History and rationale behind NCI filing NDA for sodium fluoride F18

On 12/31/2008, the NCI filed a 505(b)(2)NDA for a new strength of the discontinued drug, Sodium Fluoride F18 for injection, that had not been discontinued for reasons of safety or efficacy in order to facilitate the filing of ANDAs by any interested parties to address a recurring public health issue caused by the frequent shortages of the only approved agent for bone scanning.

Background: Sodium Fluoride F18 is a USP drug that had an NDA approved in 1972 that was withdrawn in 1975 for market reasons when a less expensive alternative became available. It can be used for bone scans with positron emission tomography (PET) to diagnose skeletal metastases from primary cancers elsewhere, a serious issue for many cancers, particularly breast and prostate, as well as some non-malignant skeletal conditions, such as fractures, arthritis, Paget's disease of bone, or infection of the joints, joint replacements or bone. There is a single approved drug that can be used and reimbursed for bone scanning, Technetium Tc 99m Medronate (Tc-99m MDP). The 2008 IMV Nuclear Medicine Market summary reports that in 2007 2.6 million bone scans were performed, the vast majority of them with Tc-MDP. However, in the last five years there have been extended widespread shortages of the radiopharmaceutical because of serious problems with the few aging nuclear reactors that manufacture the precursor isotope and these outages are expected to continue for several more years, discussed later. If patients cannot obtain bone scans, appropriate treatment for their metastatic cancer may be delayed or they may be treated with systemic therapies in the absence of definitive diagnosis, which can lead to unnecessary side effects and inappropriate expense.

Sodium Fluoride F18 has a physical half-life of 110 minutes, which means that doses must be produced on the day of use in close proximity to the patient being scanned. Therefore, multiple decentralized sites of manufacture are required.

The clinical problem: Bone metastasis is one of the most frequent causes of pain in people with cancer. When a cancer spreads to the bone, it can make the bones weaker and lead to fractures. As the cancer cells damage the bones, calcium is released. This can lead to problems from high blood calcium levels. Bone metastasis also causes other problems that can limit a patient's ability to continue usual activities and lifestyle. Certain cancers are more likely to spread to bone. These are breast, prostate, lung, thyroid, and kidney cancers. In people with breast and prostate cancer, the bone is most often the first distant site where the cancer will spread. One expert estimated that about 350,000 people in the United States who die of cancer each year have bone metastases. (Data from the American Cancer Society Website http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Are_the_Key_Statistics_on_Bone_Metastasis.asp?sitearea.)

As a result, many patients with these common cancers are screened for bone metastases, at initial presentation in a substantial fraction of the patients to assist in selecting the most appropriate therapy, and later, either as a periodic surveillance strategy or when suspicious

symptoms, such as persistent bone or joint pain, occur. Both breast and prostate cancers, for example, are now frequently diagnosed at an early stage and patients live many years with risk of metastatic disease. In 2005, approximately 2.5 million women had a history of breast cancer (http://seer.cancer.gov/statfacts/html/breast.html) and approximately 2.1 million men had a history of prostate cancer (http://seer.cancer.gov/statfacts/html/prost.html). From those two cancers alone almost 5 million people in the US are at risk for bone metastases, with only a single approved imaging agent available to provide non-invasive diagnostic information.

The Supply Problem: Major shortages of Tc-99m because of shortages of Mo-99 have occurred with increasing frequency and duration in the last few years. A shortage of Mo-99 that lasts more than a week or two leads to immediate market shortages and impact on the ability of clinicians to obtain medical scans that use this agent. Rationing of diagnostic imaging follows, with the radiopharmaceutical available only to the most urgent cases until the supply is exhausted.

