Creating Value with Repurposed Drugs in Neurological and Psychiatric Disorders
In the wake of declining R&D productivity, drug repurposing (or drug repositioning/drug rescue) is emerging as a vital strategy to speed up drug development. With established pharmacokinetics, dosing, safety and tolerability profile, repurposed compounds offer the possibility of accelerated development through NDA 505(b)(2) pathway (in the US), and reduce the risk of failure.

**What makes CNS an attractive therapeutic area for successful drug repurposing?** Central nervous system linked mainly to aminergic G-protein-coupled receptors (GPCRs) offers the possibility of a wider array of targets and pathways for drug repurposing, though permeability of blood brain barrier is a limitation. To identify novel indications for existing drugs, a thorough understanding of the pharmacodynamics, pathophysiology, molecular mechanism of various CNS disorders is required. Sponsors also need to assess IP protection challenges, and develop appropriate strategies to realize the potential of this approach. Further, the companies need to demonstrate the medical and economic benefit of the innovation to gain favorable opinion of the relevant stakeholders.

**Significant residual and emerging unmet needs in CNS disorders**

There has been significant progress in the understanding of various CNS (neurological and psychiatric) disorders. These include the identification of underlying genes, mapping of neural circuitry and neurochemical mechanisms, and the application of novel technologies to understand the pathophysiology as well as the treatment of these disorders. However, major unmet needs still remain. A leading cause of morbidity (in terms of Disability Adjusted Life Years) and mortality, CNS disorders represent the most costly form of chronic disease globally. Furthermore, a considerable proportion of people with CNS disorders remain undiagnosed and untreated.

While attempts are being made to address these unmet needs, CNS disorders, particularly psychiatric disorders are experiencing a crisis in the clinical development and regulatory approval of novel therapeutics. Factors responsible for this crisis include limited correlation of genetic findings and drug targets, paucity of new molecular targets, the increasing cost and average duration of clinical studies, high and unpredictable placebo response rate, and the heterogeneity of patient populations resulting in high failure rates in late-stage clinical trials.

At the same time, greater awareness of the disease state has resulted in recognition of a large number of rare neurological and psychiatric disorders.
Drug repurposing offers the possibility of accelerated development with lower risk of failure

With declining R&D productivity, drug repurposing (or drug repositioning or drug rescue) is becoming an increasingly common strategy to speed up drug development. Human pathophysiology is complex with many inter-connected signaling pathways. The same pathway can be involved in different disease states. As a result, a drug originally intended to be developed for one disease may turn out to be helpful in treating another. The repurposed compounds have established pharmacokinetics, dosing, safety, and tolerability profile. This offers the possibility of accelerated development and reduces the risk of failure.

Repurposing of off-patent drugs may involve currently marketed drugs or assets shelved (prior to approval) or withdrawn (after approval) for efficacy, safety or strategic reasons. Drug repurposing may be pursued either during the patents lifespan by the innovator or after the expiry of the patent by other specialty companies.

Drug repurposing is emerging as an even more important strategy due to the increasing ability to do it in a systematic, deliberate way and the attractive features of lower cost, lower risk and faster development timelines than traditional new drug development.

Versatility of G-protein-coupled receptors (GPCRs) makes CNS an attractive therapeutic area for successful drug repurposing

Companies interested in drug repurposing need to identify the appropriate therapeutic area(s) as not all of them are equally attractive. An analysis has revealed that among a list of 26 repurposed drugs, the majority (46%) were neurological drugs. This is because the central nervous system, linked mainly to aminergic G-protein-coupled receptors (GPCRs), offers the possibility of a wider array of targets and pathways that can be subjected to NME-related perturbation. The GPCR family represents the largest and most versatile group of cell surface receptors. Drugs acting at GPCRs constitute ~40% of those in current clinical use. GPCRs have a higher degree of cross-pharmacology among its members compared to enzymes, ligand-gated ion channels, or nuclear receptors. In addition, cross-pharmacology between some GPCRs and non-GPCR proteins has been also detected. Considering the fact that some GPCRs are linked to multiple therapeutic areas, drugs targeting aminergic GPCRs could constitute privileged starting points for drug repurposing.

