Commentary: Wayne Fenton’s Impact on Industry

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Wayne Fenton’s vision for people with serious mental illnesses was deep and inspiring. He was fiercely committed to improvements in patient care and management so that persons with these disorders could be fully functioning members of society. Fenton was wise enough to recognize that he could not accomplish these goals alone and understood that persistent work with many different stakeholders was necessary. His skill was to bring these diverse groups together so that their wisdom and resources could be pooled in synergistic ways.

A major focus of his vision was the recognition of the substantial unmet medical need related to schizophrenia and the urgent need for novel therapeutics to treat this illness. In order to accomplish this goal, he recognized that a new kind of partnership between academia, Food and Drug Administration (FDA), and industry was needed. This partnership must be built on inclusion, mutual respect, and synergism. Each stakeholder would contribute their area of expertise to the common goal of improving the lives of persons with severe mental illness.

Measurement and Treatment Research to Improve Cognition in Schizophrenia

The first psychopathology domain proposed by Fenton for novel drug development was cognitive impairment associated with schizophrenia (CIAS) because these deficits are major determinants of long-term work and social functioning, and existing treatments are only modestly effective, at best. Fenton’s vision led to a program entitled Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) which would form the groundwork for drug development in this area. A unique aspect of this program was engagement with industry early in the process creating a constructive synergism including industry as a key partner and stakeholder, along with academia, National Institutes of Health, and FDA.

Before embarking on a program designed to develop CIAS treatments, it was critical for industry to have an established pathway for regulatory approval. This encompassed many facets of drug development beginning with regulatory acceptance of CIAS as a legitimate indication. In addition, it was important to have an agreed-upon measurement of cognition, ie, a cognitive battery, which included agreeing on its composition and scoring, as well as practical issues such as administration length and complexity so that the battery could be administered in large multinational clinical trials. Also, key aspects of clinical trial design required clarification including duration of treatment, comparators, the need for co-primary endpoints, and clarification between design features for a monotherapy vs coadministered therapy for CIAS. A consensus view developed by the various stakeholders addressed the FDA’s concern about pseudospecificity of cognition performance change. The resulting clinical trial design was published by Buchanan et al.1

From an industry perspective, MATRICS has been a resounding success. Through the MATRICS process, all the above issues were thoughtfully debated, reviewed, and resolved with clear-cut decisions made along the way. There is now a clear pathway for regulatory review and approval for CIAS. Drug discovery and development programs for CIAS are now being initiated in industry because of MATRICS.

Treatment Units for Research on Neurocognition and Schizophrenia

Fenton viewed MATRICS as an essential first step to develop novel therapeutics for CIAS but not by itself sufficient. Following MATRICS, Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) was established through his leadership. TURNS is a National Institute of Mental Health (NIMH) network that provides infrastructure for clinical trials of pharmacologic agents that have potential as therapeutics for CIAS. Again, Fenton reached out to industry to collaborate with TURNS by encouraging the nomination of molecules from their pipelines that may have potential as a CIAS treatment but have not, in most cases,
undergone proof of concept trials. Novel agents including glutamatergic modulators, nicotinic receptor agonists, and \( \gamma \)-aminobutyric acid agonists, which may have been originally developed for other disease indications, were now being considered as potential candidates for CIAS because of TURNS.

**Negative Symptoms Project**

As was the case with CIAS, Fenton recognized that a significant deficit in the treatment of patients with schizophrenia was finding effective treatments for negative symptoms. He understood that to optimally achieve this vision academics, industry researchers and regulators must work closely together. Academic psychiatrists are needed to define and clarify the key issues to be studied, including: How can negative symptoms of schizophrenia be precisely defined? Which aspects of these symptoms must be addressed by our new treatments, eg, primary or secondary negative symptoms or both? How do we differentiate them? Industry researchers are needed to translate these issues into large-scale protocols that evaluate the effectiveness of potential pharmacological treatments and develop them into registration packages that will be acceptable to regulatory authorities around the world. Regulators are needed to ensure that key public health questions are addressed during development of new therapeutic agents.

Fenton brought attention to negative symptoms as an unmet therapeutic need at 2 critical meetings. He used the MATRICS framework for a workshop which clarified conceptual and measurement challenges and resulted in a consensus clinical trial design for a therapeutic indication for negative symptoms. At the “International Society for CNS Clinical Trials and Methodology Satellite Meeting on the NIMH Initiative Regarding Treatment Development for Negative Symptoms” held in Washington, DC, in February, 2006, Fenton brought together the clinical trials stakeholders to focus on these issues. At the meeting, participants were able to clarify existing problems related to the design of trials for the treatment of negative symptoms and began to develop solutions for them. Attendees grappled with issues around definitions of negative symptoms, appropriate endpoints, study design, and differences in approaches needed for monotherapies and adjunctive therapies. Not only were unmet needs for clinical study design for negative symptoms trials identified and explored, but approaches to labeling drugs for a negative symptoms indication were debated.

Recognizing a specific need for better instrumentation in negative symptoms trials, in a related effort, Fenton sponsored an initiative to develop an improved negative symptoms assessment scale. Again, this effort was initiated as collaboration between academia and industry to ensure that the final product is acceptable to both sets of stakeholders.

Fenton’s pragmatic, steady approach effectively brought together the key groups needed to implement his vision for the treating negative symptom of schizophrenia. His patient guidance helped to drive solutions. Although no specific treatment for negative symptoms of schizophrenia has yet been identified, studies for indications are now underway and a new negative symptom scale is in development.

**Wayne Fenton’s Legacy**

We were very fortunate and honored to have had the opportunity to work with Wayne Fenton in the partnerships he established to further the development of novel therapeutics for the treatment of cognitive impairment and negative symptoms in schizophrenia. He recognized the value of bringing together the resources and talents across industry and academia for the common goal of improving clinical outcomes in for persons with schizophrenia. Fenton’s legacy includes the adoption of partnership models built on inclusion and mutual respect described here for future collaborations to address other areas of unmet medical need.

There remains much work to be done to realize Fenton’s full vision including continued progress from the partnerships described above. His legacy will live on as novel therapeutics progress from these partnerships to improve the lives of future patients with severe mental illness.

**References**