TRANSPORT OF RADIOPHARMACEUTICALS, CRADLE TO THE PATIENT.

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ABSTRACT

This presentation looks at the constraints and challenges of moving Radiopharmaceuticals, from the raw material to the end customer, the patient.
Most Radiopharmaceuticals tend to be short half-life nuclides used to diagnose or treat disease.
This paper will concentrate on the nuclide molybdenum-99 with the daughter product technetium-99m and Iodine-123
Technetium-99m is mixed with inactive (cold) material, to prepare a radiopharmaceutical and injected into the patient, depending on the cold material; the radioactive material will concentrate in the organ(s) to be evaluated. After scanning the patient, the doctor can then make a diagnosis.
Iodine-123 is a diagnostic agent used for the detection of tumors and other diseases.
Many millions of scans across the globe are performed in a nuclear medicine department by administering a radiopharmaceutical to the patient.
Through the supply and manufacturing chain for Molybdenum-99, from reactor to manufacturer, (including the chemical process to produce sterile material) and then from the manufacturer to the end user has to be well choreographed. Any delays in any of the logistics routes cause a loss due to decay of Molybdenum99. Molybdenum has a half-life of 66 hours and delay of one day means ~ 22% loss of material and therefore subsequent doses for use with the patient. In contrast Iodine-123 has a half-life of 13.2 hours, the process of making the raw material using a cyclotron, processing and transporting must happen on the same day. Any delay invariably means that the product will not be able to be used. To add to the challenges of the product being radioactive, it also has to meet the strict requirements of intravenously injectable drugs (GMP).
Delays have an impact on the Healthcare system, not just monetary for the manufacturer but also the cost to Healthcare system for re-scheduling, loss of scanner time and of course the discomfort to the patient.

INTRODUCTION

Radiopharmaceuticals in Nuclear Medicine are mostly used for diagnosis and to a lesser extent for radiotherapy. Diagnostic radiopharmaceuticals for in vivo imaging emit suitable gamma photons. Radiopharmaceuticals for positron emission tomography (PET) are labeled with a positron emitting radionuclide.

The radionuclide in diagnostic radiopharmaceuticals has preferentially a short half-life, ranging from seconds to a maximum of a few days. In this way the radiation dose to the patient is kept to an acceptable or even a minimum level without compromising the diagnostic usefulness. On the other

hand, however, the short half-life creates a challenge with respect to on-time availability of the radiopharmaceuticals labeled with such radionuclides. In view of the continuous decay of radionuclides and the relatively short shelf-life of this kind of radiopharmaceutical preparations, scheduling of the different types of radioisotope investigations for numerous patients has to be done with high accuracy. Serious deviations from the planned scheme are not possible. The challenge and pressure for a timely availability of the required radiopharmaceuticals lies both on the shoulders of the staff of the nuclear medicine department as well as of the manufacturer and thus also of the transporters of the radiolabelled tracers or radionuclides.

Depending on the half-life of the radionuclide in these radiotracers, preparation and transport have to be done immediately (e.g. for fluorine-18 labeled fluorodeoxyglucose (FDG) with a 109 minute half-life) or within a period of 24 h. In many cases, this means a race against time. In view of the specific and high medical need for these preparations and the strict scheduling of patients, the responsibility and pressure on the manufacturer and the transport company is very high. This means on one hand that for these products the production process has to be optimally designed in order to guarantee the maximal probability of a timely and efficient radio-synthesis of the radioactive product that also meets the predetermined pharmaceutical quality requirements. On the other hand transport companies need a perfect day and night organization to assure a timely delivery of these short-lived preparations to the many nuclear medicine departments worldwide.

Every year, more than 35 million examinations and treatments with radiopharmaceuticals are performed, 20m in the USA and around 9m in Europe. About 30 million examinations are using Technetium-99M (Tc-99m) which presents unique useful medical and radiological characteristics.

