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A Comparative Study on the Regulatory Requirements for the Content of Labels and Packet Insert for Radiopharmaceuticals

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ABSTRACT
Radiopharmaceuticals (RPs) have become the new buzzword in the modern healthcare system owing to their multifarious application in diagnosis and therapy. Efforts by the medical fraternity worldwide have delivered a plethora of radiopharmaceuticals, many of which are of biotechnological origin. Since it is a niche field and the concern about radioactivity and its dose is of paramount importance, strict laws are indispensable for their labeling to ensure safety and efficacy. In India, majority of the domestic requirement of RPs is catered by Board of Radiation and Isotope Technology (BRIT) and Institute of Nuclear Medicine and Allied Sciences (INMAS) where they are prepared and labeled under strict laws. More recently, many private players are coming up with their own cyclotron facility and research labs for the onsite preparation of RPs. Unfortunately, the Drug and Cosmetic Act 1940 and Rules framed there under is silent on the aspect of labelling for such RPs due to the inclusion of RPs in its Schedule K. Therefore, it is imperative to revisit the entire corpus of limited information concerning the labelling of RPs in India. The present article provides a study of the existing requirements of labelling and packet insert as per the Drug and Cosmetic Act, 1940 and rules framed there under, and attempts to intensify the concern for comprehensive draft guidelines on the content of label and packet insert for RPs by the judicious use of scientific as well as other cognitive approaches for the purpose of implementing Indian Pharmacopoeia 2018, which contains about thirty-five monographs on RPs.
Keywords: *Radiopharmaceuticals, Drug and Cosmetic Act, Packet Insert, Label.*

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INTRODUCTION

Labels and packet inserts are a vital part of any radio-pharmaceutical preparation and contribute tremendously to their quality use by the end-users and the nuclear medicine practitioners. They provide an interface between the manufacturer and the end-users and provides critical information about the identity, potency at the specified date/time, content, storage requirements, shelf life, and the registration status of any product. They also help in preventing the risk of prescribing and dispensing error including misuse, over-use, and under-use, thereby enhancing the safety of a patient. They also help in optimizing identification which is required in the management of multiple medicines. While designing the label, it is imperative to keep in mind the standardization of product labels and choice of the appropriate format for insert as this can also significantly reduce the errors by reinforcing the pattern recognition on which humans rely when processing information. Packet insert, in particular, must be completely updated and commensurate with the ongoing medical findings. The particulars on the label should be in English language and must be in durable and legible characters which are readily discernible to the purchaser or consumer in the real-world environments or situations in which products are to be used (e.g. a nuclear medicine centres hospital room with low lighting). The label must bear on it the standard radioactive symbol and words 'Caution Radioactive Material'. Even though the human interaction with labels of radiopharmaceuticals during their use occurs in an ambient environment, their storage can predispose it to the complexity associated with multiple locations and possible environments having similar products in one place. Therefore, user testing can provide a plausible solution to this problem. It consists of method for assessing the usability, identifying problems experienced by users, followed by developing solutions to reduce or even eliminate the consequences of these problems by mimicking or simulating the circumstances/environment of product use. As most of the radiopharmaceuticals are high-risk products, it helps in determining whether or not the actual users can safely and effectively perform all the critical tasks involved in selecting and using the intended radiopharmaceuticals. Some of the methodologies

involved in user testing include Failure Mode and Effects Analysis, Comprehension Testing, Cognitive Walkthrough, and Usability Evaluation etc. More recently, the concept of Product-Use Process Maps has enabled to assess the real-time environment of use of the product and how the users will interact with it in order to identify and make decisions about its further use. Figure 1 presents the goal of labelling and its significance. Format of the label is another matter of concern. Ideally, the format must be simple, informative and free from any unsafe abbreviations. The typestyle chosen should be according to space availability and package design. It should also have adequate spacing between letters and words to enhance the elegibility and readability. The readability of label can be enhanced by using the flush left, ragged right alignment of multiple lines of text as this sort of alignment provides visual points of reference that guide the eye of reader smoothly from one line to the other [1]. Use of bullets lists should be encouraged to provide items in point form instead of complete sentences. Important points like warnings in text or pictorial format should be made more conspicuous which is important for the safe use of the product. One of the best ways to counter look-alike, sound-alike problem is to use TALLman lettering which consists of using UPPER CASE lettering to certain syllables or groups of letters within names [2, 3]. It does not depend upon type style, point size, or colour which has earned it an important tool for distinguishing among drug names [4]. It is important to note that TALLman lettering should be applied to both the outer and inner label to maintain consistency. However, it should be used only for a non-proprietary name with the text.

