

The WFNMB Survey on the Introduction of New Radiopharmaceuticals for Clinical Research: Snapshot of the International Perspective

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Abstract:

Development of new radiopharmaceuticals and their introduction into clinical trials ensures continuing improvement in the practice of nuclear medicine. Although it is crucial that safety and efficacy are established prior to use in humans, the characteristics of radiopharmaceuticals are quite different from other drugs since these agents are generally administered in trace, sub-pharmacological amounts. Diagnostic and therapeutic radiopharmaceutical agents are used only in restricted and controlled areas and are administered only by trained personnel. In many cases - as often for PET - such diagnostic agents are often used in the same institution where they are prepared. Thus, regulations for the preparation and use of radiopharmaceuticals should be different from other drugs. To evaluate the current status of radiopharmaceutical regulations, we surveyed radiopharmaceutical experts and nuclear medicine societies on an international basis. A questionnaire was provided which focused on the regulations required for the in-house non-commercial preparation of new radiopharmaceutical for routine clinical use or for use in clinical trials. Responses were received from participants in 36 countries. Although both government and institutional approval are required for introduction of new radiopharmaceuticals in the majority of countries, some countries require only institutional approval. In the case of therapeutic radiopharmaceuticals, as may be expected, only physician responsibility is more often required compared with similar approval for use of diagnostic agent in these settings. The requirement of current Good Manufacturing Practice (cGMP) for PET

agents was higher than with the other agents. This preponderance of cGMP requirements may be interpreted as much higher than may be expected, since many PET radiopharmaceuticals are used in-house and are prepared in the hospital by pharmaceutical compounding and not by manufacturing. Compounding is not regulated by cGMP requirements, which encompass specific regulations for manufacturing. Radiopharmaceuticals can often be regarded as safe because the administration dose is well below any expected toxic threshold. Thus, application of these regulations developed for general therapeutic drugs to radiopharmaceuticals is often over-regulation, which is expected to seriously affect the cost-effectiveness of radiopharmaceutical development and nuclear medicine practice.

Keywords: Radiopharmaceutical, Regulation, cGMP, Approval, Compounding, PET

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Introduction

Because the clinical benefits are often not available with complementary technologies, the development and clinical use of radiopharmaceuticals is increasing with new developments in the field of nuclear medicine. However, commercialization of radiopharmaceuticals is a time-consuming and expensive process, which lags far behind the development of promising new agents. Because of their unique characteristics, many radiopharmaceuticals can be prepared in-house or in a centralized radiopharmacy instead of by traditional central manufacturing.

The preparation of radiopharmaceuticals "in-house" or in the radiopharmacy should be defined as "compounding," which should be performed under physician prescription or order for a specified patient (1,2). The necessity of in-house radiopharmaceutical compounding increased sharply, especially after increasing use of position emission tomography (PET).

On the other hand, preparation of radiopharmaceuticals for public distribution - especially to community hospitals where in-house compounding is not possible - is required either by a registered manufacturer - which is a

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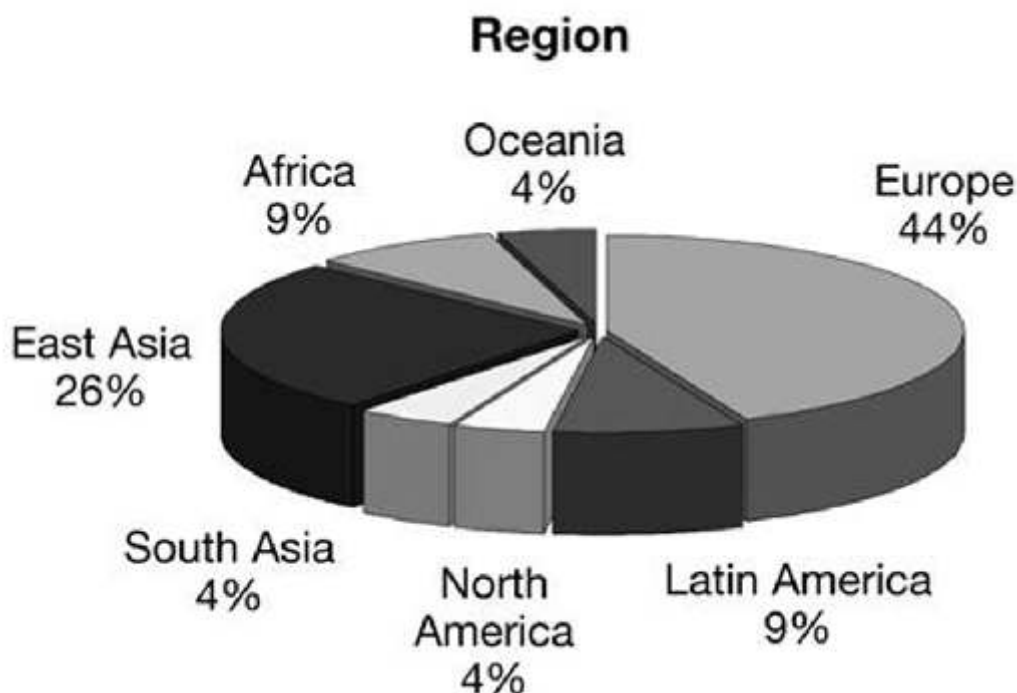