IMPACT ON NON-DELIVERY

From a cost/value point of view radiopharmaceuticals cannot be compared to “normal” products. A normal product passes from the manufacturer to the customer. Its value during the supply chain process remains constant. This does not apply to short-lived radiopharmaceuticals. Because these products have a very short lifespan due to their radioactive characteristics they often lose all value within a few hours. The product is therefore only 'completed' once it has reached the customer at the right time, in the right quantity, with the right quality.
For a hospital and the patient involved the impact of a non or late delivery is considerable.

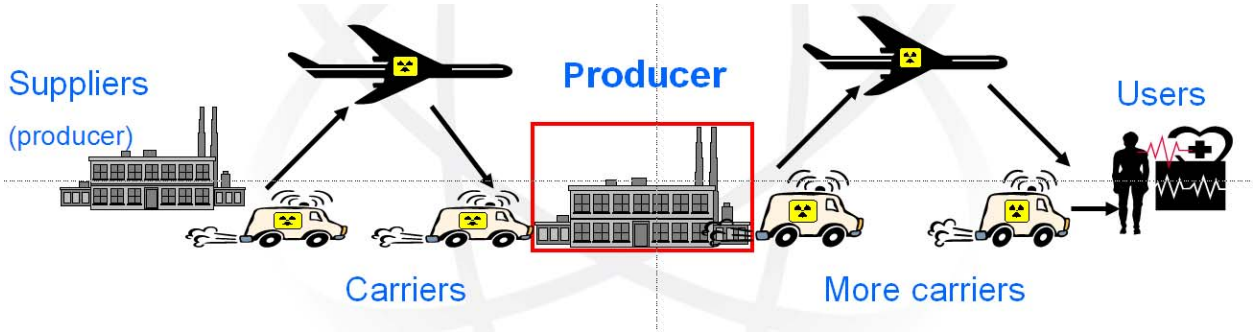
Following costs are made that cannot be recovered:

- In case of remote patients (not living close to a hospital with a nuclear medicine department), there are costs of transport to the hospital (train, flight, taxi) plus daily allowance, ranging from 40€ to 400€ per person. Medical insurance sometimes also pays for a patient companion, a family member.
- Cost for use of the gamma camera. If the radiopharmaceutical; does not arrive in time then the gamma camera will not be used and therefore loses the opportunity to diagnose the patient. The cost for a private customer (what they will invoice per test) is around 600€ per brain SPECT, 900€ for a Parkinsons diagnostics scan.

- If a shielded room is booked for a patient receiving an I131 treatment that is not performed then it is left empty and the hospital will not be making revenue for that.
- There are also intangible costs in terms of damage caused to the patients for stopping their medication or for the opposite, some have to be given a medication prior to the treatment/diagnose.
- In the case of patients that are employed, there is also an implication of losing one day of work, plus the certification that the hospital has to issue to the patient to justify to their employer the reason to have to come back for the diagnose on a later day.
- In some cases the urgently needed treatment is delayed because of inability of diagnosing the patient. This can have an effect on the prognosis of the patient.

LOGISTICS CHALLENGES

The logistics of organizing delivery is rather complicated, as we have customers all over the world. Some of the shorter living isotopes can only be supplied in a certain region or pole. For instance, I-123 products with a half-life of 13,2 hours produced in Europe are 99% supplied in Europe. Due to the short available time-span between production and administration to the patient, a max 36 hours for an extended dose, it is impossible to cover longer distances outside Europe.
But even within Europe there can be problems. It is possible to supply a hospital in Athens with a I123 product but it may be impossible to supply to the rest of Greece. This will depend on the inland logistics being available at the correct time to enable delivery of the product in time to the hospital.



<u>Availability of Airfreight:</u>
There are several capacity and availability constraints on using airfreight:
Airlines not taking Class 7 dangerous goods

- For instance, airlines like KLM and BA no longer transport any radioactive goods. Furthermore they also do not handle radioactive goods for the airlines that do take radioactive material but use their handling facilities.

Limited T.I. capacity on flights

- Some flights have capacity for T.I up to 3.0. Which means only a limited amount of material can be shipped.

Limited airline schedules

- For some destinations flight options are very limited with possible time consuming transfers.