All labels should be deliberately provided with a blank space which helps to enhance the readability of product labels. More importantly, it is also reported to improve the willingness of a reader to read and process any important information presented [5,6]. Appropriate selection of colour and contrast is another important factor to be taken into consideration while designing the labels and should be considered in conjunction with other parameters. This is particularly important where different strengths of the same product are differentiated by variations of one specific colour. Use of contrast is another important tool for designing the label as it helps to detect the differences in what is written [7]. The judicious use of colour can be made for the most important segment of a label like a warning, name of the product or its strength [8, 9].

AIM AND OBJECTIVES

The present article provides a study of the existing requirements of labelling and packet insert as per the Drug and Cosmetic Act, 1940 and rules framed there under, and attempts to intensify the concern for comprehensive draft guidelines on the content of label and packet insert for RPs by the judicious use of scientific as well as other cognitive approaches for the purpose of implementing Indian Pharmacopoeia 2018.

MATERIALS AND METHODS

The proposed draft guideline sets out the requirements for information to be included on the label and packet inserts bearing the RPs. Adoption and implementation of this uniform format regarding the contents of labels and package insert help in better quality and clarity regarding their use. The objective of this draft guideline is to provide sufficient information and guidance to the stakeholders, sponsors, manufacturers and license holders concerning the requirements for contents of labels and package insert to be used for RPs. This guideline is of interest to sponsors, manufacturers, license holders, nuclear medicine practitioners and occupational workers dealing with RPs and provides sufficient guidance for designing labels and packet inserts for RPs.

A. Outer container label - Existing requirements and recommendations

The manner of labelling in India is governed as per Rule 96 of the Drugs and Cosmetics Act, 1940 and rules framed thereunder. All manufacturers are mandated to follow this requirement strictly. However, this requirement is not commensurate to the international level. Table 1 provides a comparative account of the existing requirements as per Drugs and Cosmetics Rules 1945 and the various suggestive recommendations. The one in normal case are the requirements as per Drugs and Cosmetics Rules 1945, while the one indicated in italics are the recommendations which must be included in addition to the existing requirements while designing labels for RPs. On the basis of this comparative study, a proposed format for the contents of the label for radiopharmaceuticals is presented in the following section.

1. **Approved name of the product**: All labels must bear the approved name of the product. Sufficient care should be taken to prevent the resemblance of the name with any of the already available product in the market, thereby underlying the importance of brand name assessment.
2. **Composition, volume and strength:** The outer label of all radiopharmaceutical preparation must include the name(s) of all the active ingredients along with their quantity or proportion. This is because a single preparation can be available in variable strength. Use “mcg” rather than “µg” for micrograms quantities. Trailing zeros (e.g., “5.0”, “6.50”) and naked decimals (e.g., “.2”) should generally be avoided while referring to strength. For liquid radiopharmaceuticals preparations, it is

best to label the quantity of medicinal ingredient per millilitre. Radiopharmaceuticals are available in the different dosage form and, therefore, the radioactivity must be expressed accordingly.