Figure 1. Distribution of respondents by region

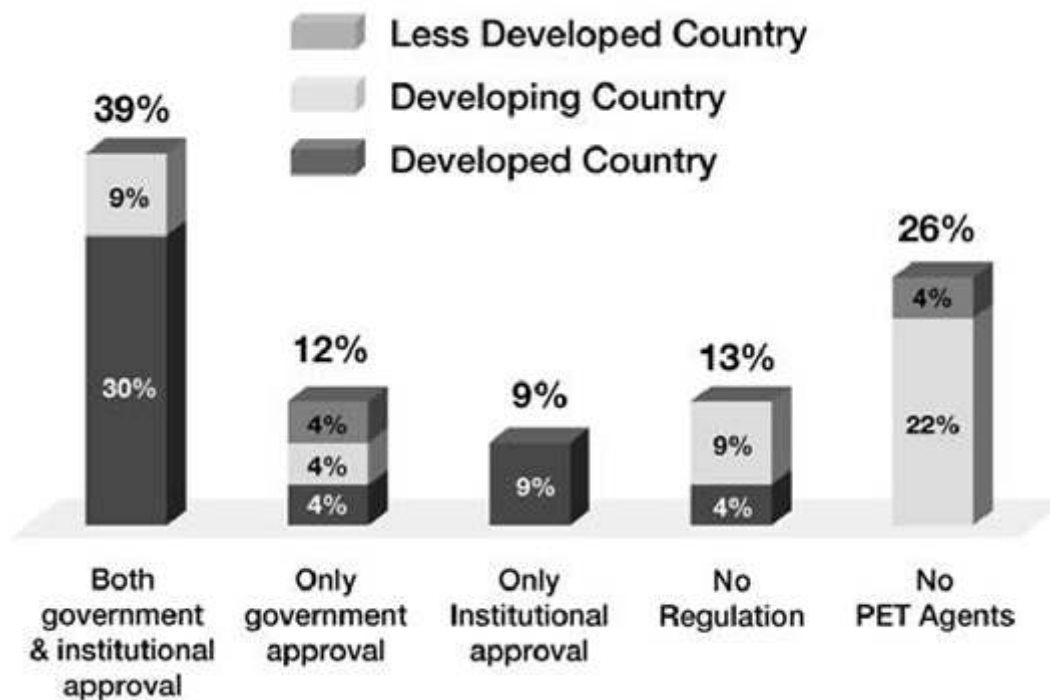


Figure 2. Regulations applying for in-house non-commercial clinical use of radiopharmaceuticals – New PET agents.

“manufacturing” process – or by compounding at a registered central radiopharmacy. For manufacturing, the registered manufacturer is liable for the safety of the preparation and must of course obtain regulatory approval for each radiopharmaceutical, following current Good Manufacturing Practice (cGMP) procedures (1, 3). In association with the World Federation of Nuclear

Medicine and Biology, we conducted an international survey to obtain an overview of the current status of requirements for introducing in-house non-commercially prepared new radiopharmaceuticals into clinical research or clinical applications. This paper is a brief summary of the analysis of these data.

