Regulatory Issues in the Use of Biomarkers in Phase 2b/3 Studies in Depression and Schizophrenia

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Current Financial Relationships

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Fundamental problem facing psychiatric drug development: Imprecise clinical targets

• Lack of biological understanding
• DSM V released in May, 2013 (with considerable controversy)
  – Irony: Even though few find DSM optimal, we all rely on it
• Major challenge facing our field: Finding better approaches to carving up the psychiatric illness space (i.e., moving beyond DSM)
Moving beyond DSM for Psychiatric Drug Development

- Phenomenological Domains (with or without biological understanding)
  - Within accepted DSM diagnostic entities
    - e.g., CIAS (cognitive impairment associated with schizophrenia)
  - Across diagnostic entities
    - e.g., agitation, impulsivity, a specific cognitive deficit
- Biological subgroups (defined by biomarkers, with or without clinical understanding)
  - Could be based on any of the many different types of biomarkers that have been proposed
  - As with phenomenological domains, could be applied within or across DSM diagnostic entities
- Research Domain Criteria (RDoC)
  - Might think of as way of combining biology and phenomenology
Illustration of the Approach from NIMH Program (Fast-Fail and RDoC)

- FAST-MAS/ Andy Krystal PI
- Fundamental change in POC paradigm
- Move away from DSM toward RDoC constructs
- Focus on target engagement as primary goal of POC
FAST-MAS Anhedonia Program: Summary of Planned Study

• Identify compound of interest
• Identify brain target (circuit) thought to be engaged by that compound (TE)
• Identify biomarker that signals TE
• Identify behavioral construct (preferably RDoC) thought to be represented by the brain target
• Compound was identified
• Ventral striatum (VS) circuit of interest (in particular, activation by monetary incentive delay task in VS)
• fMRI identified as biomarker for VS activation
• Anhedonia is the behavioral construct
  – Snaith-Hamilton Pleasure Scale (SHAPS) used as specific behavioral measure for anhedonia
FAST-MAS Anhedonia Program:
Summary of Planned Study (continued)

• Select patients based on threshold SHAPS score
• Select patients with either MDD or GAD (so cuts across DSM categories)
• Also measure HAM-D and HAM-A
• fMRI is primary outcome
Fundamental regulatory challenge to endorsing an alternative to DSM classification of psychiatric illness

• Need to provide a rationale for alternative approach
• True whether
  – Phenomenological domain
  – Biomarker-defined subgroup
  – RDoC construct
• Key regulatory issue: Pseudo-Specificity
What is pseudo-specificity?

• Potentially artificially narrow claim
• Examples:
  – Demographic subgroup, e.g., depression in women, or in elderly
  – Symptom, or symptom cluster, of defined DSM syndrome, e.g., hallucinations in schizophrenia
  – Comorbid condition, e.g., depression with cardiovascular disease, post-stroke, Parkinson’s disease
  – Subgroup defined by some biomarker without any mechanistic understanding of the relevance of this subgroup
Regulatory agencies initial rejection of claim as “pseudo-specific” might be considered a “straw man” position

- Objection may be overcome with arguments and data to show validity and value of targeting a particular domain or biomarker-defined subgroup
Approaches to overcoming regulatory concern that claim targeting a particular phenomenological domain is pseudo-specific

• Provide evidence that available drug treatments in the class do not address the domain in question
  – Little to no effect of available drugs on this domain
    • Residual phase of illness with persistence of symptoms in this domain
    • Evidence for subtype of disorder, with prominence of symptoms in this domain, and that is not responsive to available treatments
CIAS: Example of successful establishment of domain within schizophrenic syndrome

- CI is a well-established aspect of schizophrenia
- CI is not well addressed by available treatments
- CI has different time course than positive symptoms of schizophrenia
  - Present even before onset of psychosis
  - Still present in “residual” phase of illness
- Regulatory agencies have endorsed CIAS as legitimate target for drug development
Other Domains Within DSM Defined Syndromes that FDA has Accepted as Legitimate Targets for Drug Development

- Negative symptoms of schizophrenia
- Suicidal ideation and behavior in schizophrenia
- Agitation in schizophrenia and bipolar disorder
- Irritability of autism
- Impulsive aggression in ADHD
- Agitation/aggression in dementia
Demonstrating Specificity of a Particular Drug for Treating a Particular Domain or Biomarker-Defined Subgroup?

- Show specificity of response for new drug on this domain or biomarker-defined subgroup
  - New drug treats only this domain or subgroup
  - New drug superior to standard drug on this domain or subgroup
What are Biomarkers?

• Biomarkers are “measureable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans.”
• Biomarkers have many applications in drug development
• Focus here is on interest in finding biomarkers that can predict efficacy or risk associated with drug treatment, i.e., an approach to subgrouping the larger population into:
  — Responsive/non-responsive
  — At risk/not at risk
Different Types of Biomarkers

• Predictive Biomarkers
  – Useful for identifying patient subgroups that respond differentially, either for benefit or for risk

• Prognostic Biomarkers
  – Useful in predicting outcome for subgroups, independent of treatment, e.g., CV risk profile

• Surrogate Biomarkers (Endpoints)
  – Can serve as substitute for clinical endpoint, e.g., blood pressure or cholesterol
Validation (Qualification) of Biomarkers

• Analytical validation
  – Performance of biomarker assay
  – Sensitivity, specificity, PPV, and NPV of assay