Despite a large pool of off-patent molecules, suitable candidates for repurposing in CNS disorders are limited due to their inability to cross the blood brain barrier (BBB)

A major bottle-neck which limits the possibility of repurposing approved drugs for the treatment of CNS disorders is that more than 98% of all approved small molecule drugs, and almost all large molecule drugs, do not cross the blood brain barrier (BBB). To overcome this obstacle, pharma companies are developing strategies to design both small molecules as well as biologics that can be actively transported across the BBB. The application of novel technologies such as nanoparticle carriers and molecular Trojan horse (MTH) may permit more drugs/biologics to permeate into the brain, enhancing their utility in CNS disorders.
Approaches to identify the appropriate candidate for repurposing

Identifying novel indications requires a thorough understanding of the primary and secondary pharmacodynamics of the drug as well as in-depth insights into the pathophysiology/molecular mechanisms of the various neurological and psychiatric disorders. Candidate agents for repurposing may be discovered through clinico-epidemiologic, basic science, in silico and phenotypic screening approaches.

Clinico-epidemiologic approach is based on observation of drug effects in diseases other than the approved indication, in a large population. This involves systematic literature review with an eye towards new diseases. The basic science approach is based on understanding the molecular structure of the drug, its in vitro activity or measuring its impact on gene expression. In silico approaches use sophisticated bioinformatics algorithms and data mining tools to closely examine the biologic pathways that are known to interact with the pathway targeted by the drug candidate, and then to generate a hypothesis that would justify examining the compound in a different disease state.

Phenotypic screening involves testing the agent of interest directly in relevant animal models across a number of therapeutic areas. With the appropriate choice of animal models, it is possible to determine whether a candidate test agent has any activity in either a disease state or a pathway associated with a disease state, and the potential to accelerate clinical development.

The ideal candidate for a repurposing initiative would be an off-patent safe drug for which a novel target has been identified; with affinity to the maximum recommended therapeutic dose for an already-approved indication; and linked with strong supporting evidence to an unmet medical need or rare disease.

Companies are using novel strategies to secure intellectual property for repurposed products

One of the major challenges in drug repurposing pertains to securing intellectual property protection for the innovation. “Method of use” patents that cover the use of a pharmaceutical product for a specific indication or cover a method of dosing for a particular type of patient are often dismissed as incremental protection that is not as effective as a “composition of matter” patent in protecting a drug product. However, given the right set of circumstances, a “method of use” patent can be as effective as a “composition of matter” patent in protecting a repositioned drug product.

A variety of strategies have been used by sponsors to secure new intellectual property. These include pursuing a new indication for a new patentable formulation, a patentable delivery mechanism, a patentable combination of APIs or a combination with a proprietary companion diagnostic or service. A strategy also being used to secure intellectual property is to replace hydrogen with deuterium at specific positions. While this approach helps to retain the biochemical potency and selectivity, in certain cases, it modifies the metabolic fate, resulting in a favorable therapeutic profile. Several deuterated versions of approved drugs are currently under development. These include deutetrabenazine and SD-560 (deuterium-containing pirfenidone analog).

Apart from patents, exclusivity in the form of new clinical investigation (NCI) exclusivity and orphan drug exclusivity can also be used to protect intellectual property for repurposed drugs. NCI exclusivity applies to successful conduct of non-bioavailability clinical studies for a new indication, dosage strength or form, delivery method, patient population or condition of use. The drawback with NCI exclusivity is that it is limited by just 3-year duration and the geographic scope is limited to the US.

Orphan drug exclusivity is possible if a drug is repurposed in an orphan indication. The US regulations provide for 7-year orphan drug exclusivity. A drug or biologic which is currently marketed for a common indication is unlikely to be pursued by industry alone for an orphan indication. This is because the price of a drug for which a generic formulations are available, cannot be revised to match that of the orphan drug. However, a second brand strategy may be a viable option.
Drug repurposing in new CNS indications is being used to create value from off-patent molecules

Dimethyl fumarate, originally a psoriasis drug from Germany, was repurposed by Biogen Idec as a multiple sclerosis drug (Tecfidera) by developing a proprietary version and utilizing “method of use” patent. This turned out to be a blockbuster opportunity. Another example is that of memantine which was first synthesized by Eli Lilly and Company and patented in 1968. This drug was derived from amantadine (an anti-influenza agent), but was never marketed. Merz repurposed memantine for Alzheimer’s disease through “method of use” patent.

Table 1 includes select examples of drug repurposing in new CNS indications.

