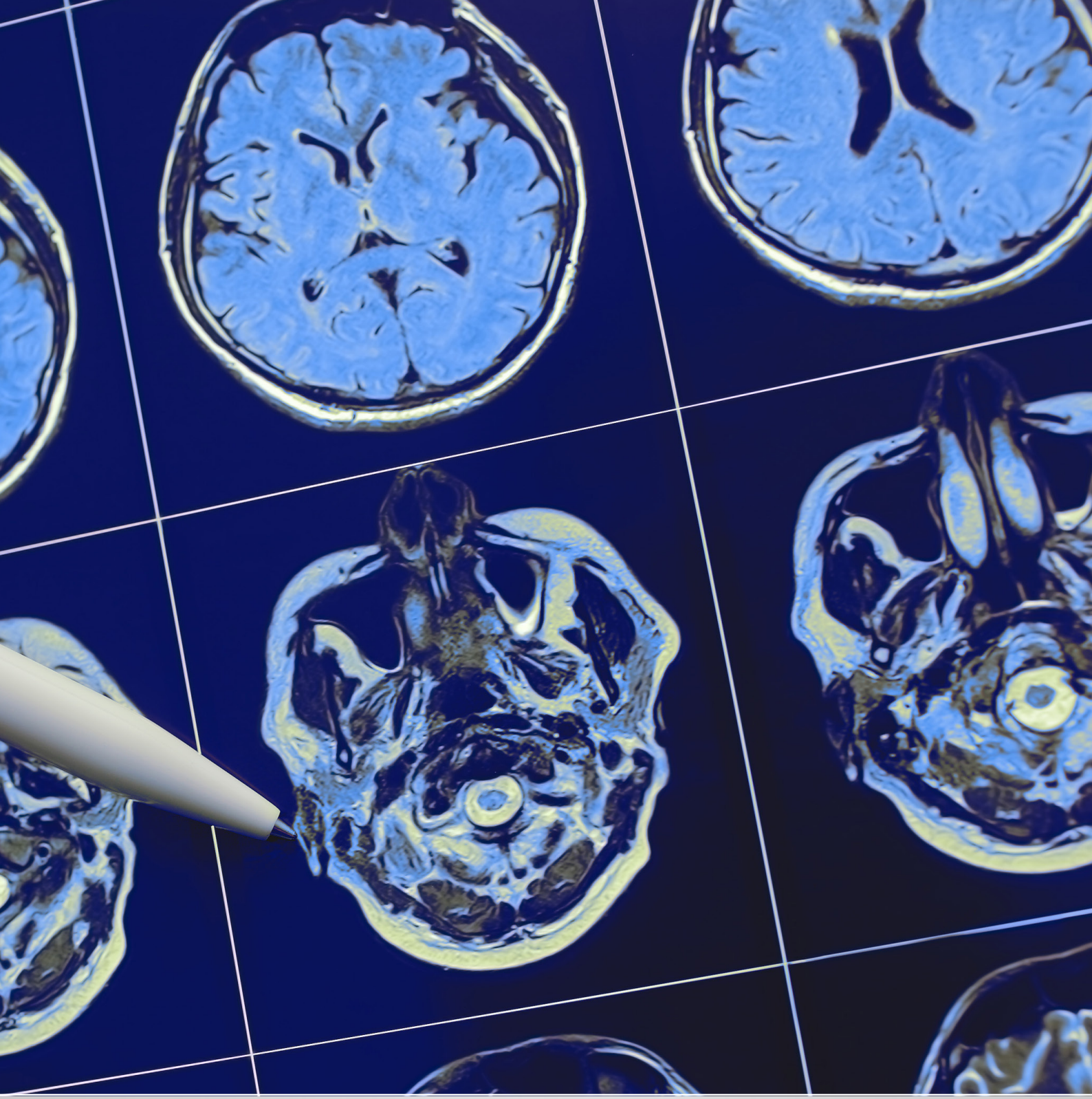
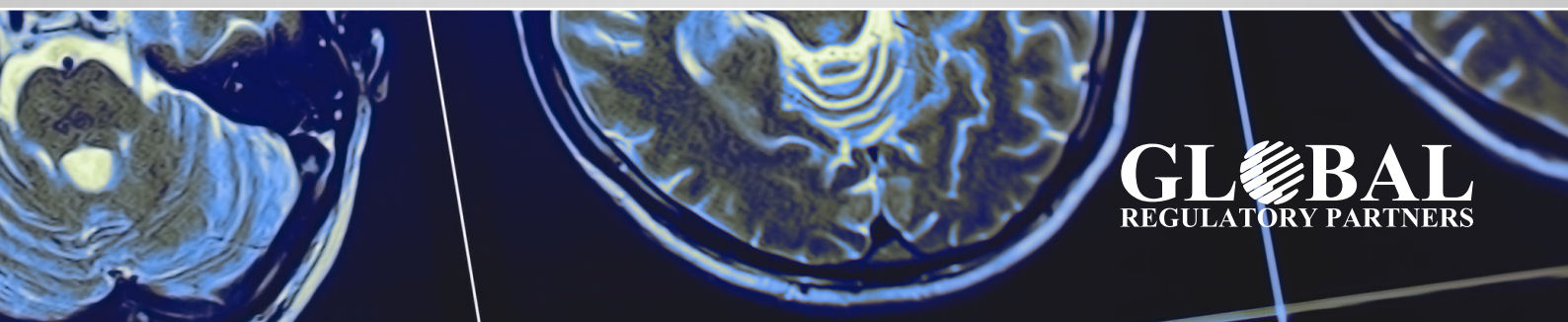


