

The regulatory dilemma for import of radiopharmaceuticals in India

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The inclusion of monographs of several radiopharmaceuticals in the Indian Pharmacopoeia has drawn the attention of drug control authorities in the country and other stakeholders. Therefore, in a move towards better regulation of radiopharmaceuticals, the Office of the Drug Controller General of India has issued some important notices concerning their import. However, these notices have resulted in several misgivings among the nuclear medicine community as appointment of patients for nuclear medicine scans had to be cancelled/rescheduled and clinical decisions delayed. An analysis of the sequence of events is presented in this study, highlighting the effects of decisions taken regarding import of radiopharmaceuticals, and suggestions to implement regulations with minimal repercussions.

Radiopharmaceuticals (RPs) are essentially pharmaceutical molecules labelled with a suitable radioactive atom, which have gained the attention of scientists from the disciplines of chemistry, biology, pharmacy and nuclear sciences worldwide in the last decade due to the impact that nuclear medicine has had in the diagnosis and management of several diseases, particularly in oncology, cardiology and neurology. This is because nuclear medicine procedures use specific RPs to image the physiology underlying the disease. The amount or mass of RPs used is in minute quantities and does not cause any noticeable pharmaceutical/physiological effect(s) and hence safe to use. In the decades of use of RPs, there are very few reports of adverse effects.

Radionuclides that are used in RPs must have certain properties: half-lives that are not too short or too long, nature of decay that is suitable for diagnosis or therapy, high specific activity, easy availability from a reactor, and medical cyclotron or radionuclide generator in which the parent radionuclide is kept and the required daughter radionuclide can be milked daily.

The availability of technetium-99m (^{99m}Tc) radionuclide ($T_{1/2} = 6$ h) generators (housing the parent Molybdenum-99 (^{99}Mo) ($T_{1/2} = 66$ h)) gave immense boost to nuclear medicine in the 1970s in India. Tc-99m is used for making a variety of innovative RPs of clinical importance. Nuclear medicine scans using ^{99m}Tc RPs are used for diagnosis and understanding of several diseases where conventional X-ray, CT and MRI imaging is unsatisfactory. The advent of positron emission tomography (PET) imaging in the 1990s gave further boost to nuclear medicine, particularly for cancer diagnosis.

The importance of RPs in the present era is apparent from the exponential rise in investment made by hospitals to set up nuclear medicine departments and procurement of state-of-the-art SPECT gamma camera, PET-scanners and medical cyclotrons. Presently, there are over 200 nuclear medicine centres in our country. The current marketplace for RPs bears testimony to this fact. In India, the Board of Radiation and Isotopic Studies (BRIT) is the main producer of radioisotopes in the government sector under the overarching surveillance of the Atomic Energy Regulatory Board (AERB), Anushaktinagar, Mumbai. However, the demand for RPs in India has exceeded the supply or availability from BRIT, leading to their import. Hospitals and institutions that wish to import RPs or radioactivity in any form, have to get No Objection Certificates (NOCs) from AERB. In the recent past, the import of RPs has come under the scrutiny of the Central Drugs Standard Control Organization (CDSCO) office, leading to various notices being issued by the Drug Controller General of India (DCGI) under the authority of the Drug and Cosmetic Act 1940 and Rules, 1945 thereunder. The present study analyses these office notices and the corresponding effects they have on the day-to-day nuclear medicine practice, and reaction from the nuclear medicine community and other stakeholders.

The office of the DCGI has issued some landmark notices concerning the import of RPs in India. A notice dated 29 December 2016, stated that all importers of RPs were required to obtain permission, prior to importing, under provisions of Drug and Cosmetic Act 1940 and Rules, 1945 thereunder, and that no concession will be made in this regard¹.

