Database identifies FDA-approved drugs with potential to be repurposed for treatment of orphan diseases

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Abstract
Facing substantial obstacles to developing new therapies for rare diseases, some sponsors are looking to ‘repurpose’ drugs already approved for other conditions and use those therapies to treat rare diseases. In an effort to facilitate such repurposing and speed the delivery of new therapies to people who need them, we have established a new resource, the Rare Disease Repurposing Database (RDRD). The advantages of repurposed compounds include their demonstrated efficacy (in some clinical contexts), their observed toxicity profiles and their clearly described manufacturing controls. To create the RDRD, we matched the US Food and Drug Administration (FDA) orphan designation database to FDA drug and biological product approval lists. The RDRD lists 236 products that have received orphan status designation—that is, were found to be ‘promising’ for the treatment of a rare disease—and though not yet approved for marketing for that rare disease, they are already approved for marketing to treat some other disease or condition. The RDRD contains three tables: Orphan-designated products with at least one marketing approval for a common disease indication (N = 109); orphan-designated products with at least one marketing approval for a rare disease indication (N = 76); and orphan-designated products with marketing approvals for both common and rare disease indications (N = 51). While the data included in the database is a re-configuration/cross-indexing of information already released by the FDA, it offers sponsors a new tool for finding special opportunities to develop niche therapies for rare disease patients.

Keywords: orphan drug; rare disease; repurposing; Orphan Drug Act; efficacy; safety

INTRODUCTION
As defined in the Orphan Drug Act (ODA) [1], rare diseases are those diseases or conditions that affect fewer than 200,000 people in the United States. Even though one rare disease might affect only a few hundred patients, the cumulative impact of those rare conditions is substantial, influencing the lives of more than 25 million people in the United States [2]. The number of rare diseases—now estimated at more than 7000 [3]—continues to increase as a result of rapid growth in our knowledge and understanding of human genetics and the biology of diseases. Rare diseases, which are often life-threatening, can affect any organ system and occur at any age—with many starting in early childhood. In most cases, therapeutic options are few or non-existent and the social and familial burdens of rare diseases are extraordinarily heavy.

In recognition of this societal need, the US Congress approved the ODA in 1983 to provide financial incentives to companies to develop therapies for rare indications. US Food and Drug Administration (FDA) created the Office of Orphan Products Development, which designates drugs and biological products as ‘orphan products’ based on their promise to treat rare diseases.
After designation, the sponsor of an orphan product may submit separate applications to FDA for the drug’s marketing approval for the orphan indication, and also gain the potential to profit from its development of an orphan product. Since the ODA became law, FDA has granted more than 2300 orphan designations to drugs or biological products, approximately 360 of which later also received approval for marketing for the orphan indication. In contrast, there were fewer than 50 drugs or biological products marketed for rare disease indications in the 17 years prior to 1983 [4]. Moreover, orphan products represent ~30% of all the new products—first-time approved by FDA—in the 5 year period 2004–08 [5]. Clearly, the ODA has stimulated orphan drug development for rare disease patients. However, these drugs only provide therapeutic options for a very limited portion of the thousands of rare diseases, most of which still need targeted and effective therapies.

Like all drugs, orphan-designated products must be proven effective and safe before FDA will approve them for marketing. To show the drug’s effectiveness, the sponsor must demonstrate substantial evidence, which is usually generated from adequate and well-controlled clinical studies. To meet the unique challenges of orphan drug development, FDA historically has incorporated flexibility in the reviews of orphan products, such as (i) approving products based on small clinical trials (For example, Aldurazyme was approved for use in patients with Mucopolysaccharidosis-I mainly based on a phase III trial of 45 patients); or (ii) allowing clinical trial designs other than the traditional randomized, placebo-controlled trial (For example, Myozyme was approved for use in Pompe’s disease patients based on two open-label studies with 39 patients in total, one of which was a historically controlled pivotal trial of 18 patients). Drug safety is initially examined through sufficient animal testing to demonstrate that it is reasonably safe to conduct the proposed clinical investigation, followed by phase I clinical trials of pharmacokinetic and pharmacodynamic studies, and later through larger clinical trials, adverse event reporting and post-marketing commitments. Meanwhile, the sponsors are required to demonstrate that a drug is manufactured in a manner that preserves its identity, strength, quality and purity in conditions that comply with current Good Manufacture Practice. Finally, the drug label should reflect its intended use appropriately.

What and where is the RDRD?
We created the Rare Disease Repurposing Database (RDRD) to further accelerate the development of new FDA-approved products for treating rare diseases. It lists 236 products that have received orphan status designation, and though not yet approved for marketing for that rare disease, they are already approved for treating some other disease or condition. These products have successfully translated from bench discovery to use in human patients; they have demonstrated safety and efficacy for use in patients for an FDA-approved indication.

