

Monday, August 11, 2014

Joseph R. Pitts.
Chairman, Subcommittee on Health
c/o Sydne Harwick, Legislative Clerk
Committee on Energy and Commerce,
U.S. House of Representatives
2125 Rayburn Office Building
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Dear Chairman Pitts.

I am pleased to be able to respond to the additional query which you sent in follow-up to my participation in the discussion of Modernizing Clinical Trials held on July 9th, 2014. Specifically, this query came from Representative Murphy on the issue of impediments to the development of innovative psychiatric drugs, which he and I agree is an area of substantial unmet need given the prevalence of mental health issues in the United States. Representative Murphy asked for me to provide expanded remarks “pertaining to the problems psychiatric drug developers face and for commentary on any potential changes that could be made to resolve this problem.” While this therapeutic area was not a part of my direct responsibilities when I was an Office Director at FDA’s Center for Drug Evaluation and Research, I did have a broad regulatory strategy and drug development role while at the Merck Research Labs and Merck’s portfolio included many drugs targeting psychiatric diseases. I saw firsthand how many drugs in this area of development failed in the late stages of clinic development, if not before. I have also taken the liberty to discuss my response with subject matter experts within my former company to assure that my response represents current state and well-targeted.

As well stated at the July 9th hearing by Rep. Murphy, despite a large number of pharmacologic agents available to treat psychiatric diseases (such as depression, schizophrenia, bipolar disorder), there remains a large number of patients who are not adequately treated for their illnesses with a resultant substantial burden on society. While some of this burden may be the result of the availability of and access to proper psychiatric care, clearly a large part of this continuing problem is a less than satisfactory array of therapeutic options. Yet, while this unmet need is substantial, global pharmaceutical companies are decreasing investment and research in the area of psychiatric drug development¹, in part due to the burden of failures in their attempts to provide better options to patients. The article cited above by Dr. Hyman (former Director of the NIMH) is, in fact, a very

good summary of some of the current challenges to this therapeutic area and aligns well to the discussions I had with other experts on some of the major impediments and issues with productivity in psychiatric drug development. I would recommend this article as a very thoughtful review.

However, let me highlight some key issues from my vantage point:

- While great advances have been made in the fundamental understanding of basic sciences and pathophysiology in a large number of human diseases, including neurology, this same kind of clear understanding of the fundamental basis of key psychiatric diseases has not been achieved (including what differentiates between the diseases/syndromes pathophysiologically). This lack of basic understanding is compounded by the lack of useful animal models for many psychiatric diseases, such as schizophrenia.ⁱⁱ To date, many advances in psychiatric drug therapy have come through serendipity rather than by design. In contradistinction to classical therapeutic science, these drugs' activities have driven the theory of disease rather than more usual and rational visa-versa. For instance, it was the association between the depletion of catecholamines (major neurotransmitters) by reserpine (a blood pressure medicine) and its frequent adverse effect of depression that led to the catecholamine hypothesis of depression – which remains controversial to this day, but has been the basis for much of the treatments developed for depression.

Great advances in the fundamental understanding of the genomic basis of disease have been achieved for many disease areas, which in turn have informed targeted drug discovery and development. A great example of this kind of mechanistic drug development is ivacaftor for Cystic Fibrosis.ⁱⁱⁱ Yet, the genetics of psychiatric diseases have proven to be exceedingly complex, despite clear heritability (particularly schizophrenia, where genetics are believed to account for 50 – 80% of the disease risk). The complex, multigenic bases of these diseases have not led to a rational set of targets for further drug discovery.^{iv} That is not to imply important advances have not been made, but clearly more understanding of the genetics, epigenetics, and other underlying pathophysiologic basis of psychiatric disorders is sorely needed in order to inform more rational drug development. This is a need best served by academic and/or governmental basic science researchers, rather than drug companies, as it involves fundamental, rather than targeted, science. Continued or enhanced government support of this kind of basic research in academia would be an important consideration for advancing this area of drug discovery.

- A second need as an underpinning of translational efforts in neuropsychiatry is the development of predictive biomarkers, not only to better identify patients at risk (which may be particularly important for enrichment and enhanced success rates of clinical trials) but also to inform proof-of-principle studies in very early clinical development. The use of biomarkers in early drug development is particularly important as predictive biomarkers

provide a means to screen compounds for likely clinical efficacy long before large investments of time and dollars are committed to the drug's development. Currently, few such biomarkers exist for psychiatric disease states. Public investments in furthering efforts to identify and validate biomarkers in psychiatry for the purposes of better identifying patients at risk as well as informing drug choice and development is clearly needed.^v This kind of research is being done and should continue to be done both in academia/NIH, as well as within the industry itself, and directed support of public/private partnerships with this specific mission would be worthy of consideration.

