The radiopharmaceutical industry and European Union regulations

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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 labelling; 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

Eur J Nucl Med (1997) 24:77–79

Historical introduction

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

1. 22 December 1986 – Council Directive 87/22/EEC: Approximation of National Measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology.
2. 3 May 1989 – Council Directive 89/343/EEC: Extending the scope of Directives 65/65 EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals.

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.

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

65/65	First General Regulation	26/01/65
75/319	Second General Regulation	20/05/75
75/318	Analytical and Pharmacotoxicological clinical standards	20/05/75
87/22	High Tech – Biotech	22/12/86
93/41	High Tech – Biotech	30/04/92
89/343	Radiopharmaceuticals	03/05/89
92/27	Labelling	30/04/92

Commission directives

90/18	GLP	13/01/90
91/356	GMP	17/07/91

Council regulations

297/95	Fees – EMEA	15/02/94

Principal guidelines

MAB (murine)	June 1987
Analytical Validation	July 1989
MAB (human)	July 1993
Radiopharmaceuticals	December 1990
Radiopharmaceuticals based on monoclonal antibodies	May 1991

ARPE's activities

Registration of existing radiopharmaceuticals

A proposal was developed for a Coordinated Abridged Procedure which involved abridged applications for a restricted list of products whose use was well established and which were already on the market in several EEC countries. From the list proposed by the radiopharmaceutical manufacturers, 63 radiopharmaceuticals were accepted by the CPMP.

According to this procedure, individual producers would (by 31 December 1991) notify individual member states and the EEC of their product licensing intentions. This would be followed (by 30 April 1992) by applications 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 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 publication 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/Pharmacy (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 collaboration 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 manufactured, 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 largest 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-language labelling for all elements of product labelling (vial labels, shield labels, tin can labels, etc.): (a) would introduce 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 accepted 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 despite 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

and understood by the patient, even though radiopharmaceuticals (whether radioactive or not) are *never* intended to be delivered to the patient for self-administration. The presentation and specific wording of this document differs for the various authorities. ARPE wrote to these authorities requesting that, although the nature of radiopharmaceuticals precludes the necessity for this type of document, they would nevertheless agree to accept a single uniform model for all countries in the national language. This point was first raised in May 1995 and some authorities insist that these Patient Information Leaflets be finished before the end of September.

3. More recently, France has requested that, for the existing radiopharmaceuticals, a special "*Note d'intérêt therapeutique*" be answered by way of a "transparency file". This contains chapters like: drug characteristics, therapeutic interest, packaging and medico-economic evaluation.

Future of radiopharmaceuticals

The radiopharmaceutical industry is faced with several important threats which have a direct effect on the future of nuclear medicine.

Licensing – orphan drugs

It is clear that the ratio between the expenses before marketing and the expected sales of a new radiopharmaceutical is very high. It would be advantageous if radiopharmaceutical dossiers could be given special consideration, taking into account this restricted use and the limited numbers of patients who will be treated with any given radiopharmaceutical, so that the delay before licensing could be shortened. Certain epidemiological considerations, for example, are not relevant to radiopharmaceuticals, which do not have the wide distribution of other pharmaceuticals. Equally, the strict viral requirements for biotechnological products are not adapted to radiopharmaceuticals based on monoclonal antibodies.

ARPE hopes that the Commission and the Council will be considering an Orphan Drug Directive in the near future, and that it will be involved in the discussion of these matters from the outset. Several existing radiopharmaceuticals, and a number of future radiopharmaceuticals are clear candidates for orphan drug status.

Radiopharmaceutical practice

The preparation of the final radioactive compound, the preparation of the dose to be administered and its administration to the patient all take place in the department of nuclear medicine. It would benefit all parties if there was a uniformity of legal requirements within the European Union which would ensure the quality and efficiency both of the administered product and of the medical procedure. It should also be recognized that the nuclear medicine practitioner is correctly informed and properly skilled to assume the double responsibility of radiopharmacy and nuclear medicine. Should it be decided that the responsibility for the preparation and the dispensing of the final radiopharmaceutical must rest with a radiopharmacist, then his role must be clearly defined and his ability must be recognized by the institution of a structured study programme so that this would constitute a real and recognized speciality.

Radiopharmaceuticals based on positron emitters

This particular group of radiopharmaceuticals is produced and directly administered to patients within special units, generally called medical cyclotrons; only a few positron emitters allow the production and dispatch by manufacturers to several users within a radius of 50–100 km. A special medical status should be accorded to these special institutions and, here again, the double responsibility, pharmaceutical and medical, must be clearly defined.

It is possible to have the preparation of pharmaceuticals recognized as an official activity at the stage of the publication of the monographs through the channel of the European Pharmacopoeia.

Once again, it is essential that we unify European attitudes to these questions if we are ever to achieve true technical, scientific and medical unity in Europe.

Conclusion

Each day, the newspapers report that the pharmaceutical industry is faced with takeover bids involving several giant manufacturers. During the first 2 decades of its existence, nuclear medicine was promoted and developed through the collaboration between medical researchers and chemists, physicists and pharmacists working in national nuclear plants. From 1970 on, private companies became an active partner for nuclear medicine, and a number of important mergers have since reduced the number of manufacturers who are active in the field. Today, only large radiopharmaceutical manufacturers or smaller specialized producers are still present on the market. Their survival, however, depends on the goodwill of their chosen partner, nuclear medicine. It also depends on the socio-economic conditions and on the existence of radioiosotope-producing reactors. And finally, although the economic importance of the field of radiopharmaceuticals is very limited in comparison to pharmaceuticals, the very existence of radiopharmaceutical manufacturers depends on their ability to access the largest possible market for their products. The harmonization of national laws by the Council is the first step towards achieving this access. The next step must be the ironing out of all national differences in order to arrive at a truly single law within the European Union.