National Cancer Institute

Lessons learned: NCI's FLT F-18 IND and F-18 NaF NDA

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Disclaimers

- Opinions are mine alone
- NCI, NIH, and FDA have not approved anything I say
- No financial conflicts of interest
- No professional or academic conflict of interest

Status:
Molecular Imaging Probes – CIP IND

- [18F]-FLT – proliferation
- [18F]- FMISO - hypoxia
- [18F]- FES – estrogen receptor
- [18F] – Sodium Fluoride – bone seeking
- ferumoxytol – blood pool, delayed detection of inflammatory macrophages

[18F] fluorothymidine: early 2000's

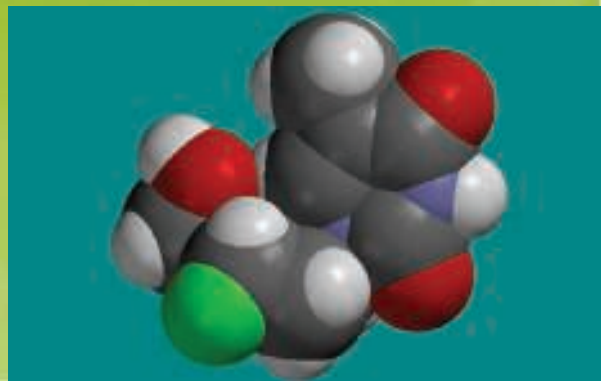
- No USP monograph
- No multicenter trials
- Most human research under RDRC
- "Generic" drug – no IP
- 2004 IND filed by CIP
  - Univ. Wash. first site
  - Tracer synthesis at 4 contract trial sites
  - Object: multicenter trials

Did this work?

- Not as well as we wished
  - Chemistry issues
  - Public access to regulatory documents limited
- 2006: expanded access and out-reach
  - Web posting, implicit click-thru MTA
  - LOA given to qualified entities on request
  - Regulatory “hand-holding” for PIs
  - Engaged the major commercial suppliers

Current Status

- Commercial firms - drug master files (DMF)
- LOA provided to legitimate entities
  - 6 companies for drug development
  - 18 academic sites
  - 1 Society
- LOA from Medivir for pharm-tox data
- Cooperative activities
  - Contract trials
  - Clinical Center Trials
  - ACRIN multicenter trials



Trials now posted

- More than 50 trials, at least 8 multicenter; around half dependent on LOA from NCI
  - Variety of tumors
  - Diagnosis, response to therapy
  - Correlation with Ki67
  - RT planning
  - Evaluation of new therapies
- US and Europe/Asia- 75% are US
- Academic and industrial –20% companies

Lessons learned

- Commercial entities best for manufacturing
  - Understand the logistics
  - Strong incentive for national CMC uniformity
- Regulatory ignorance is astonishingly high: "I don't need an IND/DMF because…"
  - "I am using the same synthesis that NCI filed"
  - "I am an academic not a company"
  - "My IRB approved, why would I need more?"
  - "I registered for the SNM Trial Network"

The Challenge

- Coherent data are needed for registration
  - Safety, Efficacy – current literature poor
  - How to facilitate pooling for “paper” NDA?
    - Minimum imaging/data protocol
    - Minimum safety reporting
    - Minimum chemistry reporting
- Challenge to scientific societies here

A LITTLE BIT ABOUT OUR OTHER INDS

FMISO

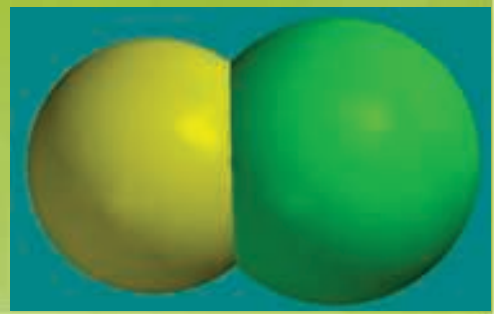
- **[18F] fluoromisonidazole (FMISO)**
- **Hypoxia - trapped in cells in absence of O2**
- **Contract trial at Univ Wash: response to CRT**
- **ACRIN: response to CRT in GBM**
- **Regulatory documents posted on website**
- One company has DMF

FES

- 16α-[18F]Fluoro-17β-estradiol (FES)
- Binds to estrogen receptor
- Regulatory documents posted on website
- Manufactured at Univ Wash
- Contract trial at Univ Wash, response to Rx
- No DMF (to my knowledge)