3. **Dosage form**: The label must contain information regarding the dosage form in which the preparation of the radiopharmaceutical is available.
4. **Name and address of the manufacturer/authorization holder**: Each label should have detailed information about the name and complete postal address of manufacturer to enable the manufacturer to be uniquely identified and to facilitate the public contact.
5. **Authorization number**: Each manufacturer is provided with a specific authorization number which must appear on the label of the radiopharmaceutical.
6. **Total Radioactivity:** The label must bear details regarding the quantity of radionuclide present in the radiopharmaceutical preparation, expressed in terms of the total activity of the radionuclide in the container, in MBq (or mCi) or the strength in MBq per ml at the time of calibration.
7. **Sterility and apyrogenicity:** Some radiopharmaceuticalslike those available in kit formare made extemperously and therefore they should be essentially sterile and free from pyrogen. This must be reflected on their label.
8. **Excipient:** A radiopharmaceutical preparation contain, in addition to the radionuclide, some excipientswhich are necessary for making the final product. The label of radiopharmaceutical should enlist the name and quantity of each of these excipients. For single-dose injection, excipient must be expressed as the quantity of that excipient in the whole container, while for multidose injection, it must be expressed as the quantity of that excipient in one millilitre of the injection.
9. **Route of administration:** The labels for radiopharmaceuticals must contain a statement about its approved route of administration, such as 'For oral use', 'Intravenous', or 'Intraperitoneal' as the case may be.
10. **Directions for use**: The label must also contain suitable direction for use. If there is insufficient space on the outer label, a statement stating that those directions for use are set out on a leaflet inserted must be given. For radiopharmaceuticals available in kit form, it is important to have clear instruction for reconstitutionas failure to do can result in improper scans or even more serious effects.
11. **Storage conditions/precautions:**Some radiopharmaceuticals can be stored at room temperature but some may require refrigeration for storage. Therefore, a clear statement about the storage requirements and precaution must be specified in this section.
12. **Batch number**: The batch number is a unique set of character assigned to each lot of product being manufactured or prepared. However, recent studies have shown that it has been misinterpreted as the expiry date in some cases [10]. Therefore, they should be best written as 'Lot number', 'Lot no.', or 'Lot' suitably located away from expiry dates.
13. **Manufacturing date:** Each label must give sufficient information regarding the date and in some cases the time, of manufacture of the product and measurement of radioactivity.
14. **Expiry date**:Keeping in view the limited shelf life of most of the radiopharmaceutical products, it is important to assign expiry date in the most suitable manner. It is preferred to include all three components of the date (year, month, and day) for most of the preparations and even the day and time for some very short half-life preparations.
15. **Caution/Warning:** This is one of the most important parts of the product label and should be prominently displayed on the label. It should be explicit yet concise [11, 12]. It is important to consider human limitations, situation and the environment in which the product shall be placed in order to minimize human error [13]. Ideally, warnings should be deliberately placed at a location which requires physical interaction with it for completing the procedure of use [14]. Using a single word (e.g., 'WARNING' or "ALERT') in bold, capitalized in high contrast and appropriately bordered is one of the ways for an effective display of warning [15, 16].
16. **Precaution for disposal:** The radioactive nature of radiopharmaceutical preparation can pose harm to both men and the environment even after their use. Therefore, the label must contain precaution regarding disposal of unused radiopharmaceuticals or radioactive waste materials derived from such products, if any.
17. **Barcoding:** Recent technological advances in form of barcoding and radio frequency identification has greatly revolutionized the way labels are made and utilized for various stages including procurement, management of inventory, storage, preparation, dispensing, and even the administration [17]. It also helps in establishing the authenticity of the product during its transit within the supply chain as it is encoded with all the necessary and approved details of the product.

However, it should not be used as a substitute for the information required directly on the label and insert. During dispensing, it is recommended to use an identification system based on colour coding as it can help to reduce and prevent the incorrect administration of radiopharmaceuticals. The basic setup is to give a separate colour designation to each class of radiopharmaceutical. The lead vial shield containing the multi-dose stock solution (from which other unit doses shall be drawn) should be colour coded at the top and bottom with coloured tape. The syringe used for withdrawing dose from such vial should be labelled with the same colour coded pressure-sensitive label like that on stock solution vial shield. The syringe shield is also similarly colour coded which provides a three-step, colour matching system (stock vial, syringe and syringe shield) and effectively helps in preventing any misadministration to the patient as the pharmacist delivering the dose has to check the preparation thrice for its colour.

18. **Transport requirements:** The label of radiopharmaceutical product must contain mandatory information related to the national transport regulations for radioactive products. Radiopharmaceuticals are transported in Type A package. For this, the permitted activity A1 in the special form and that for A2 in other than special form from AERB should be referenced. Here, A1 designates the maximum activity which can be transported in Type A package when the material is in the special form. A2, on the other hand, designates the maximum activity which can be transported in Type A package when the material is not in the special form. Reference to TREM card must also be stated on the label of the radiopharmaceuticals. TREM stands for 'Transport Emergency Cards' which are carried by workers during the transfer of radioactive material. It contains detailed information about radio-active compound being transported and instructions to the driver or emergency responders in case of any incident. In addition to it, placards are also available which can be placed on outer containers, trucks or other vehicles used for the transport of materials.

