European Medicines Agency

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Report to the European Commission on the Supply Shortage of Radiopharmaceuticals (Status as of 24 October 2008)

I. INTRODUCTION

The European Medicines Agency (EMEA) was made aware in the evening of 29 August 2008 by a Rapid Alert issued by the Dutch Authorities (Dutch Health Care Inspectorate) of potential shortages of radiopharmaceuticals due to the temporary shut down of the High Flux Reactor (HFR) in Petten by the Nuclear Authority in the Netherlands. The HFR in Petten seems to be responsible for the production of about 60% of all radioisotopes used as part of radiopharmaceutical medicinal products in Europe and about one third of the world supply.

After the annual shut down for maintenance in August, the reactor could not start up because there were "gas bubbles" seen in the cooling system, which could not be explained. The Nuclear Research and consultancy Group (NRG), the company operating the HFR in Petten, investigated the issue and informed the public that they would not produce any medical isotopes for a number of months. According to the latest information published on the NRG website, this would be the case until mid February 2009.

There are four other reactors worldwide used in the production of medical radioisotopes. These are located in Belgium, France, South Africa and Canada. The reactors in Belgium and in France were undergoing planned maintenance, when the HFR in Petten stopped its production, leading to a shortage of supply of some radioisotopes.

In the letters sent by the European Commission (DG ENTR) on 12 September 2008 to the Executive Director of the EMEA and to the Chair of the Heads of Medicines Agencies (HMA) Management Group, the EMEA was requested, in close collaboration with the European Commission and HMA, to (1) analyse the situation, (2) develop potential approaches to address any problems, and (3) develop a communication strategy.

II. ANALYSIS OF SUPPLY SHORTAGE IN THE EU AND ACTIONS TAKEN

2.1. Centrally Authorised Radiopharmaceutical Products

Further to the Rapid Alert issued by the Dutch Authorities, the EMEA had initial contacts with all Marketing Authorisation Holders (MAHs) of centrally authorised/processed radiopharmaceutical medicinal products. There are currently 7 approved centrally authorised products (ZEVALIN, NEOSPECT, QUADRAMET, YTRACIS, YTTRIGA, DATSCAN and LEUKOSCAN).

These radiopharmaceutical products either contain a radioisotope (QUADRAMET, YTRACIS, YTTRIGA and DATSCAN) or are kits to be radio-labelled with a radioisotope prior to their use (ZEVALIN, NEOSPECT and LEUKOSCAN).

The EMEA liaised with the concerned companies and Rapporteurs to assess whether the shut-down of the HFR in Petten had an impact on the supply or use of these products.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Three products (Leukoscan, Neospect and Quadramet) were potentially impacted by the reactors' closures. Considering that diagnostic/therapeutic alternatives were available, the Committee for Medicinal Products for Human Use (CHMP) concluded during its September 2008 meeting that this did not raise any public health concern and that taking into account the available information no further actions were necessary for these products.

2.2. Mo-99/Tc-99m generators

Generators are devices, containing a relatively long-lived 'parent' radioisotopes adsorbed on a stationary phase that can be supplied to Nuclear Medicine departments where they are used to produce a short-lived radioisotope for radiolabelling. The most commonly used radiopharmaceuticals for diagnosis are labelled with the radioisotope Technetium-99m (Tc-99m), which is obtained by elution of a Molybdenum-99/Technetium-99m generator.

Nuclear reactors are used to irradiate uranium and this process results in fission (decomposition) of uranium in about 200 different radioisotopes, one of which is Mo-99. The irradiated uranium then needs to be purified, in order to extract the Mo-99. In Europe, this extraction can be done only at 2 facilities, namely by IRE in Fleurus (Belgium) and by Mallinckrodt Medical/Covidien (also located in Petten). However, IRE was out of operation at the time further to inspection-related issues.

The supply of Mo-99/Tc-99m generators was affected by the shut-down of the reactor in Petten that occurred during the planned maintenance of the other 2 European reactors (BR2 in Mol, Belgium and OSIRIS in Saclay, France). According to information from Member States, the supply was on average reduced to 50 % of the normal supply. This was considered manageable by Member States by prioritising more urgent clinical procedures at the hospital level.