REGISTRATION OF RADIOPHARMACEUTICALS IN BRAZIL



GLOBAL
REGULATORY PARTNERS

DEFINITION

Radiopharmaceuticals are pharmaceutical products in a ready-to-use form suitable for human use. They are composed by a non-radioactive element (charger or binder) and a radioactive element (radionuclide), including components extracted from radionuclide generator. They are used for diagnostic or therapeutic purpose.

CLASSIFICATION

ANVISA classifies radiopharmaceuticals in the following 3 categories:

1. Ready-to-use radiopharmaceuticals;
2. Non-radioactive components used with radioactive components;
3. Radionuclides, including eluates of radionuclide generators

REGISTRATION PROCESS

Step 1: Application for GMP certification

As part of the registration process of a radiopharmaceutical product in Brazil, the applicant must obtain first, a Certificate of Good Manufacturing Practice (CBPF) for each manufacturing site of the drug product from Anvisa.

The Certificate of Good Manufacturing Practice (CBPF) is issued by Anvisa for each manufacturingsite after reviewing the application for GMP certification submitted by the applicant and conducting successfully a GMP inspection to the manufacturing site.

Content of the application for GMP certification:

- Petition form completed, stamped and signed;
- Valid Good Manufacturing Practice certificate (GMP) issued by the health authority of the country where the product is manufactured. Certificates issued in english, spanish or portuguese will be accepted without the need of a sworn translation;
- Site Master File (SMF) of the manufacturing site subject to GMP inspection
- Periodical Product Review (RPP);
- Inspection Report from other health authorities in the country of origin if available.
- Receipt of payment of Anvisa fee for GMP application

Step 2: Registration dossier submission

The registration dossier should be translated in portuguese.
The content of the registration dossier for radiopharmaceutical product is here below:

Sections	Description of documents
Administrative information	1. Proof of Payment of Anvisa fee; 2. Completed Application form provided 3. Copy of the Company's Operating Authorization (AFE) or itspublication in the DOU in Brazil; 4. Copy of the Certificate of Technical Responsible issued by the Regional Pharmacy Council; 5. List of countries where the product is registered; 6. Copy of the GMP Certificate issued by Anvisa to the manufacturing site and GMP Certificate from country of origin; 7. Proof of registration of the imported drug in the country of origin(CPP); 8. Specification of the drug to be imported; 9. Trademark certificate of the drug in Brazil; 10. Copies of the current package leaflet; 11. For imported radiopharmaceuticals in bulk, GMP Certificate issued by Anvisa for performing the local packaging operations; 12. For imported radiopharmaceuticals in bulk, specification andjustification of product validity(*), when supplied by the manufacturer and after reconstitution, when applicable. (*) the expiration date is determined from the date of manufacture of the product abroad, and not the date of packaging here in Brazil.
Technical Information	1. Name and address of the manufacturer(s) of the drug substanceand of the radiopharmaceutical drug product; 2. Pharmacological properties of the drug product; 3. Information about the physical-chemical characteristics of the drug substance; 4. Technical information on the drug product; 5. Information on the radionuclide and radiochemical properties of the radiopharmaceutical finished product.

Sections	Description of documents
Production and Quality Control Information	1. Production report: complete formula with description of allcomponents; quantity of each component with its functionin the formula and respective quality specifications; minimum and maximum industrial lot size; description of all production steps, including cleaning and measures to avoid contamination; equipment used with details of the design, operating principle and maximum individual capacity; descriptionof computerized control malfunction indicators; validation of controls of critical parameters of the production process; methodology of in-process controls; code or convention used by the company to identify the production lot; 2. Quality control of all raw materials; 3. Quality control of the finished product; 4. Purity of raw materials; 5. Impurities; 6. Specifications of primary packaging material; 7. Copies of the last 3 manufacturing batches; 8. Description of all stages of production: equipment used, sourceof target material and irradiation site; isolation or fabrication ofthe raw radioactive material, including nuclear transformation; transformations that are not of interest but may occur under the irradiation conditions used due to isotopic impurities present in the target material; irradiation conditions; effect of variations in nuclearreactions; description and validation of separation processes and influence of the geometry of the target chamber and its material; 9. Results of the accelerated stability studies of three pilot batchesand long-term stability studies of commercial batches; 10. Package insert, containing the specifics of the radiopharmaceutical drug; 11. Layout of label , primary and secondary packaging of drugproduct;