B. Requirements for Packet Insert

Packet Insert (PI), also called Prescribing information, is another indispensable regulatory requirement for all RPs and contains a summary of essential scientific data for their safe and effective use. PI is approved by the national regulatory authority of the country in which it is to be marketed. It is primarily meant for a health care provider and contains the necessary scientific and practical information about the administration and better use of a product, although a part of it is also dedicated to the patient. It is an important information tool for the prescriber and aids to thoroughly educate the patients about all aspects concerning the use and associated risks of the drug. It can be used as a standard of care and contains potential legal weight. It must be accurate and commensurate to the ongoing scientific information on all aspects of important clinical findings and adverse effect on the use of RPs.

PI contents and the Indian scenario: PI is on intense importance for developing countries like India where access to the latest medical findings is not possible owing to the lack of suitable number of practitioners. The contents and headings of packet insert are enlisted in section 6 of **Schedule D** (II) of Drug and Cosmetic Act 1940, and rules framed there under and are grouped into two sections - **Section 6.2** which relates to the importance of clinical use of drug and **Section 6.3** detailing the pharmaceutical information. However, it is not commensurate to the international level, thereby necessitating a need to reexamine the set of limited information to be supplied in a PI. Table 2 provides a comparative account of requirements for packet inserts and provides recommendations for its further improvement. Those in normal case are the requirements as per Drugs and Cosmetics Rules 1945 while the one indicated in italics are the recommendations which must be included in addition to the existing requirements. On the basis of the above study, a detailed comprehensive draft guideline is proposed on various important sections of packet insert as described below:

1. **Simple/Boxed Warning:** This is one of the most important and critical aspects of a packet insert and must give a concise summary of clinically significant adverse reaction, warning and risk on the use of the radiopharmaceutical. It should preferably be in a bullet form so that necessary information is clearly visible and understandable. It is usually intended to highlight prescribers regarding any serious adverse reaction and its frequency while using the radiopharmaceuticals.
2. **Batch number**: Same as that mentioned on the label.
3. **Name of the medicinal product:** This section should include the name of the radiopharmaceutical product. Any proprietary or company names should be avoided.
4. **Qualitative and quantitative composition**: This section must focus on the detailed composition of radiopharmaceuticals product in terms of qualitative and quantitative aspect. It should include the physical half-life of all the radionuclide present and the necessary details about important nuclear physical characteristics like energies of the principal particle and the photon emissions, in addition to other physical or chemical information. However, this information is not required for

radiopharmaceuticals available in the kit form as the radionuclide is not a part of the kit at the time of preparation. Therefore, the composition part of any kit should be better reflected in dosimetry.

5. **Indications**: In simple terms, 'indication' means the reason to use a certain medicine. As radiopharmaceuticals can be used for both diagnostic and therapeutic purpose, it is important to specify this in the indication section of packet insert including limitations of its use, if any.
6. **Posology and method of administration**: Posology, in simple terms, means dosage. For radiopharmaceuticals, different dosage pattern exists depending upon the population subset. Dosage relates to the amount of activity range expressed in MBq. The dosimetry should be stated both for the patient receiving the radiopharmaceuticals as well as the staff administering it. All radiopharmaceutical preparations should have dose based on a patient of an average weight of 70 kg. However, the pediatric population require dose adjustment which can be referenced from bodies specialized in radiation protection and dosimetry. Consideration also needs to be given to patients having kidney and liver impairment. Appropriate direction must also be given regarding the method of administration depending upon the type of radiopharmaceuticals. For example, kits for radiopharmaceuticals should have the direction for reconstitution before use along with necessary precautions to be observed while handling or administering the preparation. Also, for radiopharmaceuticals used for diagnostic purpose, the delay between administration and imaging should be clearly written to better aid the practitioner for better image quality.
7. **Pharmaceutical form**: Radiopharmaceuticals are available in different pharmaceuticals forms. Therefore, all products should be specified as per their type. For products available in kit form, the pharmaceutical form of the final product should appear in heading under 'Instructions for Preparation of Radiopharmaceuticals'.
8. **Contraindications**: Contraindication, in simple terms, means a condition/factor to withhold a certain medical treatment due to the harm that it could cause the patient, i.e., information about 'who should not take this product'. The presence of a radiation-emitting radionuclide in the radiopharmaceuticals product, or an excipient, can cause a hypersensitivity reaction to the patient. If such a condition is established in the form of an already available report, this section of prescribing information should bear reference to it and describe the type and nature of the reactions that have been reported. However, if no such situation exists for the radiopharmaceuticals, this should be written 'none'.
9. **Precautions for use**: The inherently hazardous nature of radiopharmaceuticals along with the varied type of population on which it is used mandates utmost precaution for their preparation and use by nuclear medicine practitioners, pharmacist, health personnel and patients. This section of packet insert must contain a warning regarding the receipt, storage and use of any radiopharmaceuticals only by the personnel who are well trained and qualified on all aspects of radiation safety and aseptic procedures. More importantly, this section of prescribing information should include a concise summary of clinically most significant safety concerns while using the radiopharmaceuticals, the recommendation for monitoring the patient during/after use and the nature and severity of risk involved in their use or any other safety measures that can be taken to prevent or mitigate harm.
   For patients with the renal problem, the impaired physiological excretion of radiopharmaceutical can predispose the patient to extended exposure. Therefore, radiation exposure must be justifiable by the likely benefit. The packet insert must contain directions for patients to drink a lot of water immediately after administration as this helps in fast physiological excretion of radionuclide from the body. Radiopharmaceuticals available in kits form must have clearly written precaution for undergoing a preparative procedure prior to use. Most importantly, all packet inserts must have as low as reasonably achievable (ALARA) statement for its use and the ways to achieve it.
10. **Interaction/Adverse reaction**: Various drug interactions may occur on the use of radiopharmaceuticals which may have a profound effect on the diagnostic accuracy or even the therapeutic outcome of a procedure. Interaction of a radiopharmaceutical can occur with other prescription, over-the-counter drugs and even with food and show a clinically significant effect on the subject. All such sort of interactions, including the instructions for their prevention or management should be present in this section. It is suggested to include only the generic name of the interacting substance. If possible, the mechanism of interaction must be described briefly.
    All adverse reactions, including the criteria used to determine their inclusion, should also be reported in this section. They should be presented in a tabulated form in decreasing order of frequency. Adverse reactions should be categorized according to the organ system and frequency as this can greatly assist in locating relevant clinical information. Special emphasis should be given to serious adverse effects if any.
11. **Use in a specific population (Fertility, pregnancy and lactation)**: Extra care should be observed while administering the radiopharmaceutical to women of childbearing age, ongoing pregnancy or