• Clinical validation
  – Depends on type of biomarker: prognostic, predictive, or surrogate
  – For predictive, it is sufficient to validate only for a particular drug (RCTs establish clinical validity)
  – For prognostic and surrogate, clinical validation has to be broader
Examples of Biomarkers

- Imaging measures
- Serum assays
- Genetic assays
- Physiological measures
- Histopathologic findings
- Psychological tests
- Demographic variables (age, gender, race)
Two Ways for Biomarker to Subdivide the Population
(Assume Marker: M+/M-)

Biomarker Status
M+/M-

Predicts PK Difference (Exposure)

Predicts PD Difference (Not Exposure Related)

Efficacy Difference

Risk Difference

Efficacy Difference

Risk Difference
Genomic Biomarkers as Predictors of Exposure
(Pharmacokinetic)

• Genetically polymorphic P450s associated with differences in plasma levels, resulting in differences in efficacy and safety
• Several with known differences that are reflected in labeling for certain drugs (including some psychiatric drugs):
  – CYP2B6
  – CYP2C9
  – CYP2C19
  – CYP2D6
Biomarkers as Predictors of Response (Pharmacodynamic)

- **Efficacy**
  - Non-Psychiatric
    - Herceptin (trastuzumab)

- **Safety**
  - Psychiatric
    - Carbamazepine/SJS
Herceptin (trastuzumab)

- Her-2 gene expresses cell surface receptor needed for cell growth
- Her-2 gene over-expresses in about 30% of breast cancers
- Trastuzumab is an antibody that blocks the cell surface receptor
- Kit available for identifying this subgroup of breast cancer patients
- Clinical trials included mostly over-expressing patients
- Labeled Indication: only for over-expressing patients
Carbamazepine/Serious Skin Reactions

• SJS/TEN incidence with carbamazepine
  – 1-6/10,000 in Caucasians
  – 30/10,000 in some Asian countries

• Strong association between HLA-B* 1502 variant and SJS/TEN with carbamazepine
  – Variant found mostly in Asian populations
  – PPV: 0.1; NPV: 1

• Labeling for carbamazepine
  – Test for variant in Asian patients
  – Use alternative drug if positive for allele, unless compelling reason
Practical Issues in Utilizing Biomarkers in Psychiatric Drug Development

• What is needed to get biomarker into labeling?
• Focus on efficacy (safety is somewhat different discussion)
• Importance of coherent hypothesis testing strategy for biomarker program
Approaches to Efficacy Determination in Psychiatric Drug Development (Focus on Responder vs Non-Responder)

• Compare drug and placebo on proportion of “responders”
• Goal: Show population effect [drug beats placebo, i.e., statistically significant p-value (p< 0.05)]
• Need clinically meaningful measure of “response”
• Easier in some areas, e.g., if mortality is the endpoint
• Not so easy in psychiatry: no clear definition of “response”
  – May rely on percentage reduction for standard rating scale (e.g., 50% reduction on HAMD total score), but no universal agreement on such arbitrary definitions
  – Could use “remission,” but few drugs would win if this were the standard
• Another advantage: could think about the value of biomarkers in the language of medical decision making
  • Sensitivity, specificity, PPV, NPV, ROC curves, etc.
Approaches to Efficacy Determination in Psychiatric Drug Development
(Focus on Change from Baseline for Illness Severity Measure)

• Compare drug and placebo on change from baseline to endpoint on a standard measure of illness severity (e.g., MADRS or PANSS total score)
• Most common approach in drug development programs
• Goal: Show population effect [drug beats placebo, i.e., statistically significant p-value (p< 0.05)]
• Rarely try to set a standard for a minimum required “effect size”
• Typically effect sizes for psychiatric drugs are quite modest, however one measures “effect size”
Problems and Challenges in Hypothesis Testing for a Biomarker (Regulatory Expectations for Phase 3 Program)

• Assume focus is on an accepted DSM diagnostic category, e.g., schizophrenia

• Ideal approach from regulatory perspective:
  – Develop a valid and reliable biomarker assay before phase 3
  – Have capability to establish biomarker status for all patients prior to randomization
  – Conduct stratified randomization (M+/M-)
  – Have clear plan for hypothesis testing that includes marker status (+/-) and adjustment for all parameters of interest (marker status, dose, primary and key secondary endpoints)
Deciding on Role of Biomarker in Development Program
(This decision will drive hypothesis testing strategy)

• Sponsor wants broad claim in “population” but also wants to claim added benefit in M+ patients
  – Testing would likely begin in broad population and then proceed to marker subgroups

• Sponsor recognizes that biomarker may “salvage” program that might otherwise fail
  – Might reasonably begin testing with M+ patients and then move to M-
Other Considerations in Programs Including Biomarker Information

• Approaches to including both retrospective and prospective data in support of labeling for biomarker status
• Adaptive strategies to increase power to detect biomarker subset effects (e.g., increasing sample size for M+ group)
• Problem of incompleteness of biomarker information for all patients in sample
• Need for co-development of diagnostic kit for assessment of biomarker status
Summary

• Regulatory agencies are not fundamentally opposed to considering alternative approaches to carving up the psychiatric illness space
• But there is a need to come prepared with strong arguments and data to support an alternative approach to diagnosing psychiatric illness
• Also helpful to have some reasonable consensus in support of the alternative conceptualization
• Also useful to note that robust findings in studies using the alternative approach that show convincing clinical benefits have a way of overcoming initial regulatory reluctance