Regulatory Implications for Novel Approaches to Developing Treatments for the Schizophrenias

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Potential Conflicts

• No conflicts at present time
Fundamental problem facing psychiatric drug development

• Lack of biological understanding
• Plato: “successful theories should carve nature at its joints”
• Given lack of biological understanding, we instead “apply a cookie cutter to the dough of nature”
• Endless iterations of DSM
  – Irony: Even though no one finds DSM acceptable, we all rely on it (it’s all we have)
Moving beyond DSM for Schizophrenia

- Phenomenological Domains (even without biological understanding)
  - Within accepted 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)
  - Could be within or across diagnostic entities
  - Biological approaches to subgrouping
    - Neurotransmitter deficiencies
    - Circuit deficiencies
    - Genetic subtypes
- Research Domain Criteria (RDoC)
  - Might think of as way of combining biology and phenomenology
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
  – Biological subgroup
Regulatory agencies might initially reject alternative approach ("straw man" position)

• Objection may be overcome with arguments and data to show validity and value
• Approach depends on type of classification strategy
• For domain or biological subgroups within syndrome, might show different time course or response to treatment for different domains/biological subgroups within that entity
• For domain or biological subgroups across diagnostic entities, might show similarity in subgroups regardless of the diagnostic entity
  – Might think of pain or fever as being examples of this type of entity in human illness more broadly
CIAS: Example of successful establishment of phenomenological subgroup 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
Trial design is based on conceptualization of phenomenological domain subgroup: CIAS as Example

• CI most problematic in residual phase of illness, when positive symptoms are reasonably controlled

• Design implications:
  – Study in residual phase of illness
  – Add-on design
  – All patients treated with agent to control positive symptoms
  – Randomize to adjunctive cognitive enhancing (CE) drug or pbo
  – Show advantage of adjunctive CE drug
Approach for biological subgroup within an accepted diagnostic entity (e.g., schizophrenia) defined by a biomarker

- Regulatory agencies view this as a situation requiring hypothesis testing
  - As a way of establishing validity of the subgroup
- Stratified randomization based on marker positive (M+) vs. marker negative (M-) status
- Show that M+ patients are the ones who benefit from treatment (or have greater benefit)
Conceptualization of biological finding might also have important impact on trial design

• For example, suppose a biomarker is discovered in prodromal phase of schizophrenia that reliably predicts subsequent onset of psychosis

• Could provide support for studies looking at prodromal patients with goal of preventing onset of psychosis

• Markedly different approach to doing studies:
  – Delay or prevention, as opposed to current approach of symptomatic studies in patients who have already developed a schizophrenic syndrome
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)
Additional Problems and Challenges in Hypothesis Testing for a Biomarker

• Dealing with imbalanced distribution of marker status
  – Ideal would be 50:50
  – More likely imbalanced

• Deciding on hypothesis testing strategy
Dealing with Imbalanced Distribution of Marker Status
(Problems with Different Types of Imbalance)

• Most of population is M+ (>80%)
  – Utility of marker would be doubtful
  – Insufficient power to establish lack of signal in M- patients

• Most of population is M- (>80%)
  – Insufficient power to establish efficacy in M+ patients
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-
Difficult Statistical Issue: Assessing Efficacy in M- Subgroup

• Regulators will always want to try to assess efficacy in M-subgroup
• Problem is in deciding how to interpret a finding of no difference between drug and placebo in M-patients
  – What is the standard for ruling out an effect in the M-subgroup?
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