breastfeeding. This is because the use of radiopharmaceuticals for this class of population can result in unnecessary exposure to the radiation. Although there are some radiopharmaceuticals which can be used in pregnancy, it is suggested to use them only in indispensable cases when the likelihood of the benefit far exceeds the associated risk to the mother and foetus. Adequate information about whether or not any sort of radioactivity will be excreted into breast milk should be appropriately addressed. If any such excretion is reported for a certain radiopharmaceutical, it is best to stop breastfeeding until zero excretion is observed.

12. **Drug abuse and dependence**: This section of prescribing information must contain information regarding the susceptible group of patients for which any sort of abuse and the associated adverse effects can occur on the use of the drug. Additionally, it should also contain the data regarding dependence, if any, on its use, and the quantity of drug triggering such dependence.
13. **Overdose**: All radiopharmaceuticals are administered by well trained and experienced nuclear medicine specialists and any change of overdose is highly improbable. Nevertheless, the packet insert should contain sufficient information regarding the various sign, symptom, and other clinically significant laboratory findings and complications associated with the drug overdose. More importantly, it must contain details about micturition, defecation, or forced diuresis technique for dealing with such overdose, if any.
14. **Pharmacodynamic properties**: This section should include details about the mechanism of action of the radiopharmaceutical at the activity concentration used and the associated biochemical or physiological effect of radiopharmaceuticals or their breakdown product. This section should also contain details of the amount of exposure from the recommended dose used, particularly for therapeutic radiopharmaceuticals. However, diagnostic radiopharmaceuticals at low concentration do not have a significant pharmacodynamic effect which should be clearly mentioned.
15. **Pharmacokinetic properties**: Each radiopharmaceutical has a specific tissue uptake and distribution pattern, clearance behaviour and biological half-life. Therefore, this section should give detailed information on all such aspect including its major metabolic pathway for elimination, biological half-life and effective half-life. This section must also contain information regarding the bioavailability, minimum concentration (Cmin), maximum concentration (Cmax), time to attain the maximum concentration (Tmax), area under curve (AUC) and the volume of distribution (Vd).
16. **Preclinical safety data**: Sufficient data on the toxicological studies of radiopharmaceutical using mice/rats or other animal models should be presented to justify its use on humans. This should include data on safety pharmacology, mutagenesis, repeated dose toxicity, genotoxicity studies, carcinogenic potential, and reproduction and developmental toxicity at the recommended dose. Such conclusions, which are based on the animal data and are necessary for safe and effective use of the drug in humans, must be identified as such and must be included with human data.
17. **Route of administration**: Radiopharmaceuticals can be administered by different route depending upon their type. It can be intravenous, oral, both oral and intravenous, intraperitoneal, intracisternal, inhalational, ocular, interstitial, intra-articular or even intracavitary. Therefore, prescribing information should clearly contain this information.
18. **Effects on the ability to use machines and drive**: Depending upon the type of radiopharmaceuticals, no effect, negligible effect, minor or major effect can be observed on their usage. All such concern should be appropriately addressed in this section.
19. **Undesirable effects**: The administration of a radiopharmaceutical to a patient can cause a significant effect on the genetic level depending upon the dosage and type of radiopharmaceuticals used. Therefore, their packet insert should include such concern giving the frequency of effects and sufficient details about exposure to ionising radiation along with its potential for the development of disorders at the hereditary level.
20. **Incompatibilities**: Radiopharmaceutical can show a high degree of incompatibility if not used with the approved excipient. This is particularly seen for radiopharmaceuticals available as kits which have to be reconstituted before final administration. Therefore, an indication regarding the product not to be mixed with other medicinal products must be specified.
21. **Shelf life/Expiry date**: Radiopharmaceuticals have varied shelf life depending upon its type and the radionuclide present in it. For example, shelf life as packaged for sale, shelf life after dilution or reconstitution according to the direction (as in kit). Therefore, this section should give adequate information about all such aspects of the product.
22. **Special precautions for storage**: The presence of radiation-emitting radionuclide in radiopharmaceuticals mandates special shielding requirements during their storage which depends upon the type of radiopharmaceutical and the amount of radioactivity.