- As for clinical trials, there are a variety of issues that may be impacting the relatively low success rate for psychiatry drugs entering into phase 3 (many of which fail for efficacy). These factors include:
 - Highly variable diseases (where the “placebo effect” may be substantial, due in part to “regression to the mean” in patients who are enrolled for a certain high level of disease symptomatology)
 - Imprecision in enrollment criteria due to lack of definitive, differentiating diagnostic criteria, compounded by a lack of characterizing biomarkers for disease state/activity
 - Imprecision of current clinical trials endpoints, much of which are based on questionnaires and subjective assessment tools, rather than a measurable physiologic parameter or other objective measures
 - The need to provide evidence to payers and practitioners of therapeutic superiority over existing drugs, most of which are generic (this complicates the design of the trials, but even for well-designed trials this sets a high bar for efficacy and/or safety)

Addressing the unmet psychiatric need through novel drug development requires advances in a number of areas, including the basic sciences of psychiatric diseases. Some of these factors could be improved if the issues highlighted above were successfully addressed (e.g., fundamental discovery science and development of biomarkers). However, like many areas of drug development/clinical testing, the reduction of inefficiencies in trial design/conduct and factors that add noise to the trial results (particularly the imprecise or indiscriminate inclusion of patients) is also needed. This is largely the purview of the industry itself and correctly so. That said, as in many areas, having standing networks of high quality clinical trial sites that can rapidly recruit well-characterized, appropriate patients to new trials would be advantageous. Since one would want sophisticated screening and enrollment of patients, any such networks should include academic medical centers as key contributors. The establishment of funded, standing networks would reduce factors that add to the substantially to the costs of drug development (irrespective of failure rates), such as site identification, patient identification, IRB clearance, etc.

A final thought on the industry's pull back from investment in this disease area: in counter distinction to an area of drug development like antibiotics, one thing that does not seem to be a factor in the dwindling R&D efforts is economic reward. While most important psychiatric drugs are now off patent, recent history in the industry shows that this area of drug development, when successful, has led to high revenues during the drug's exclusivity. Indeed, if one were to be able to understand sufficiently the basic causes of a condition like the cognitive impairment in schizophrenia (which is not at all addressed by current anti-psychotics), a successful program addressing this need would surely result in a sizeable market/revenue opportunity.

The issues behind the low productivity for meaningful therapeutic advances in psychiatric therapeutics are daunting and deep. However, as I stated in the hearing itself, I do not believe the fix to these issues relates to developing accelerated pathways to approval, since the fundamental sciences remain inadequate and, in particular, we do not have sufficient surrogate endpoints that would form the basis for being able to speed development (let alone improve clinical success rates). What is needed is to bring our considerable and potent tools of scientific discovery to bear in a cohesive, coherent effort to systematically advance the fundamental understanding of psychiatric disorders in terms of biologic causes and the pathophysiologic distinctions between the diseases. Only through such understanding will there come to pass a more informed, targeted and rational development of new therapeutics with a resulting increase in the chance of clinical success that is so very necessary to address the large remaining unmet medical needs in this vexing area of medicine.

Sincerely,



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ⁱ Hyman, Stephen. Psychiatric Drug Development: Diagnosing a Crisis. *Cerebrum* (April 2013)
[http://www.dana.org/cerebrum/2013/psychiatric_drug_development_diagnosing_a_crisis/]

ⁱⁱ Conn, PJ; Roth, BL. Opportunities and Challenges of Psychiatric Drug Discovery: Roles for Scientists in Academic, Industry and Government Settings. *Neuropsychopharmacology* (2008) 33, pp 2048-60

ⁱⁱⁱ <http://www.cff.org/treatments/therapies/kalydeco/>

^{iv} Ozomaro, et al. Personalized Medicine in Psychiatry: Problems and Promises. *BMC Medicine* (2013); 11:132

^v Wiedermann. Biomarkers in Development of Psychotropic Drugs. *Dialogues Clin Neurosci* (2011); 13:225-234