Questions/Answers Regarding Sodium Fluoride F18

1. Who was the PI/Company that submitted the project?

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.

2. What group (*e.g.*, DDG, JDC, RAID, *etc.*) did the application come through?

This was an NCI initiated activity.

3. Why did they request NCI involvement (i.e. what critical role(s) did NCI play in moving the agent forward that the PI/company wasn't able to do themselves)?

Sodium Fluoride F18 is a USP drug that had an NDA approved in 1972 that was withdrawn in 1975 for market reasons when a less expensive alternative became available.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. 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. 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.

This NDA could not be filed by any of the commercial radiopharmaceutical firms since there is no patent protection and no exclusivity by official rule made in 2000. It would therefore not be economically feasible. However, once an NDA is approved, we will immediately permit all interested parties to file ANDAs as a generic drug, which have no fees

4. What was believed to be the therapeutic target or MOA of the agent at the time the project was taken on by DCTD? If not known, please indicate. If the target or MOA was identified at a later date, when and by whom (DCTD, PI, others)?

Sodium fluoride has the longest retention time in the bone, making it useful for performing bone scans. Deposition of ^{18}F-fluoride in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the 18F-fluoride from the blood perfusing the bone. 18F-NaF uptake and retention in bone depends on the area of the "exposed" bone surface, which is larger in a variety of benign and malignant bone disorders. The relationship between osteoblastic and osteoclastic activity determines the incorporation of 18F-NaF into the bone matrix

5. What other therapeutics were available or known to be in development for that target/tumor type at the time the project was taken on by DCTD.

Technetium- 99m (Tc-99m) (half-life 6 hrs) is a decay product of molybdenum-99 (Mo-99) (half-life 66 hrs) that is widely used in diagnostic imaging. 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)
- 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

6. Briefly explain the rationale behind NCI's decision to accept this project (interesting target, unmet need, exciting pre-clinical data, etc).

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.

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. Failure of Tc supply can cause 50,000 bone scans a week to be delayed or denied.

7. If other therapeutics against the target/tumor type became available at a later date, when did they emerge and at what stage in NCI's involvement in the project was this? Was NCI's role complete by the time these others emerged on the scene?

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, Technetium Tc 99m Medronate (Tc-99m MDP), became available. This is currently the only approved drug that can be used and reimbursed for bone scanning.

8. What date (year) did NCI's involvement begin and end?

In 2008 the NCI filed a 505(b)(2)NDA. That NDA was approved by the FDA in January 2011.