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Review

Commercial viability of CNS drugs: Balancing the risk/reward profile

Ginger S. Johnson [1]

Defined Health, 25-B Hanover Road, Suite 320, Florham Park, NJ 07932, USA

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ABSTRACT

CNS has historically been a formidable therapeutic area in which to innovate owing to biological (e.g., complex neurobiology, difficulty reaching the target), as well as clinical (e.g., subjective clinical endpoints, high placebo response, lack of biomarkers) challenges. In the current market where many of the larger diseases are dominated by a generic standard of care, commercial challenges now make the triple threat of scientific–clinical–commercial risk too much for many players to tackle. However, opportunities do exist for smaller biotech companies to concentrate on narrowly focused patient populations associated with high unmet need for which risk can be tightly defined. In CNS, there are two major areas to balance the risk/reward profile and create commercially viable opportunities:

1) Orphan indications, typically where there are no good therapeutic options, and,
2) Distinct, definable segments of larger patient populations for which drugs exist, but which remain associated with major unmet needs (e.g., refractory patient populations).

To realize value, all companies (start-ups and big players) must define, measure and quantify clear and meaningful value to all stakeholders: physicians, patients, caregivers and payers.

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Introduction: In CNS, the risk/reward balance for new drugs has tipped toward risk

The neuropsychiatric community is painfully aware that, as a therapeutic area, CNS disorders are notoriously associated with significant scientific and clinical development risk (e.g., complex neurobiology, inadequate animal models, difficulty reaching target and/or off-target effects, subjective clinical endpoints, high placebo response rates, and paucity of reliable biomarkers). The development attrition rates bear this out with a less than 10% chance of success in moving drug candidates from first in man to FDA registration. In fact, CNS has historically had the lowest rate of success in the clinic among all therapeutic categories (only oncology and women's health being lower) (Kola and Landis, 2002).

In the past, companies were willing to take on the scientific and clinical development risks inherent to CNS drug development, particularly for the big CNS disease categories (e.g., depression, migraine, schizophrenia, ADHD) in the hopes of realizing the commercial reward. However, in the context of an increasingly generic standard of care (at least for the majority of patients), the added commercial risk has made

E-mail address: gingerjohnson@definedhealth.com.
Available online on ScienceDirect (www.sciencedirect.com).
[1] Defined Health (http://www.definedhealth.com) is a leading biopharmaceutical business development strategy consulting firm whose clients include a mix of pharma, biotech and specialty pharmaceutical companies, and royalty and private equity investors.

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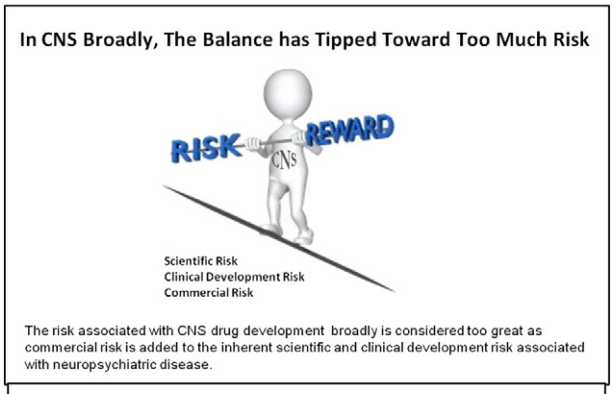
CNS too much for many companies to tackle. As a result, we have seen several major CNS players (e.g., AstraZeneca, GlaxoSmithKline, Novartis) spinning out their neuroscience programs or exiting the space entirely. However, a group of companies (e.g., Biogen Idec, Lundbeck and Teva) see opportunities to balance the risk and continue to focus R&D efforts in this space.



In CNS, the risk/reward balance has tipped.

Opportunities to balance the risk in CNS

For any therapeutic area, it is imperative that researchers keep an eye toward the commercial viability of a potential new product from the earliest stages of development; clearly outlining anticipated factors of compelling clinical differentiation that will resonate with all ultimate stakeholders: patients, clinicians and payers. True differentiation is obtained in the form of meaningful medical benefit to the patient, over and above the current standard of care, which justifies a price and reimbursement status that translates to a viable business case (given the size of the target patient population). Potential for differentiation should be considered in the context of the future competitive environment (and how that will impact the future standard of care), including new products on the market as well as the entry of additional cheap, generic alternatives. Increasingly, stakeholders (with payers leading the way) are asking for proof of meaningful differentiation through longer term outcome studies and quality of life (QoL) endpoints to answer the "so what?" question (e.g., what does improved cognition in a schizophrenic patient mean for his/her ability to live somewhat independently, maintain employment, reduce his/her economic burden on the healthcare system?).