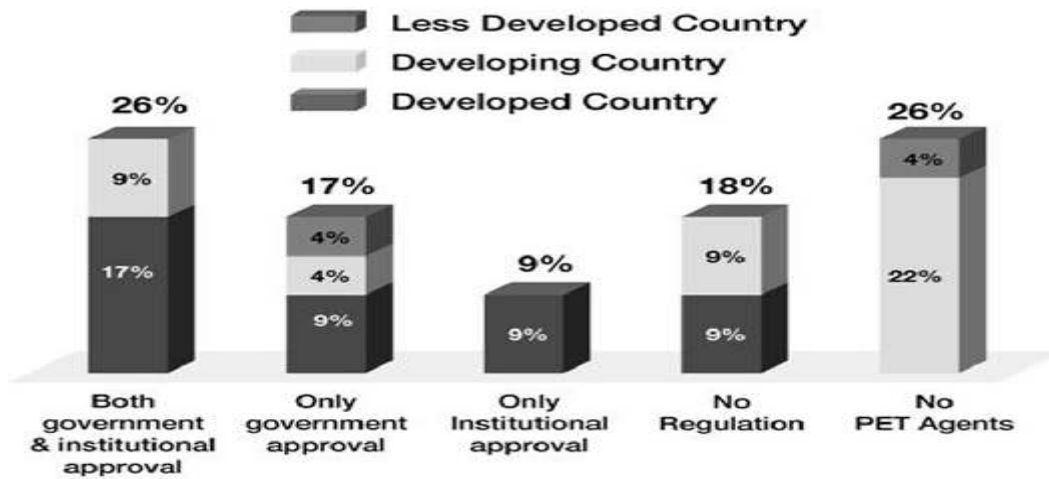


Figure 3. Regulations applying for in-house non-commercial clinical use of radiopharmaceuticals – PET agents listed in national pharmacopeia but which cannot be obtained from a manufacturer.

Methods

A survey questionnaire was prepared which requested information on local/regional current regulations for in-house preparation and clinical use of non-commercial radiopharmaceuticals. The questions were grouped into PET agents, non-PET imaging agents and therapeutic agents. The questionnaire was provided on an international basis to 76 national nuclear medicine societies and 240 selected experts, and the responses collected over a 6-month period via facsimile or e-mail. The pooled answer sheets from 36 countries were cross-tabulated according to the Gross National Income (GNI) per capita and analyzed using a Microsoft Excel program.

Results and Discussion

From the distribution of respondents, the European respondents had the highest response rate of 44% (Figure 1). Although both government and institutional approval is required for clinical use of new PET agents in 39% of the countries, this level decreases to 26% for the PET agents listed in the national pharmacopeia. The tendency is more distinct in developed countries than in developing and less developed countries (Figures 2 and 3).

In the case of non-PET imaging agents, although a higher percentage of countries are required to obtain both government and institutional approval for clinical application of both new agents (56%) and the agents listed in the national pharmacopeia (43%), the same tendencies with the PET agents were found. Thus, both government