This was followed by another office notice issued on 20 February 2017, according to which importers of ^{99m}Tc -generators were required to draw samples at the port from the first five imported generator consignments from a given supplier. These samples had to be subjected to various quality control (QC) tests at one of the two designated national institutions located at Delhi and Mumbai. According to the notice, the generator consignment(s) should be released only after the QC test results were satisfactory². On the same day, another notice regarding import of RP products for *in vivo* or *in vitro* diagnostics stated that Form 10 license may be granted without registration certificate for import of *in vivo* RP products having no indigenous manufacturer, while those having an indigenous manufacturer were required to obtain Form 10 license according to the existing requirements of Drug and Cosmetic Act 1940 and Rules, 1945 thereunder³.

Two more orders from the office of the DCGI came out in April 2017 and May 2017 regarding RPs. The first one was issued on 28 April 2017, concerning the requirements of importers and/or end users for ^{99m}Tc -generators and other RPs, in which it was directed that importers who apply online or offline to various CDSCO offices in Form 12AA and/or Form 12A shall be granted the import license in Form 11A and/or Form 12B immediately within 2 h from receipt of request⁴. Another notice on 1 May 2017 stated the mandatory requirement of import license according to the existing requirements of Drug and Cosmetic Act 1940 and Rules, 1945 thereunder for RPs being imported in India with reference to CDSCO Headquarter letters dated 12 September 2016 and 13 October 2016.

The second notice also stated that if the results of testing fail, no import shall be permitted from that manufacturer and that the stock already imported or in transit shall be required to be disposed of or returned back. It also mandated a timeline of ten working days for submission of a sample for analysis post receipt of the imported sample, failing which no further imports would be allowed⁵.

The above-mentioned notices by the DCGI had a direct bearing on the import and supply of technetium-99m, a radioisotope used extensively in nuclear medicine diagnostics, and the corresponding delay in various nuclear medicine procedures throughout India. It led to halt in the supply of ^{99m}Tc RPs when the ^{99m}Tc-radionuclide generator was not available for two weeks in a row while the mandated QC tests were in progress, leaving hundreds of patients waiting for nuclear medicine scans with various ^{99m}Tc RPs. In all, more than 200 centres across India were affected due to the sudden introduction of regulations by the Office of the DCGI. This effect was reported in national newspapers in the first week of May 2017.

It was apparent that there were several misgivings concerning the notices from the Office of the DCGI and that the Office had not taken into account aspects concerning the import of RPs. Nuclear medicine physicians and experts on RPs stated that their views could have been considered before the notices were issued so that inconvenience to doctors and patients could have been minimal. Details of these aspects are discussed below.

The fact that ^{99m}TcO₄⁻ produced from a ^{99m}Tc-generators is an active pharmaceutical ingredient, rather than a finished RP product, was not addressed adequately in the office orders. However, to enable in-house production of ^{99m}Tc RPs fulfilling pharmacopoeia requirements, manufacturers assemble ⁹⁹Mo-^{99m}Tc generators in sterile and shielded assembly lines so that when sterile, pyrogen-free saline (supplied along with the generator) is used to elute ^{99m}Tc, the product expected is sterile and endotoxin-free ^{99m}TcO₄⁻ solution. ^{99m}Tc-generator technology is well validated, having withstood the test of time and is approved for use in the country of production. Hence ^{99m}TcO₄⁻ from the generator can be released for use in patients after completing the essential tests, viz. radionuclide purity, radiochemical purity, Mo-99 break-

through and pH, which can be completed in less than an hour. This process of release of short-lived RPs for use in patients is known as ‘parametric release’⁶. The remaining tests like sterility and bacterial endotoxin tests are performed daily for the shelf-life of the generator, on one of the sample generators from the lot produced.