Optimally, companies would like to target indications in which signals of differentiation (either efficacy or safety/tolerability) can be established at an early point in development (i.e., Phase IIa) to improve the odds of later-stage probability of success. These opportunities are likely to target narrowly-focused patient populations associated with high unmet need for which risk can be tightly defined.

In CNS, there are two major areas to balance the risk/reward profile and create commercially viable opportunities:

1) Orphan indications, typically where there are no good therapeutic options, and,
2) Distinct, definable segments of larger patient populations for which drugs exist, but which remain associated with major unmet needs (e.g., refractory patient populations).

Examples of opportunities in CNS orphan indications

Orphan diseases in general are defined as serious, chronically and/or progressively disabling disorders that can be life-limiting and life-threatening. According to the US National Institutes of Health, there are over 68,000 orphan or rare diseases. In the US, a disease is considered to be 'orphan' if it affects fewer than 200,000 individuals, and in the EU orphan is defined as having a prevalence of fewer than 5 in 10,000 people (National Institutes of Health). The Orphan Drug Act was approved in 1983 in the US to support and promote the development of treatments for rare diseases, creating much promise in terms of potential development and commercialization benefits, including:

- low cost/short development timelines,
- a friendly and collaborative regulatory authority,
- economic incentives,
- minimal commercialization efforts (optimally via small, targeted sales forces promoted to highly specialized physicians who treat highly motivated patients),
- pricing flexibility, and
- 7 yrs of market exclusivity.

While the advantages outlined above certainly look attractive, they are not always obtainable, particularly those that relate to ease of development and the ability to obtain a high price tag. Even in orphan disease, the value of the drug must justify the price. However, biotechs (large and small) and big pharma see the possibilities and are actively pursuing orphan indications. A fairly recent study notes that in 2009, big pharma accounted for over 40% of the total orphan drug approvals by the FDA (Ariyanchira, 2010). GSK, Novartis and Pfizer all have publicly stated their dedication to orphan diseases. Relevant to CNS, Pfizer clearly states their interest in neurodegenerative disorders and proteinopathies.

Why the interest in orphan diseases? It's a BIG and rapidly growing market. Looking at a subset of orphan diseases (inherited metabolic disorders), Cowen estimates the global market to be $5.7 billion in 2011; expected to reach over $13 billion by 2017. Via its lysosomal disorder franchise (Cerezyme/imiglucerase, Fabrazyme/agalsidase beta, Myozyme/alglucosidase alfa, and Aldurazyme/laronidase), Genzyme, now a wholly owned subsidiary of Sanofi, had the greatest dollar share (55%) in 2011. Shire had the second largest franchise in 2011, supported by sales of Elaprase (idursulfase) and Vpriv (velaglucerase) (Cowen and Company, 2012). Other companies with strong orphan disorder franchises include Alexion, BioMarin, Viropharma, Dyax, Amicus, Corcept, Raptor and CSL Behring. A recent Reuters report shows that *all* orphan drugs generated over $50 billion in 2011 with a compound annual growth rate of over 25% between 2001 and 2010 (Thomson Reuters, 2012). Based on these data, the study predicts that the growth rate of launched orphan drugs will outshine that of the non-orphan drugs over the next 30 years. However, of the 60 or so orphan drugs on the market, less than 20% are CNS related. Compare this to oncology, which dominates orphan drug approvals, accounting for 33% of the total from 2006 to 2011. The preponderance of oncology in orphan drugs is driven by high unmet need in cancer, certainly, but also (and very importantly) the ability to stratify patient segments by clinically distinct cancer subtypes, often with genetic associations.

When we look at the pipeline, only 37 of the 460 drugs orphan drugs in development (8%) are for CNS indications. And, despite the high unmet need associated with most of the hundred or so CNS orphan indications, the pipeline is focused on just a few, including:

- Neurodegenerative Disease (e.g., Amyotrophic Lateral Sclerosis, ALS; Huntington's Disease, HD; Progressive Supranuclear Palsy, PSP)