23. **Container nature and contents and special equipment for use, administration or implantation**: Radiopharmaceuticals are available in both single-dose and multiple-dose form. Therefore, it is important to specify this in the prescribing information accompanying the radiopharmaceuticals.
24. **Precautions for handling and disposal**: The administration of radiopharmaceutical is accompanied by a simultaneous problem concerning waste disposal, both from the patient and the product itself. This is because the use of radiopharmaceuticals on patients at certain doses can predispose the accompanying caregivers to radiation exposure and the associated complications from contamination. Therefore, this section must include precautions for relatives, caregivers and the accompanying hospital staff regarding precaution to be observed from vomiting or other excreta from the patient. Kits are nonradioactive before extemporary preparation. But once reconstituted with a radionuclide, adequate direction for their shielding must be mentioned.
25. **Marketing authorization holder and its number**: All the necessary correspondence and communication details consisting of name and address, telephone number, fax and the Email ID of marketing authorization holder must be included in this section.
26. **Date of first authorization/renewal of the authorization**: Marketing authorization given to a product should be renewed on a regular basis, the details of which should be included in this section along with the date of first authorization/approval.
27. **Recent major changes/ Revision date of text**: The ongoing scientific and technical progress including evidence related to any new indications and dosage, strengthening a warning, a successful clinical trial program, adverse effect reports from post-marketing studies from manufacturer or physicians, clinical efficacy and safety, or any other form of interaction of radiopharmaceuticals necessitates an update to the contents of prescribing information. Therefore, in the light of any new approval or changes to the approved labelling, this section of prescribing information should contain all major changes and revise the text accordingly to prevent the labelling to become inaccurate, false, or even misleading.
28. **Direction for use/Instruction for preparation of pharmaceutical**: Radiopharmaceuticals are available in many forms including ready-to-use preparation or as kits. They may require certain manipulation before final administration to the patient which can be as simple as mixing of an eluate of a generator containing the radionuclide with the contents of kits or a complex multistep procedure of radiolabelling followed by adequate quality control testing. These tests help to ascertain the strength of final preparation or at least give a visual confirmation of the quality of the reconstituted parenteral solution. All such requirements should be clearly mentioned in this section of the prescribing information.
29. **References**: There are many authoritative scientific bodies and organizations present whose work can be referenced for further detailed information regarding a particular topic. For example the recommendations regarding dose adjustment for the pediatric population. As such information is critical to proper use of a product, the prescribing information must contain a reference to such details at the appropriate places.
30. **Patient counselling information statement/Information for the patient**: This section of prescribing information is exclusively meant for the patient and helps them to use the drug in a safe and effective manner. It should consist of detailed information as presented below:
    - Name of the product and its use
    - Information before using the product
    - Direction regarding the procedure to use it
    - Possible side effects on its use
    - Storage requirements and contents of the pack

