Clinical Development of Functional Neuroimaging Radiopharmaceuticals (FNR)

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Presentation Overview

• FNR definition & examples
• FNR agents reflect normal or altered physiology/function
• Physiological images need to become clinically useful tools for approval & label
• Scope of FNR agents
• Road map
• Key elements
• References
Definition

Functional Neuroimaging Radiopharmaceuticals (FNR) are diagnostic PET & SPECT radio-pharmaceuticals used in the assessment of the function of various systems of the central nervous system in normal and disease states.
Some FNR Agents

• Cerebral Metabolism Agents
  – Glucose, Aminoacid, Nucleic acid, etc.

• Neuroreceptor & Transporter Agents
  – Pre synaptic & Post synaptic
    • Dopamine, Opioids, Serotonin, Benzodiazepine, etc.

• Agents not included
  – Blood flow and perfusion, BBB integrity, CSF flow and dynamics, tissue pH, etc.
Images Reflect Physiology

Provides functional information at a molecular or cellular level
- physiological and or
- biochemical and or
- metabolic

Visualization of targeted mechanism of action
- increase/decrease in uptake
- site/s, location
- features (pattern, symmetry)
- specific, non-specific
18F-DOPA PET Uptake* Differential Diagnosis

↓ Putamenal
- Idiopathic PD (early and late)
- Neuroacanthocytosis
- Pallido-Ponto-Nigral Degeneration
- Guamanian patients with Lyticco-Bodig
- MND/PD-Dementia complex
- Shy-Drager Syndrome
- Striato Nigral degeneration
- Wilson’s Disease

↓ Striatal
- Idiopathic PD (early and late)
- MSA (Multi System Atrophy)
- CBD (Cortico Basal Ganglionic Degeneration)
- PSP (Progressive Supranuclear Palsy)
- RLS (Restless leg syndrome)
- Post encephalitic Parkinsonism
- ALS (Amyotrophic Lateral Sclerosis)
- MJD (Machado Joseph Disease)
- Lesch-Nyhan Syndrome

* Ref: July 2000 public meeting (slides 23, 24)
FNR Images Intrinsically

Show

Altered function in several diseases with similar pattern/findings
- Presence or absence of function
- Measurable Quantitatively or Qualitatively

But Does It?

- Narrow the differential or identify a specific disease
- Direct treatment
- Direct additional diagnostic tests
- Provide prognosis
- Outweigh risks

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Functional Level Data Also Needs……..

• To provide medical understanding of the meaning of the observed alterations
• To provide clinical understanding of its meaning to a patient
• To address - when is the test needed and in whom - such that benefits of the drug/test may be weighed against risks
Scope of FNR

Evolving field with potential clinical uses

- Diagnosis (disease, pathology, functional abnormality, etc.)
- Monitoring response to treatment - management & outcome
- Progression of disease - prognostic value
- Screening - identify at risk population
Scope of FNR

Various diseases with potential clinical uses-

– Movement Disorders
– Dementia
– Psychiatric Disorders
– Etc.
Threshold to Cross

How then to make “use” of an image that reflects a functional mechanism of action?

DEMONSTRATE CLINICAL USEFULNESS

For Approval & Label

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Therefore, the purpose of this presentation is--

To bring into focus the key elements in the Phase 3 efficacy development of Functional Neuroimaging Radiopharmaceuticals that will facilitate approval
Phase 3 Clinical Trials

• CFR- Phases of Investigation- 21 CFR 312.21
  – Benefits to outweigh risks even if the risks are low

• Draft Medial Imaging Guidance Document
  – Part 3
Aim of FNR Phase 3 trials

Prospectively define the setting of implementing an established functional mechanism of action as visualized on an image that can be interpreted with consistency to provide useful information that will benefit the patient.
Road Map

Adequate Preclinical

Endpoint
- Qualitative
- Quantitative

Study Design
- Setting
- Blinded Read
- Analysis

Functional Image
- Diagnosis
- Response
- Screening
- Progression

Clinical Endpoint
- Truth/Reference
- Comparator

Validation

VALIDATED MEASURE

Benefits over Risks

ADDED VALUE

Useful Information

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Road Map-Harmonization

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  Qualitative

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Key Components
FNR Phase 3 studies

- Prerequisites
- Study Design, Setting, Image interpretation, Analysis, Clinical endpoint, Verification, etc.
- Harmonization of Key Elements
- Added Value Assessments
Prerequisites

- Adequate Preclinical Development
- Adequate Clinical Phase 1 & 2 Development
  - Reproducible imaging methodology & technology & information (quantitative v/s qualitative)
  - Proof of concept for sought indication established
  - PK/PD & Dosimetry evaluated
  - Dose or targeted range established
  - Target population identified

(Reference: Draft Medical Imaging Guidance)
Design

Design, Analysis, Interpretation, Verification
– Prospectively Defined Objectives, Hypothesis, Clinical Setting, Endpoints, Image Analysis Plan
– Blinded Reader Protocol (Interpretation)
– Statistical Methods and Plan
– Verification of Image Findings
  • Comparison to accepted truth/gold/reference standard
– Others

(Reference: Draft Medical Imaging Guidance -Part 3)
Harmonization

Harmonization Amongst Key Elements

- Setting & Positioning
- Indication/Intended Use
- Endpoint/s & Image Features & Image Analyses
- Target population
- Statistical Plan & Accepted Truth/Reference Standard
Setting

Setting & Positioning

• Why order the test?
• In whom?
• Who will be using the test results?
Added Value

– Useful information
  • How will test results be used in patient management over existing diagnostic tools?
  • How will test results complement existing diagnostic tools’ results?
  • Is information helpful- in what way?

– Benefits over risks
  • How will the patient be affected by the test & its result?
  • Risks: drug, procedure, type of information (not useful or false)
References

• FDA Guidances
  – Draft Medical Imaging Guidance (Guidance for Industry, Medical Imaging Drug and Biological Products, Parts 1-3)

• Links to Public/Advisory Meetings
  – \(^{18}\text{FDOPA} \) in Movement Disorders (July 28, 2000)
    http://www.fda.gov/cder/regulatory/pet/transcript7282000.txt
  – \(^{18}\text{FDG} \) in Dementia (November 18, 2002)
    http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3907T1
Thank You