In-house preparation of ^{99m}Tc RPs requires addition of a known quantity of the sterile and pyrogen-free ^{99m}TcO₄⁻ into ‘cold-kits’ containing the pharmaceutical ligand in calculated quantities with reducing agents, buffering agents and other excipients. Thus, each ^{99m}Tc RP has a specifically formulated ‘cold-kit’, which has a long shelf-life when stored at the specified temperature. The formulation of cold-kits is clearly specified in the production and QC monograph by the manufacturer, whether in India by BRIT or by manufacturers abroad. These formulations are validated by making several batches and several vials from each batch are used to prepare the ^{99m}Tc RP, which is then subjected to all the tests as specified in the monograph for ^{99m}Tc RP in the pharmacopoeia of the country where the cold kit is formulated. For example, BRIT follows the monographs in the *Indian Pharmacopoeia*. Since the cold-kits are formulated with sterile ^{99m}TcO₄⁻, eluted from the generator, once again aseptically, to prepare ^{99m}Tc RP, the latter can be expected to fulfil the pharmacopoeia specifications with a high degree of confidence. Therefore, short half-life RP preparations are released for use in patients before the results of all quality control tests. This mandates a robust quality assurance approach during their manufacturing as mentioned above, which helps in achieving a product having predetermined characteristics and quality attributes. The DCGI notices strangely skipped this cri-

tical concept of parametric release for short half-life products.

In India, there are a number of technetium generator suppliers, both domestic and international. The domestic supply has largely been catered by BRIT which has three types of technetium generators, namely TCM-1, TCM-2 and TCG. TCM-1, also known as COLTECH generator, is the latest and most user-friendly. These BRIT-produced generators are supplied according to a set dispatch schedule after approval by the Radiopharmaceuticals Committee (RPC), constituted by the Department of Atomic Energy (DAE). The RPC has nominees from the DCGI and Food and Drug Administration, Maharashtra. Any request for a generator placed to BRIT is confirmed subject to prior approval/authorization of these interested laboratories/facilities by AERB. Table 1 presents an overview of some of the important technetium generator suppliers in India.

As a routine practice, these ^{99m}Tc-generators are usually received on every Saturday/Sunday for use from the following Monday to Friday/Saturday. Since the ^{99m}Tc-generators have only a few days of shelf-life, all generators from a given supplier received on a given day would be from one production batch. Since users are from all over the country, the generators would be shipped to different locations where individual testing is required. The most controversial decision taken by the DCGI was regarding the import of technetium-99 generators and the requirement to draw samples at the port of entry from the first five imported consignments followed by their testing at one of the two national institutions. The supply chain for ^{99m}Tc-generator consists of manufacturers from abroad (usually) who deliver the consignment to importers (nuclear medicine

Table 1. List of important technetium-99m radionuclide generator suppliers in India

Radionuclide generator supplier	Trade name
BRIT	COLTECH Generator [®] , GELTECH Generator [®]
SDS Life Sciences Pvt Ltd	SDS Gen [®]
GEEBEE International	Unitech [®]
ANSTO Health	Gentech [®]
GE Healthcare	Drytec [™]
IBA Molecular	TEKCIS [®]
Lantheus Medical Imaging	TechneLite [®]
Mallinckrodt Pharmaceuticals	Ultra-Technekow [™] DTE Generator

BRIT, Board of Radiation and Isotope Technology; ANSTO, Australian Nuclear Science and Technology Organization, and IBA, Ion Beam Applications.

physicians at hospitals) who are actually the end-users and numbering around 200. In a normal routine, each end-user imports one generator per week from different suppliers. Hence the requirement to provide five generators for testing to the designated centres from each of the available suppliers is out of the scope of the capacity of testing centres and the budget of the end-users.

At a recent meeting of the Drugs Technical Advisory Board 2018 at DGHS, Nirman Bhawan, New Delhi, a proposal to amend schedule D of the Drugs and Cosmetics Rules, 1945 was considered, in order to provide exemption for RPs from the provisions of chapter III of the Drugs and Cosmetics Act, 1940 (ref. 7). However, the members did not agree to the proposal and further stated that all indigenous manufacturers of radiolabelled drugs/molecules and RPs shall be brought under the purview of the Drug and Cosmetic Act 1940 and Rules, 1945 thereunder. It was also decided that a full-fledged wing for regulations of RPs shall be set up at CDSCO, which shall work in conjunction with DAE for exercising regulatory control on these compounds.