Sodium Fluoride F-18

- Sodium [18F]-fluoride
- The clinical need
  - Diagnose bone metastases (breast, prostate)
  - Other bone diseases
  - Technetium 99m shortages
- CIP IND, ACRIN multicenter trial
- Multicenter trial by AMI
- CIP filed NDA (12/2009)



18-F-SODIUM FLUORIDE NDA

National Cancer Institute

Clinical Issues

- Bone seeking radiopharmaceutical
- Only approved agent is Tc-99m medronate (MDP)
- 2.6 million bone scans in 2007
  - 450 k new breast and prostate cancer diagnoses
  - 5 million breast and prostate cancer survivors
  - Multiple orthopedic indications
- Tc-99m eluted from Mo-99 generator
  - Resupply every 7-10 days
  - Shortages frequent
  - Primary use is cardiac imaging

Technicium Supply

- Five foreign commercial reactors (used to) 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).

} 85%

- Newly approved
  - Poland Maria (1975)
  - Australia OPAL

Reactors off line

- Chalk river most recently
  - 11/2007 – 12/2007 (Act of Parliament)
  - 5/2009 – 6/2010 (??)
- Petten
  - 8/2008- 2/2009 (no repairs)
  - 2/2010 - 8/2010 (??)

Result

- Cancer patients cannot get bone scans
- Patient populations most affected
  - Breast
  - Prostate
  - Lung
- Delays treatment decisions, distress for patients and caregivers

Alternative

- 18F-Sodium fluoride PET scan
- Highly effective
- Used since 1962
  - NDA 17–042 in 1972 as a bone imaging agent
  - Marketing suspended in March 1975
  - Not withdrawn for safety or efficacy reasons
- 505(b)2 or 505 (j) specifically permitted
- 2 hour half-life requires decentralized manufacture

Other relevant information

- USP monograph established
- FDA drafted CMC and labeling in 2000
- Can be made on any medical cyclotron
- Clinical use is legal as practice of pharmacy
- Not routinely reimbursed

Response to 2007 shortages

- Cancer Imaging Program lead
  - Filed IND and planned trials with NaF
  - Filed NDA (before latest supply problems)
- Partnered with commercial firms
  - Multiple sites of manufacture
  - Drug Master Files
- Strategy
  - Obtain NDA approval
  - Withdraw when ANDA's filed

Questions to resolve

- NDA or ANDA?
  - Dose higher than RLD – 10-15 mCi vs. 2-4 mCi.
  - Neither clinical nor pre-clinical data needed
- Multiple DMFs –
  - Are there known issues?
  - Are the commercial entities prepared?
- Can NCI “distribute” a drug?

Unanticipated issue

- Prescription Drug Fees
  - Filing fees explicitly waived in 2000 FR notice
  - We assumed the other fees were also
- Establishment fees
  - 1/6 of non-PET fee= $76,267/site each year
- Product fees - $79,720/product each year
- Waiver process, but apparently VERY unlikely

Regulatory Progress

- NDA 12/2008
- CR 6/2009
- DMF issues – almost resolved
  - Multiple unrelated reviews
- PAI issues -- resolved
- Pediatric dosimetry request
  - Unresolved safety questions
- Response to CR within next several weeks

Lessons learned

- Companies unprepared for intensity of PAI
- Companies unprepared for intensive DMF review
- FDA unable to do a comprehensive DMF review
- Decentralized manufacturing has unique issues
- CMS denied reimbursement – and took 9 months to do so
- Regulatory system not a good fit for micro-dose drugs with 2 hour half life

The future is here before we are ready

- Next 18 months
  - 150 –300 FDG sites are mandated NDA/ANDA
  - Our NaF experience is discouraging
- Are the manufacturers ready for this?
- Is FDA ready for this?
- Will FDG have regional shortages?
- Will FDG be reimbursed?
- Will any other PET agents be approved?

Which way will it be?

A clear path forward?

Or beltway gridlock?

Thank you for your attention

Weblinks

- CMC SOPs that you can customize (ignore the specific drug – 95% are for general operations):
  http://imaging.cancer.gov/programsandresources/Cancer-Tracer-Synthesis-Resources
- Guide to Regulatory Submissions – in comprehensible English – orientated to biologicals but very valuable Here under Regulatory Affairs (and much more there): http://web.ncifcrf.gov/research/bdp/documents/Request.aspx
- FDA guidances: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- My email address: jacobsp@mail.nih.gov.

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