Abstract. After a brief historical introduction to Council Directives relating to the manufacture of radiopharmaceuticals, the work of the Association of Radiopharmaceuticals Producers - Europe (ARPE) is discussed. ARPE has played a significant role as an officially recognized interlocutor with the EEC, influencing decisions on the registration of radiopharmaceuticals and labeling; this role is reviewed and difficulties identified. The future of radiopharmaceuticals is then considered; it is emphasized that harmonization of national laws by the European Council would represent a first step to enabling radiopharmaceutical manufacturers to access the largest possible market for their products.

Key words: Radiopharmaceutical industry - European Union - Association of Radiopharmaceuticals Producers - Europe - ARPE - Council Directives

Registration

Effect of registration

The various EEC rules which regulate the field of radiopharmaceuticals are published in the form of Directives and Decisions. To date there have been 33 Council Directives, one Council Decision and one Council Regulation. In order to clarify these, numerous guidelines have been published:

- 11 Quality Guidelines
- 10 Biotechnology Guidelines
- 7 Pharmacotoxicology Guidelines
- 10 Clinical Guidelines (General)
- 12 Clinical Guidelines (Therapeutics)
- 3 Information on Medicinal Products

With only a few exceptions (such as Directives on vaccines, serums and allergens, or Guidelines on quality of herbal remedies), these documents must be taken into consideration by manufacturers when they are preparing files for the registration of radiopharmaceuticals. The most important documents for radiopharmaceuticals are listed below.

Principal council directives

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Occasional survey

The radiopharmaceutical industry and European Union regulations

C.J. Fallais, S. Sivewright, J.R. Ogle
Association of Radiopharmaceuticals Producers – Europe, Rue de la Pepiniere 1/2, B-1000 Brussels, Belgium

Historical introduction

With regard to European Union (EU) regulations, the key dates for the manufacturers of radiopharmaceuticals have been:


Directive 87/22/EEC was studied, proposed and published without any contact or any form of consultation with the radiopharmaceutical industry. When the radiopharmaceutical manufacturers discovered the various constraints this Directive imposed on their products which had been developed in the preceding 5 years in the high tech and biotech fields, they decided to create an official association which would be officially recognized as an interlocutor by the EEC, and which could therefore receive information direct and have the right to discuss and comment on the new proposed regulations.

By the time Directive 89/343 was published, the Association of Radiopharmaceuticals Producers – Europe (ARPE) had been formed and had become an official correspondent of the Commission’s DGIII.
RegistFation of existing Radiopharmaceuticals

ing available data or published literature as appropriate. Parts III and IV and the draft Summary of Product Char-

This would be followed (by 30 April 1992) by applica-
tions from each producer containing Administrative (Part I), Labelling (Part V) and Chemistry and Pharmacy (Part II) support information for each individual product. The abridged aspect of the applications would concern Parts III and IV and the draft Summary of Product Characteristics (SPC) of each listed type of product, where ARPE would present (by 30 June 1992) a single file of administrative, pharmacological/toxicological and clinical support using available data or published literature as appropriate. The assessment would be shared between the competent authorities of member states. Arising out of the review would be generic SPCs which, after adoption and publi-
cation by the top EC pharmaceutical committee (CPMP), would be used by manufacturers as the basis for individual product pack leaflets. Following this, individual national marketing authorizations could be granted to each manufacturer on successful completion of the review of their Administrative (Part I), Chemistry/Phar-

macy (Part II) and Labelling (Part V) files.

The proposal was endorsed and published by CPMP in September 1991. After detailed consultations between regulators and industry, the involvement of EANM members as collaborators in the generation of expert pharmacological/toxicological/clinical reviews was agreed and taken forward in a seminar organised by ARPE, and held in November 1991 in Brussels, with EEC, national experts and EANM experts.

The CPMP accepted to examine all documents in one language, English.

During this Coordinated Abridged Procedure, ARPE has been involved in (a) discussions concerning the technical content of the files, Part III and Part IV, and (b) the translation of the approved SPCs into all the EU languages (now including Swedish and Finnish). In total, 62 files and 62 SPCs have been prepared, discussed or commented on and finally approved by the CPMP.

Unfortunately, it now appears that the institution of the European Medicines Evaluation Agency (EMEA) in London has thrown a spanner in the works of this collabor-

ation as ARPE seems to have disappeared from the mailing list and has not received any official documents since the EMEA came into being.

The EU Directives provide a minimal framework of legislation, and national authorities are free to add their own requests for additional information.

Labelling

Radioactive radiopharmaceuticals are fully manufac-
tured, tested and dispatched to all EU member states (and others) in single batches, several times each week. Kits are similarly dispatched during a short marketing period relative to their individual shelf life, and the larg-
est batches to be produced consist of only a few thousand vials and kits.

The radiopharmaceutical industry was strongly of the opinion that to insist on the introduction of user-lan-
guage labelling for all elements of product labelling (vi-
al labels, shield labels, tin can labels, etc.): (a) would in-
troduce complexity and the opportunity for errors, (b) would place further cost penalties on an industry in which batch production is of necessity small and (c) failed to recognize the very high level of professionalism of the users (nuclear medicine physicians), who have ac-
cepted single-language labels for more than 30 years.

As several national authorities maintained their insistence on the use of national language(s), ARPE lost this battle and the manufacturers are now in the process of reconsidering the labelling of products in order to satisfy these authorities, but at the price of an increase in production costs which this inevitably implies.

Some other examples of national requirements which inevitably lead to delays in registration and considerable additional costs to the industry, are listed below:

1. Spain requires the translation into Spanish of the expert reports for all products to be registered, and this de-
spite the fact that the Spanish representative in the CPMP approved the SPCs based on this English document.

2. Several countries now require a Patient Information Leaflet with simplified language which can be read...