However, the EMEA and the European Commission were informed on 16 September 2008 by the European Association of Nuclear Medicine (EANM) that the reactor in South Africa would also go on scheduled maintenance on 28 September 2008. The EANM considered that as of that date, unless urgent measures were undertaken, the shortage would become critical.

The OSIRIS reactor (in Saclay, France), was scheduled to re-open after maintenance on 18 September 2008. The uranium targets irradiated in the OSIRIS reactor are purified and extracted by IRE (in Fleurus, Belgium). These targets have a different form and geometry and are transported in different containers than the targets of Covidien which are normally irradiated in the reactor of Petten or in the reactor of Mol (Belgium).

The EMEA was informed by the EANM that a short-term solution had been designed in which Mallinckrodt Medical/Covidien in Petten would perform the extraction of Mo-99 from the uranium targets irradiated in Saclay. For that purpose, Mallinckrodt Medical/Covidien had to modify its normal procedures in order to handle in a safe and correct way these targets that are normally purified at IRE. Authorisation from Regulatory Authorities to amend the European Drug Master File (EDMF) of Mo-99 held by Mallinckrodt Medical/Covidien would be required as well as the relevant security and transport authorisations for these uranium targets.

According to the EANM, such alternative would enable the supply of Mo-99/Tc-99m generators to reach a level of 70-80% of normal supply.

An urgent teleconference with representatives of the European Commission (DG ENTR), Member States and the CMD(h) chair was organised by the EMEA on 18 September 2008. During this teleconference, an *ad hoc* procedure to change national licences was proposed by the EMEA and was agreed upon, as no other legislative tools to address this issue in a short timeframe were available. It was agreed that the UK and Denmark would act as Rapporteur and perform the scientific assessment on behalf of all the other Regulatory Authorities.
The *ad hoc* procedure focused on the application of the already established concept of work sharing with respect to the scientific assessment, hence making best use within the EU Regulatory System Network of the available resources and avoiding duplication of work, whilst guaranteeing that all

Member States involved had the possibility to review and comment upon the scientific assessment done.

The EMEA contacted the Member States on 18 September 2008 to obtain the list of Marketing Authorisations of Mo-99/Tc-99m generators in the EU. Based on information provided by the Member States on 19 September 2008, the EMEA contacted the 3 identified MAHs (Mallinckrodt Medical/Covidien, GE Healthcare and Cis Bio International) to offer them the possibility to submit supportive data through this *ad hoc* procedure. This proposal was acknowledged and welcomed by these MAHs. A fourth MAH was also contacted but did not acknowledge receipt of the EMEA's proposal.

In order to implement this proposal, minor changes to the manufacturing process of the active substance sodium molybdate (Mo-99) described in the restricted part of the EDMF held by Mallinckrodt Medical/Covidien would be required (through the submission of appropriate variation applications).

The supportive data and applications were submitted by the 3 MAHs to the UK and Denmark on 22 September 2008. The Rapporteurs' Joint Assessment Reports were circulated to all CMD(h) members on 24 September 2008. Three Member States commented on these Assessment Reports, stating that they agreed with the conclusions from the Rapporteur countries. The scientific assessment was completed at CMD(h) level on 25 September 2008. The implementation of the positive outcome of the review was to be done at national level (through corresponding type IB variations). As of 24 October 2008, most Member States had already benefited from this *ad hoc* procedure, for at least one authorised generator.

In parallel, the EMEA and the European Commission were informed on 24 September 2008 that the Dutch nuclear safety authorities had granted their approval on 23 September 2008, for the processing on the nuclear site of Petten, of the uranium targets irradiated in the OSIRIS reactor in Saclay, France. Furthermore, DG SANCO informed the EMEA on 2 October 2008 that the transport of uranium targets between the OSIRIS reactors and Petten already had started and the purification was ongoing in Petten.

Further, the EMEA identified 6 Member States (Czech Republic, Estonia, Finland, Lithuania, Poland and Sweden) that might benefit from this *ad hoc* procedure for generators from other companies than the 3 main MAHs identified. The EMEA subsequently enquired with these Member States whether this *ad hoc* procedure should be applied also to those other products. Following communication with the concerned Member States, it became apparent that the need for a "2nd wave" *ad hoc* procedure to be applied to other products authorised was not considered necessary by any of those 6 Member States.