### Table 1: Select Examples of Drug Repurposing in CNS Indications

<table>
<thead>
<tr>
<th>Original Product</th>
<th>Original Indication</th>
<th>Differentiated Product (Company)</th>
<th>New Dosage Form</th>
<th>New Indication</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl Fumarate</td>
<td>Psoriasis*</td>
<td>Tecfidera (Biogen)</td>
<td>Proprietary Delayed Release Capsule Formulation</td>
<td>Relapsing Forms of Multiple Sclerosis</td>
<td>US FDA Approval (2013)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Depression/ Anxiety</td>
<td>Silenor Tablet (Pernix Therapeutics)</td>
<td>Low Dose Tablet</td>
<td>Insomnia</td>
<td>US FDA Approval (2010)</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Parkinson’s Disease</td>
<td>Emsam (Somerset/Mylan)</td>
<td>Extended Release Transdermal Film</td>
<td>Major Depressive Disorder</td>
<td>US FDA Approval (2006)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Sedation/ Anxiolysis/ Amnesia/ Seizures</td>
<td>USL261 (Upsher-Smith laboratories)</td>
<td>Intransal</td>
<td>Seizure Clusters</td>
<td>Phase III Ongoing</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Influenza A/ Parkinson’s Disease/ Drug Induced Extra-Pyramidal Reactions</td>
<td>ADS-5102 (Adamas Pharmaceuticals)</td>
<td>Extended Release Sprinkle</td>
<td>Multiple Sclerosis and Walking Impairment</td>
<td>Phase II Ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Levodopa-Induced Dyskinesia</td>
<td>Phase III Completed</td>
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</tbody>
</table>

* DMF was not approved but Fumaderm®, a specific mixture of dimethylfumarate and monoethylfumarate salts, was registered in Germany for the treatment of Psoriasis since 1994

Sponsors need to build reimbursement and commercialization considerations early in development

In addition to intellectual property protection, pharma companies must design an appropriate development program to gain regulatory approval. The repurposing approach generally leverages a type of new drug application (NDA) called 505(b)(2), in which one or more investigations that the applicant relies on was not conducted by the applicant, and no right of reference has been obtained from the original applicant. Types of information that can be leveraged in 505(b)(2) include published literature and the FDA’s prior findings of safety and efficacy.

Even after gaining regulatory approval, commercial returns depend on payers providing coverage and reimbursement when a therapy is prescribed to a patient. Payers require demonstration of clear clinical benefit at a reasonable cost to cover a new formulation, altered dose, route of administration, and/or combination therapy over existing approved drugs. If generic versions are available, the challenges are even greater, since payers can promote a “generic switch” even if branded drugs have a new indication.
Conclusions and way forward

Significant unmet medical needs remain in the management of neurological and psychiatric disorders. Due to a variety of R&D challenges, the success rate of new chemical entities/new biologic entities securing approval is limited. A strategy of systematic drug repurposing may address unmet needs and provide significant value to companies and patients. To accelerate the development of repurposed drugs, better access to data, new models of collaboration and tools/technologies are being developed. Table 2 provides select examples of these enabling developments, some of which are already being applied to CNS disorders.

Table 2. Enabling Developments for Drug Repurposing

<table>
<thead>
<tr>
<th>Access to Data</th>
<th>Collaboration Models</th>
<th>Tools/Technologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Rare Diseases Repurposing Database (RORD)</td>
<td>NIH/NCATS New Therapeutic Uses Program</td>
<td>Astellas and NuMedii</td>
</tr>
<tr>
<td>Database of products that have received orphan drug designation and are already marketed for the treatment of some other disease; an initiative to accelerate the development of products to treat rare diseases</td>
<td>Collaborative program designed to develop partnerships between pharmaceutical companies and the research community by matching researchers with select pharmaceutical industry assets to test ideas for repurposing drugs</td>
<td>Discovery collaboration to identify new indications for a number of Astellas compounds with the use of NuMedii’s predictive intelligence technology</td>
</tr>
<tr>
<td>Healx (UK Company)</td>
<td>CureAccelerator.org (Cures within Reach)</td>
<td>NFFinder</td>
</tr>
<tr>
<td>Integrates data sources for drug repositioning for patient groups and industry, focused on rare diseases</td>
<td>Interactive, online platform to support research on repurposing drugs; collaborations connect researchers and funders for repurposing research</td>
<td>Web-based bioinformatics tool for comparison of gene expression profiles for drug repositioning</td>
</tr>
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