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
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Status:
Molecular Imaging Probes – CIP IND

- $[^{18}F]^{-}\text{FLT}$ – proliferation
- $[^{18}F]^{-}\text{FMISO}$ - hypoxia
- $[^{18}F]^{-}\text{FES}$ – estrogen receptor
- $[^{18}F]$ – 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
• [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
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).

- Newly approved
  - Poland Maria (1975)
  - Australia OPAL
Reactors off line

• Chalk river most recently
• 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):

- Guide to Regulatory Submissions – in comprehensible English – orientated to biologicals but very valuable Here under Regulatory Affairs (and much more there):

- FDA guidances:

- My email address: jacobsp@mail.nih.gov.