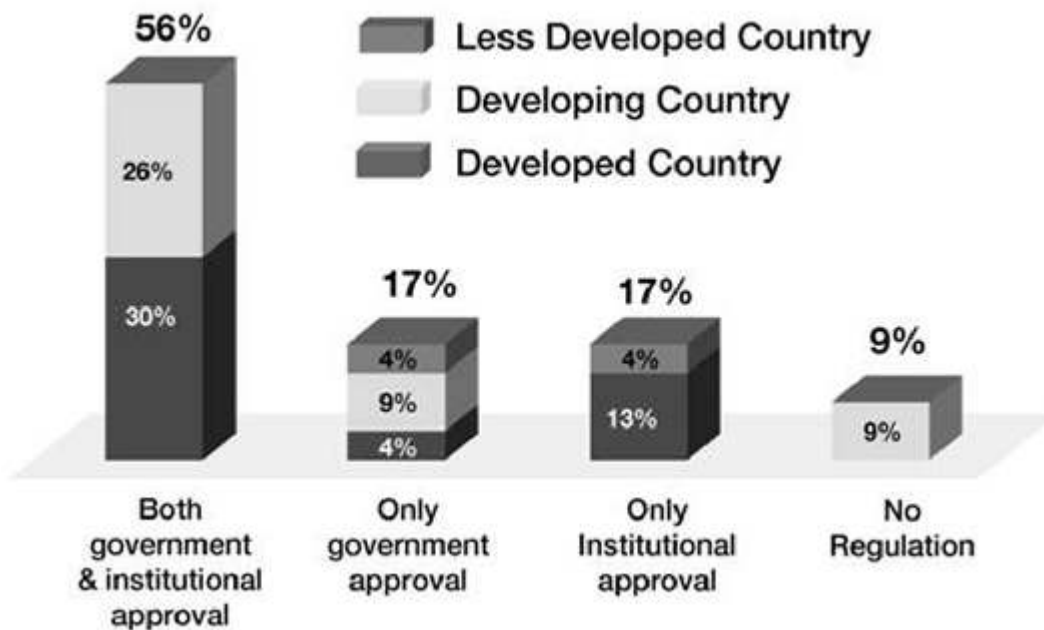


Figure 4. Regulations applying for in-house non-commercial clinical use of radiopharmaceuticals – New non-PET imaging agents.

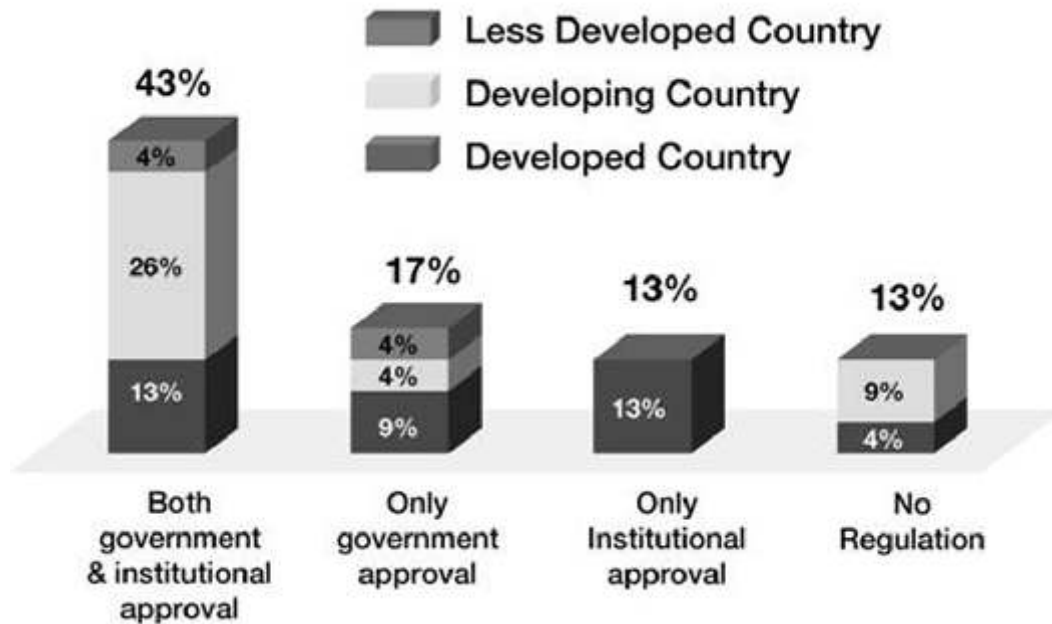


Figure 5. Regulations applying for in-house non-commercial clinical use of radiopharmaceuticals – Non-PET imaging agents listed in national pharmacopeia but which cannot be obtained from a manufacturer.

and institutional approval are required in a lower percentage of countries with the agents listed in the respective national pharmacopeia, and the tendency is more distinct in developed countries than in developing and less developed countries (Figures 4 and 5).

The cGMP requirements for in-house non-commercial preparations of radiopharmaceuticals for PET agents and non-PET imaging agents were 43% and 42%, respectively. However, at least 38% and 48% of the countries do not require cGMP for preparation of PET and non-PET imaging agents, respectively (Figures 6 and 7).

For production of high quality safe radiopharmaceuticals, application of cGMP regulations would be adequate. However, radiopharmaceuticals often have several different features from ordinary drugs. Thus, the regulation

of radiopharmaceuticals should be different from other agents.

The cGMP regulation should be applied for manufacturing of drugs for public supply. However, if the cGMP regulations are applied for in-house non-commercial production of radiopharmaceuticals, this will require unattainable funding and resources and represent over-regulation, and would act as an obstacle for the progress of Nuclear Medicine.