Reliability

Even if all the requirements are fulfilled and products arrive in time at the airport there are still several things that can go wrong with a product that has a "MUST GO as booked" status.

- Booking process
  - Multiple parties are involved in the complex booking process. Errors can be made, good communication is essential.
    - Manufacturer →Booking Agent → Global Sales Agent →Airline
  - TI capacity on aircrafts is not always known and if known can still change due to change in aircraft.
    - Several (competing) producers can book on the same flight with limited TI capacity. Airlines make the choice who to reject.
- Physical transport
  - From producer to end-user the products are sometimes handled by 6 or more different companies. All of them have to do the right job in the limited time-frame.
    - Manufacturer →Carrier → ground handler → airport Cargo agent →airline →airport Cargo agent →carrier → CUSTOMER
      This increases the likelihood of making errors or having delays.
- Other issues have an impact on the reliability of the shipment:
  - Technical problems, missing paperwork, weather issues, volcano ash clouds, security clampdowns, strikes of airport staff or air traffic control.
- Denial of shipments
  - An additional problem is that individual pilots sometimes refuse to take radiopharmaceutical cargo along once they see the cargo is Class 7. This can either be triggered because of a lack of knowledge or misinterpretation of the IATA regulations, or simply fear for radioactive products, i.e. a lack of knowledge about what radioactivity actually is and what it can be used for. Many people are not aware of the fact that radioactive pharmaceuticals exist and have a high impact on patient treatment and welfare.
- Awareness of the nature of the product
  - Lack of awareness can cause problems at acceptance and can even be more difficult in case of transfers

Yet, in spite of all these problems, there is a growing number of customers.

The overall distribution reliability, despite all the challenges, is between 98 and 99%
Though this may seem very good compared to other businesses; of every 1000 patients 10 to 20 will not be treaded or diagnosed in time.

All the above explains why distribution of radiopharmaceuticals is a very challenging process. After all, we have to deal with two sets of regulations: regulations that apply to medicines and regulations that apply to radioactive substances. The regulations on transport of medicines are particularly strict (Good manufacturing Practice GMP and Good Distribution Practice GDP). Also the transport of radioactive materials, in turn, has to comply with the regulations on transport of dangerous substances (ADR for road and IATA for air), plus any other country restrictions for the transport of radioactive material.

Keeping all this in mind, we often have to be more catholic than the pope to have our products delivered to their destinations in time. Even if only one of our permits should not be in order, such as a permit relating to the Transport of Dangerous Substances Act, we may find ourselves with a ban on transport. It may come as no surprise that the distribution of our products forms a considerable amount of the costs involved in the process. On average this is 20 percent of the sales value of the product.

CONCLUSIONS

The radiopharmaceutical business is a model just in time business, due to the nature of the process of diagnosis and treatment of diseases, orders can be received on the day of manufacture and dispatch for delivery and administration the next day. The supply chain from manufacture to the end customer, the patient has to be very robust. It is very dynamic compared to the transport of other nuclear material were the paperwork and transport can take months or sometimes years to organize.

The radiopharmaceutical industry is complying with all relevant regulations (transport, pharmaceutical and license conditions). We would like to make the public and regulators aware that additional (national and international) requirements related to transport of RAM may have a negative effect on transport of radiopharmaceuticals. This is especially so now that an era of new to be built nuclear reactors is on the horizon, there is always a problem of looking at only one part of the industry that then effects detrimentally the other part. We as AIPES are worried that the increase in regulations and fees can be too burdensome for small dedicated specialized carriers and they will come out of the transport of RAM which leads to denial of shipment.
The other effect can be that if you overregulate the RAM transport in comparison with other DG, the public perception that Class 7 material is far more dangerous than other classes might further increase the fear. This is in reality unfounded in view of the excellent safety record.
The industry must work with the regulators to educate both the transport industry and the public in the positive use of radioactive material.
The regulators must ensure that the safety of supply of radiopharmaceuticals is secured by not over regulating both international and national regulations in an already very safe industry.

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