RESULT AND DISCUSSION

The name of radiopharmaceutical must be followed by a statement regarding its use, either for diagnostic or for therapeutic purpose. It must also state information to the patient regarding the possible exposure to radiation and an assurance that the clinical benefit on the use of product far outweighs the associated risk of exposure to the radiations. The use of radiopharmaceuticals may be unsuitable for a special class of population like pregnant women, break feeding mothers or even to patients who are allergic to one or other ingredient of the preparation of the radiopharmaceutical. Moreover, the dose requirements for pediatric population are far less than those required for adults, thus necessitating dose adjustments. Drug interactions may occur with radiopharmaceuticals if the patient is already on some other medication. More importantly, the inherently hazardous nature of radiation necessitates their removal from the body as soon as possible after study which is possible only if the patients are directed to drink plenty of water during the first few hours after administration. Therefore, this section should give plenty of such above-

mentioned instruction to the patient before using the product. Radiopharmaceuticals are administered to the patients by well-trained and qualified nuclear medicine specialists or technologists. This section should give ample assurance to patients that such products shall be used by specialists and at a minimum dose recommended as per the patient requirements. Also important is to specify the duration of the procedure and necessary precautions for avoiding contact with pregnant women and young children who are most susceptible to radiation. Side effects on the use of radiopharmaceuticals should be added in this section along with a statement that the given radiopharmaceutical shall deliver a low amount of radiation to the patient which have the least risk of cancer or any other hereditary abnormalities. Lastly, the storage of radiopharmaceuticals is done in a shielded environment to prevent any harm from radiation emanating from them. Although, compliance with storage requirements is solely the responsibility of hospital staff, yet the patients must know such information to enable better safety culture.

Fig. 1: Significance and the goals of Labeling.

TABLE 1: A DETAILED ACCOUNT OF REQUIREMENTS FOR LABELS IN INDIA

Contents of Label
Approved name of the product
Composition and Volume/Weight
Dosage form
Name and address of the manufacturer/authorization holder
Authorization number
DIN
Total Radioactivity
Sterility and apyrogenicity
Excipient
Route of administration
Directions for use
Storage conditions/precautions
Batch number
Manufacturing date
Expiry date
Caution/Warning
Precaution for disposal
Barcoding
Transport requirements

TABLE 2: A DETAILED ACCOUNT OF REQUIREMENTS FOR PACKET INSERT IN INDIA

Contents of Packet Insert
Simple/Boxed Warning

Batch number
Name of the medicinal product
Qualitative and Quantitative Composition
Indications
Posology and method of administration
Pharmaceutical form
Contraindications
Precautions for use
Interaction/Adverse reaction
Use in a specific population (Fertility, pregnancy and lactation)
Drug abuse and dependence
Overdose
Pharmacodynamic properties
Pharmacokinetic properties
Preclinical safety data
Route of administration
Effects on the ability to use machines and drive
Undesirable effects
Incompatibilities
Shelf life/Expiry date
Special precautions for storage
Container nature and contents and special equipment for use, administration or implantation
Precautions for handling and disposal
Marketing Authorization holder and its number
Date of first approval/ authorization and its renewal
Recent major changes/ Revision date of the text
Direction for use/Instruction for preparation of pharmaceutical
References
Patient counselling information statement/Information for the patient

CONCLUSION

The inclusion of radiopharmaceuticals in Schedule K of Drug and Cosmetic Act, 1940 and rules framed thereunder and the risk associated with the exemptions provided for their preparation and sale by anyone under this schedule can tremendously predispose the patients to potential health hazards. The requirements set out in the proposed guidelines for their labelling and packet insert, at par with pharmaceuticals, shall provide for a better and learned intermediary between manufacturer, prescriber and patient, and also helps in overcoming other associated risks. While the label helps in preventing the risk of prescribing and dispensing error and management of multiple medicines, the information mentioned in the packet insert is of intense importance for the medical practitioner and patient. A comprehensive and harmonized PI is of intense importance for developing countries like India due to lack of access to the latest information and an inadequate doctor-patient ratio. Therefore, compliance with the proposed guidelines and its regular monitoring for effective implementation is imperative so that access to the latest information on this latest scientific modality is accessible to all users and other stakeholders.

CONFLICT OF INTEREST

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