In the light of various DCGI notices, some reforms are required to better regulate RPs in the best interest of nuclear medicine practitioners, radiopharmacists, end-users and society at large, in order to implement the required regulations governing their import without affecting the continuous supply of RPs. It is suggested that the DCGI should immediately meet the Expert Committee on Radiopharmaceuticals (ECRP) involved in drafting RP monographs for the Indian Pharmacopoeia, RPC of BARC, BRIT and AERB to draft the regulations. The ECRP, RPC, BARC, BRIT and AERB have important complementary and non-overlapping roles regarding the use of RPs in India. The concept of parametric release should be addressed and a clear statement concerning the release of short half-life RPs based on the concept of parametric release should be specified, provided a robust quality assurance system is in place. Regarding the need to test each of the consignments before re-

lease, an appropriate solution is to perform quality-control tests on a single sample generator from each of the available suppliers, while the remaining generators can be released on the basis of results of parametric tests. Regarding the requirement to test each of the consignments from a single lot received, it should be sufficient to start QC tests on a sample generator from any supplier at the entry ports and, if found to satisfy parametric release, the generators can be released from all the ports. The sample generator can be retained by the test laboratory for rest of the QC tests.

Alternatively, if the generator is approved for use by the FDA/pharmacopoeia of the country of manufacturer, then testing on import can be waived – similar to the AERB permitting import of radiation emitting equipment if a type-approval certificate is available from the country of manufacture. It is reiterated that the $^{99m}\text{TcO}_4^-$ produced from ^{99m}Tc -generators is an active pharmaceutical ingredient, rather than a finished RP. Even $^{99m}\text{TcO}_4^-$ utilized for thyroid scans uses the eluted $^{99m}\text{TcO}_4^-$ after it is suitably formulated in physiological saline.

The above reforms will help in achieving balance in the supply of RPs in the ongoing change of regulatory landscape at the national level concerning their import. A regulatory set-up ambient for end-users and/or importers and drug control authority is the need of the hour. This can be achieved by also holding consultative meetings with end-users and/or importers, and various experts from the nuclear medicine community before coming up with any government notice/regulation. Otherwise, the future import and continuous supply of radio-nuclide generators (^{99m}Tc , ^{68}Ga , ^{82}Rb) and RPs (diagnostic and therapeutic), much needed for patients in India, could be affected.

Conflict of interest: The authors declare that they have no conflict of interest.

1. File No. 29/Misc./4/2016-DC (101), Director General of Health Services (DGHS), Central Drugs Standard Control Organization, Government of India (GoI), 29

December 2016; <http://www.cdsc.nic.in/writereaddata/Notice%20Radio-Pharmaceutical.pdf> (accessed on 15 December 2018).

2. File No. DCG (I)/Misc/2017 (11), DGHS, Office of Drug Controller General (India), Import and Registration Division, GoI, 20 February 2017; <http://www.cdsc.nic.in/writereaddata/radiopharma.pdf> (accessed on 15 December 2018).
3. DCG (I) Misc/2017 (21), DGHS, Ministry of Health and Family Welfare, Drug Controller General (I), GoI, 20 February 2017; http://www.cdsc.nic.in/writereaddata/notice-20_2_2017.pdf (accessed on 15 December 2018).
4. File No. DCG (I)/Misc/2017 (11); DGHS, Office of Drug Controller General (India), Import and Registration Division, GoI, 28 April 2017; <http://www.cdsc.nic.in/writereaddata/Radiopharmaceutical%20Order.pdf> (accessed on 15 December 2018).
5. File No. DCG (I)/Misc/2017 (11), DGHS, Office of Drug Controller General (India), Import and Registration Division, GoI, 1 May 2017; https://cdsc.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NDc2 (accessed on 15 December 2018).
6. MoFHW, *Indian Pharmacopoeia*, Ministry of Health and Family Welfare, GoI, 2018.
7. Minutes of the 78th Meeting of Drugs Technical Advisory Board, New Delhi, 12 February 2018; http://www.cdsc.nic.in/writereaddata/Minutes%20of%2078th%20DTAB%20Meeting%20held%20on%2012_02_2018.pdf (accessed on 15 December 2018).

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