If the benefit from the investment for cGMP is higher than the projected cost, then implementation of such programs should be encouraged. However, if the cost for implementation of a cGMP system would be significantly higher than any expected benefit, it would seem that the GMP regulation should be discouraged.

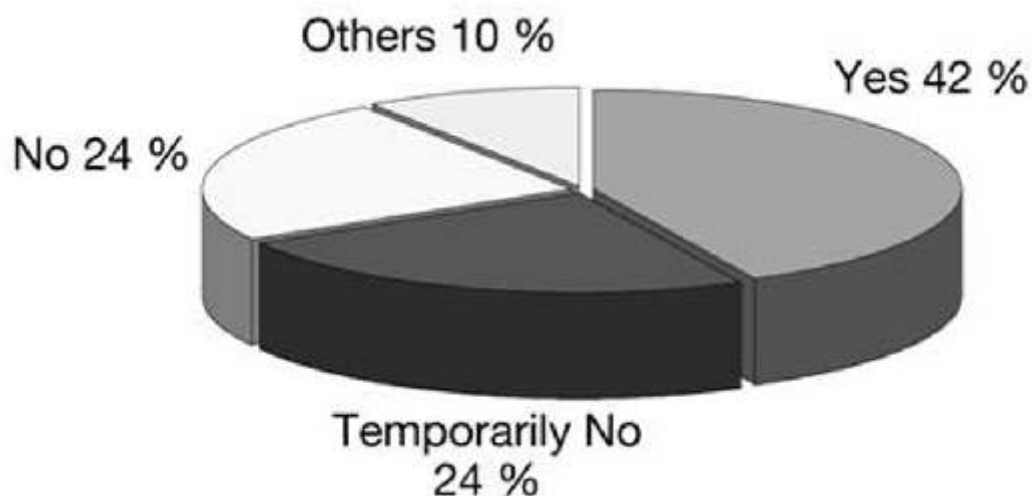


Figure 6. Requirement of cGMP for in-house non-commercial preparation of radiopharmaceuticals – PET agents

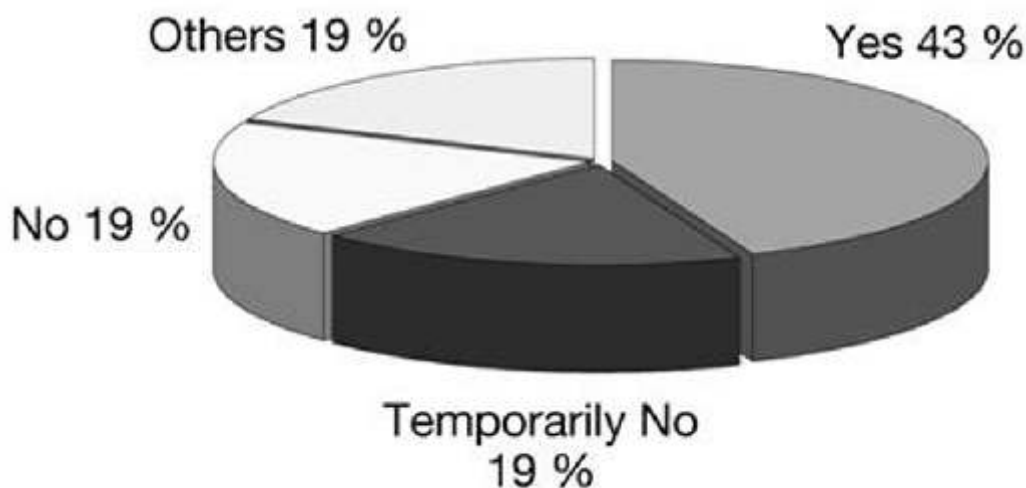


Figure 7. Requirement of cGMP for in-house non-commercial preparation of radiopharmaceuticals – Non-PET imaging agents.

Radiopharmaceuticals are generally administered in minute amounts and are used only in restricted and controlled areas. Highly trained personnel are required for their administration and the radiopharmaceuticals are often used in the same place where they are prepared and compounded. Since the radiopharmaceutical market is so much smaller than the general drug market, the issues for preparation and use of these agents are different and these differences should be incorporated into the regulatory processes. Thus, the factors should be considered seriously for cost-benefit evaluation of the regulation of radiopharmaceuticals.

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