Based on the currently available information (as per 24 October 2008), i.e. the overall analysis of the supply situation of Mo-99/Tc-99m generators in the EU, on the current status of nuclear reactors for production of radioisotopes and on the alternative manufacturing process facilitated by the *ad hoc* procedure, it can be stated that the situation seems to be under control, and that no further action is necessary in the short-term.

2.3. All other radiopharmaceuticals

In order to analyse the overall situation, the EMEA contacted the Member States on 15 September 2008 requesting information on all non-centrally authorised radiopharmaceuticals, including feedback on the status of their supply.

Overall, it can be concluded on the basis of the information available that there are no serious problems of supply shortage of these other radiopharmaceuticals, as alternative sources or alternative diagnostics/treatments are available.

III. FIRST REFLECTION ON MEDIUM AND LONGER TERM ASPECTS

In order to address the request from the European Commission to further elaborate on the strategy to address the supply shortage of radiopharmaceuticals (including longer term aspects) a **Task Force** was set-up. This Task Force on supply shortage of radiopharmaceuticals comprises representatives of the European Commission, HMA and EMEA. The first meeting of this Task Force was held at the EMEA on 2 October 2008.

The remits for this Task Force were agreed as follows:

- On the short-term, to analyse the progress made for solving the supply issue;
- To look into the long-term situation in case such an issue would happen again and also to consider the situation in 5 to 6 years when several reactors are likely to have been shut-down.

The Task Force agreed with the EMEA's short-term analysis on the supply of radiopharmaceuticals and the conclusions as outlined above, and discussed medium and longer term aspects.

RECOMMENDATIONS:

As regards the procedural aspects for amending national licences, it was recommended that in the future a more transparent way to appoint CMD(h) Rapporteurs in such urgent situations would seem advisable. It was also agreed that although the current legislative tools do not seem to be the most suitable for this kind of situation, there is the possibility to adjust the available regulatory procedures on a case-by-case basis (as it has been demonstrated through this *ad hoc* procedure). The Task Force considered this *ad hoc* procedure an example of successful collaboration within the EU Regulatory System Network that enabled prompt action for a large number of national licences.

Regarding the **medium-term** aspects, the following was recommended:

- A "lessons learnt" from this exercise should be drafted;
- A better coordination of scheduled maintenance of reactors should be encouraged;
- Uranium targets used in the different reactors in the EU should be standardised.

Regarding the **longer term** aspects, the following recommendations were made:

- <u>Future capacity of production</u>

The reactors currently used in the EU and worldwide for the production of radioisotopes are old and by 2015, most of them will have to permanently close down. Other reactors currently used for research purposes could be "upgraded" in the future to be used also for production of radioisotopes. Thus, there seems to be a need to make an inventory of the reactors and their production capabilities as well as the current and future need of radiopharmaceuticals in the EU.

- <u>Exploring possibilities for alternatives to radiopharmaceuticals</u>

The CHMP during its preliminary discussions was of the view that consideration should be given to alternative diagnostic/therapeutic procedures (including those currently available as well as new emerging options) to better understand the place of radiopharmaceuticals in clinical practice in the EU in the longer term.

It is recommended that all stakeholders (nuclear physicians (e.g. EANM), industry (e.g. Association of Imaging Producers & Equipment Suppliers (AIPES)), other clinicians (e.g. radiologists specialised in techniques such as MRI, CT and PET scan) are involved in such a discussion. If such recommendation is agreed upon, the EMEA proposes to make best use of the available scientific expertise in the EU by consulting the CHMP Scientific Advisory Group on Diagnostics, reinforced with additional experts e.g. from the former radiopharmaceuticals *ad hoc* group.

The Task Force could continue to be involved in such longer term aspects as per its agreed remit.

IV. COMMUNICATION STRATEGY

A public statement was issued on the EMEA website on Wednesday 1 October (see http://www.emea.europa.eu/pdfs/human/press/pus/50169808en.pdf). The "Report to the European Commission on the Supply Shortage of Radiopharmaceuticals" will be made public after consideration by the European Commission's Services.