Background: Technetium- 99m (Tc-99m) is a decay product of molybdenum-99 (Mo-99) that is widely used in diagnostic imaging; in 2007, there were more than 18 M injections of Tc-99m radiopharmaceuticals, approximately 80% for cardiac indications and 20% for bone imaging. Mo-99 is made by U-235 fission, mostly in highly enriched uranium nuclear reactors. The Mo-99 (half-life 66 hours) is purified and packed into "generators" that are shipped approximately twice a week to radiopharmacies and used to prepare Tc-99m (half-life 6 hours) radiopharmaceuticals. The Mo-99 obviously cannot be stockpiled because of its short half-life. With such a tight time requirement, any interruption in the routine operations of any of these reactors will lead to supply shortages of the medical isotope in a matter of days.

Five foreign commercial reactors produce 95% of the world supply:

- NRU at Chalk River in Canada (1957),
- HFR at Petten in the Netherlands (1961),
- BR-2 in Belgium (1963),
- OSIRIS at Saclay in France (1966) and
- SAFARI-1 at Pelindaba in South Africa (1965).

These reactors are near or past their expected useful life and the now-frequent shut-downs are evidence of that. There is no US domestic source of Mo-99, despite multiple efforts over the last few decades to develop a domestic supply plan. Of the foreign sources, just two produce 85% of the world's supply (Chalk River and Petten). Chalk River supplies most of the US Mo-99.

The FDA has recently approved more reactors, but the capacity of these is relatively small

- OPAL (Open Pool Australian Light Water reactor) 7/2009
- IAE POLATOM'S Maria Research Reactor 3/2010

February 2010 to September 2010: The high flux reactor at Petten in the Netherlands was shut down for planned repairs to its cooling system.

May 2009 to August 2010: Chalk River reactor was shut down May 14, 2009 after a power outage. Subsequently, a heavy water leak was detected and the reactor could not be restarted until repairs were completed. Atomic Energy of Canada has estimated that repairs would take at least three months, but the independent engineers suggested that the repairs could take a year or more were correct. Another extended outage is scheduled for spring 2011

August 2008 to February 2009: The high flux reactor at Petten (opened 1961) in the Netherlands was shut down unexpectedly for repairs to its cooling system at the same time Chalk River, OSIRIS and BR-2 were off-line. Petten was reopened in February, without actually making the repairs because all European reactors that produced Mo-99 were off-line again and the EU requested that a way be found to restart it. Additional monitoring was put in place, but the repairs needed to be made at some point, necessitating an extended shut down in 2010.

November 2007 to December 2007: Chalk River was shut for routine maintenance and the AECL would not permit it to reopen, pending installation of a backup system. The Canadian Parliament passed an emergency law directing that the reactor be reopened (and the agency head was fired). The maintenance violation that the AECL was reacting to has not been corrected yet. The repairs will need to be made at some point, necessitating shut down for extended period of time.

Minor Shortages occur constantly. We were provided a confidential listing from 2008 from a major radiopharmacy operation with around 150 locations in the US. Fifty-three shortages are listed, most for all locations. Delivery delays of several hours were common, as were activity shortages. After the Petten reactor was shut down, they received mostly 20-50% of need through the rest of the year.

Medical Impact. In 2007, IMV reported that approximately 15.7 M cardiac perfusion injections (8.5M visits) used Tc-99m and approximately 2.6 M bone scans were performed with Tc-99m. Cardiac scans can be also be performed with Tl-201 or Rb-82 (PET), but currently the only approved bone scan agent is Tc-99 MDP. Failure of Tc supply can cause 50,000 bone scans a week to be delayed or denied.

NaF F18 can be used for bone scans – it is more expensive than Tc-99m, but has been reported by multiple investigators to be superior in detection of bone lesions. At this point in time, it is legal to use it under USP manufacturing standards, like all USP PET radiopharmaceuticals, until 2 years after the FDA issued special cGMP regulations for PET radiopharmaceuticals on Dec 12, 2009. That deadline is now set at December 12, 2011. However, it is not reimbursed or reimbursed either as a generic PET procedure or the same as an MDP scan. Since it is not promoted, it is not widely known that it is available and from what sources. Several clinical trials are currently planned or underway that would provide appropriate data to support reimbursement. In February 2011, it will be added to the National Oncologic PET Registry (NOPR) that will permit reimbursement with evidence development.
http://www.cancerpetregistry.org/