Sections	Description of documents
Pre-clinical and clinical information	1. Reports of preclinical studies including toxicology studies; 2. Reports of phase I, phase II and phase III clinical studies conductedon the radiopharmaceutical product, accompanied by bibliographicreferences when available; 3. For radiopharmaceuticals that are listed in **Annex I** of regulation **RDC No. 64/2009**, that are well-known products, preclinical and orclinical reports can be replaced by bibliography analysis and data. For radiopharmaceuticals that include the combination of 2 or more active ingredients, the following should be provided as well: 1. Relative pharmacological studies of the combinedactive ingredients; 2. Controlled clinical trials for each therapeutic indication, provingthat the associations do not increase the risks when compared with the use of each active ingredient separately.

Sections	Description of documents
Specific Clinical data for Diagnostic Radiopharmaceuticals	For radiopharmaceutical products used for diagnostic, the following requirements should be taken into consideration: ➢ The efficacy of the product should be determined byevaluating its ability to provide useful clinical informationin a defined clinical setting related to the proposedindication(s) for use. ➢ The accuracy and usefulness of the product should be determined by comparison with a reliable assessment of current clinical status. A reliable evaluation of the current clinical status can beprovided by a diagnostic standard or by demonstrated standardsof accuracy. In the absence of such a diagnostic standard, theclinical status must be determined by another way, such as bypatient evaluation. ➢ The safety of the product should be defined for eachradiation dose to be administered to the patient. The doseshould be established based on the evaluation of theradiation dosimetry in human and data collected from animalstudies using the appropriate animal models. It is not necessaryto establish the maximum tolerated dose. The safety profile of the product should be determined based on : • The adverse reactions reactions collected after the product's administration to patients. • Resultsofhumanexperiencewiththediagnosticradiopharmaceutical for other indications. • Results of any previous human experience with the diagnostic radiopharmaceutical, when the same chemical entity wasused in a previously studied products. The amount of safety data that is required depends on the characteristics of the product and availability or not of safety information on such product. Safety information should also include the following information: • Product activity; • Detailed instructions for its preparation and its quality controls; • Storage conditions and shelf life before and after preparation. • Route of administration; • Biological half-life

ANVISA REGISTRATION TIMELINES AND FEES

TIMELINES AND VALUES	
Analysis of Registration Dossier by Anvisa	Up to 180 days
Registration Validity	5 years (may be revalidated for equal and successive periods)
Certificate of Good Manufacturing Practices	R$ 72,804.90 Brazilian reais for each manufacturing plant involved in the production of the drug

DRUG REGISTRATION FEE						
ANVISA	GROUP I	GROUP II	GROUP III	GROUP IV	SMALL-SIZED COMPANY	MICROENTERPRISE
NEW DRUG	R$ 157,416.00	R$ 133,803.60	R$ 110,191.20	R$ 62,966.40	R$ 15,741.60	R$ 7,870.80
SIMILAR DRUG	R$ 41,000.40	R$ 34,850.34	R$ 28,700.28	R$ 16,400.16	R$ 4,100.04	R$ 2,050.02
GENERIC DRUG	R$ 11,714.40	R$ 9,957.24	R$ 8,200.08	R$ 4,685.76	R$ 1,171.44	R$ 585.72

COMPANY CLASSIFICATION	
GROUP I: LARGE-SIZED COMPANY	ANNUAL REVENUE EXCEEDING R$ 50 MILLION REAIS
GROUP II: LARGE-SIZED COMPANY	ANNUAL REVENUE BETWEEN R$ 20 AND 50 MILLION REAIS
GROUP III: MEDIUM-SIZED COMPANY	ANNUAL REVENUE BETWEEN R$ 6 AND 20 MILLION REAIS
GROUP IV: MEDIUM-SIZED COMPANY	ANNUAL REVENUE EQUAL OR LOWER TO R$ 6 MILLION REAIS
SMALL-SIZED COMPANY	ANNUAL REVENUE BETWEEN R$ 360 THOUSAND REAIS AND R$ 4.8 MILLION REAIS

REFERENCES:

- Anvisa's Website. Companies Regularization - Certificate of Good Manufacturing Practices. Link: http://antigo.anvisa.gov.br/registros-e-autorizacoes/empresas/cbpf
- Regional Pharmacy Council of the State of São Paulo. Radiopharmacy. 1st edition. 2019. Link: http://www.crfsp.org.br/images/cartilhas/radiofarmacia.pdf
- Resolution of Board of Directors - RDC No. 64 of December 18, 2009. Provides on the Registration of Radiopharmaceuticals. Link.: http://antigo.anvisa.gov.br/documents/10181/2718376/%284%29RDC_64_2009_COMP.pdf/32cc99bf-c251-42de-99b4-4abddb47e6c3
- Resolution of Board of Directors - RDC No. 10 of March 21, 2011. Provides on the quality assurance of imported drugs and makes other arrangements. Link.: http://antigo.anvisa.gov.br/documents/10181/3315504/%284%29RDC_10_2011_COMP.pdf/12352a77-c0ea-4c10-96e0-a551140a4d7b
- Resolution of Board of Directors - RDC No. 9 of February 20, 2015. Provides on the Regulation for conducting clinical trials with drugs in Brazil. Link.: http://antigo.anvisa.gov.br/documents/10181/3503972/RDC_09_2015_COMP.pdf/e26e9a44-9cf4-4b30-95bc-feb39e1bacc6
- RDC 22/2006: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2006/res0222_28_12_2006.html
- Complementary Law No. 123/2006: http://www.planalto.gov.br/ccivil_03/leis/LCP/Lcp123.htm#art88

ANNEX I OF RDC 64/2009

ACTIVE PRINCIPLES OF RADIOPHARMACEUTICALS OF CONSECRATED USE

1. Marked Molecules

- Iobenguane sulfate (I-131) (MIBG Sulfate)
- Iobenguane (I-123)
- Iodinated human serum albumin (I-131)
- Sodium iodohippurate (131I)
- Ethiodized Oil (I-131) (Ethiodol)
- Chromium edetate (Cr-51)
- Chromated serum albumin (Cr-51)
- Samarium lexidronam (153 Sm)
- Samarium hydroxyapatite (153 Sm)
- Fludeoxyglucose (18 F)
- Pentetreotide (111 In)
- Octreotate (177 Lu)
- Yttrium-90 citrate colloid (90 Y)
- Hydroxyapatite (90 Y)

2. Primary Radioisotopes

- Gallium citrate (Ga-67)
- Sodium chromate (Cr-51)
- Sodium iodide (I-123)
- Sodium iodide (I-131)
- Iodine (I-131)
- Thallous chloride (TL-201)
- Sodium pertechnetate (Tc 99m)
- Sodium fluoride (F-18)

3. Lyophilized Reagents for Marking with 99mTc

- Technetium (Tc 99m) pentetate
- Technetium (Tc 99m) succimer
- Technetium (Tc 99m) glucoheptonate
- Technetium (Tc99 m) dysophenin
- Technetium (Tc 99m) medronate
- Technetium (Tc 99m) pyrophosphate
- Technetium (Tc 99m) dextran-500
- Technetium (Tc 99m) dextran-70
- Technetium (Tc 99m)-tin colloid
- Technetium (Tc 99m) albumin aggregated
- Technetium (Tc 99m) bicisate
- Technetium (Tc 99m) sodium phytate
- Technetium (Tc 99m) sestamibi
- Technetium (Tc 99m) glucarate
- Technetium (Tc 99m) exametazime
- Technetium (Tc 99m) tetrophosmine
- Technetium (Tc 99m) colloidal sulphur

ABOUT GLOBAL REGULATORY PARTNERS, INC

Global Regulatory Partners Inc, (GRP) provides regulatory affairs, clinical, quality and safety services to medical devices and pharmaceutical companies globally. As a qualified and licensed legal representative with offices in USA, China, Japan, Brazil, Mexico and Argentina, the company can represent life science companies in those countries and help them register their products in compliance with local regulations and in record time.

For additional information, please contact us at info@globalregulatorypartners.com

GLOBAL REGULATORY PARTNERS

Corporate Office

Address:
550 Conchituate Rd, East Wing, Suite 25,
Framingham, 01701, Massachusetts , USA

Email:
info@globalregulatorypartners.com

Website:
www.globalregulatorypartners.com

Telephone:
781.672.4200

Brazil

Rafael Marino Street, NETO 600
Karaiba Garden
UBERLANDIA – 38411-186
Minas Gerais (MG)
Telephone: (+55) 34-3235-1971

Japan

Toranomon 40MT Buildings 7th floor
Minato-ku, Tokyo, 105-0001 Japan
Telephone: (+81)-3-4530-9824

Mexico

Lake Alberto 442 – 5th floor
Tower A – Office 509
Col. Anahuac 1st Section
Delegation Miguel Hidalgo, C.P. 11320
Telephone: (+52) 55 7312 4169

China

21st Centry Tower, Suite 6030, 6/F
210 Centry Avenue, Pudong District
Shanghai, 200120
Telephone: (+86) 021-517-27278