The RDRD can be found on the FDA web site: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm. Products that were designated but not yet approved for treating the designated disease were compared to a list of products that have been approved by FDA for any indication. The resultant products were separated into three tables: orphan-designated products with at least one marketing approval for a common disease indication ($N = 109$); orphan-designated products with at least one marketing approval for a rare disease indication ($N = 76$); and orphan-designated products with marketing approvals for both common and rare disease indications ($N = 51$). The examples of each table (Tables 1–3) are shown here. The tables include designated product and designation sponsors’ names, the not-yet marketed orphan designation and its effective date, the marketed indication(s), ‘trade names’ and the sponsors of the marketed products. A product can have more than one orphan designation (see example in Table 2). The 236 products listed in RDRD represent 420 orphan designations that are not yet approved for marketing. Likewise, a product can also have more than one approved common or rare disease indication. In these cases, the multiple indications are listed in consecutive rows under the same product name. The tables are in Microsoft Excel format, which is easy to search and sort.

The purpose of RDRD and its advantages
Repurposing FDA-approved products has practical advantages over novel compounds that are as yet
### Table 1: Example of Table I in the Rare Disease Repurposing Database

<table>
<thead>
<tr>
<th>Product name</th>
<th>Orphan status designation date</th>
<th>Designated but not yet approved orphan indications</th>
<th>Sponsors holding orphan designations</th>
<th>Trade namesa</th>
<th>Approved common disease indicationsb</th>
<th>Sponsors of approved products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>1 August 1989</td>
<td>For use in conjunction with BCNU in the treatment of brain tumors</td>
<td>Medco Research, Inc</td>
<td>Multiple brands</td>
<td>Conversion to sinus rhythm of paroxysmal supraventricular tachycardia, including that associated with accessory bypass tracts (Wolff-Parkinson-White syndrome)</td>
<td>Multiple sponsors</td>
</tr>
<tr>
<td>Albuterol</td>
<td>12 March 2002</td>
<td>Prevention of paralysis due to spinal cord injury</td>
<td>MotoGen, Inc</td>
<td>Multiple brands</td>
<td>For the prevention and relief of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm</td>
<td>Multiple sponsors</td>
</tr>
<tr>
<td>Alefacept</td>
<td>19 December 2007</td>
<td>For use as prophylaxis of rejection in patients receiving allogenic solid organ transplants</td>
<td>Astellas Pharma Global Development, Inc</td>
<td>Amevive</td>
<td>Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy</td>
<td>Astellas Pharma US, Inc</td>
</tr>
</tbody>
</table>

aIf there are more than two trade names and/or sponsors for the same approved indication, ‘multiple brands’ or ‘multiple sponsors’ are used instead of listing all the brands/sponsors. bAny information about the product after approval for marketing is not included in this database.

### Table 2: Example of Table 2 in the Rare Disease Repurposing Database

<table>
<thead>
<tr>
<th>Product name</th>
<th>Orphan status designation date</th>
<th>Designated but not yet approved orphan indications</th>
<th>Sponsors holding orphan designations</th>
<th>Trade names</th>
<th>Approved rare disease indications</th>
<th>Sponsors of approved products</th>
</tr>
</thead>
<tbody>
<tr>
<td>111 Indium</td>
<td>10 June 1999</td>
<td>Treatment of somatostatin receptor positive neuroendocrine tumors</td>
<td>Louisiana State University Medical Center Foundation</td>
<td>Octreoscan</td>
<td>Indium In-III pentetreotide is an agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors</td>
<td>Malinckrodt</td>
</tr>
<tr>
<td>pentetreotide</td>
<td>16 June 2006</td>
<td>Treatment of neuroendocrine tumors</td>
<td>Radiolotope Therapy of America Genzyme Corporation</td>
<td>Ceredase</td>
<td>Use as a long-term enzyme replacement therapy for children, adolescents and adult patients with a confirmed diagnosis of Type I Gaucher disease who exhibit signs and symptoms that are severe enough to result in one or more of the following conditions: (i) moderate to severe anemia; (ii) thrombocytopenia with bleeding tendency; (iii) bone disease; (iv) significant hepatomegaly or splenomegaly</td>
<td>Genzyme Corporation</td>
</tr>
</tbody>
</table>
unapproved for use in treating any human disease. Foremost, safety data are far better developed for approved products that have been in the marketplace. With the tested dosages and formulations, approved products have demonstrated their pharmacological activity, have known toxicity profiles both in animals and in humans and have well-studied pharmacokinetics and pharmacodynamics. In addition, sponsors of approved compounds already have demonstrated their ability to manufacture drugs in accordance with good manufacture practice requirements. It is essential to produce quality products consistently both before and after receiving marketing approval.

While clinical trials and possibly further animal testing for a newly proposed orphan indication are required to establish the efficacy and safety in patients with a rare disease, previous knowledge and experience can save costs and development time for the new indication. For example, if a drug’s dosage and route of administration is the same for a proposed new indication, early phase human testing could move faster than de novo development. This can be good news for both patients with rare diseases and for orphan drug developers.

In the absence of any new drug development incentives for the repurposing of already approved products, commercial interest in such repurposing is likely to be limited to those products which hold only an approval for a rare disease. For products with a common disease approval, an added rare disease indication can contribute only a tiny fraction of additional sales. At the same time, sponsors often worry that requisite clinical trials may uncover previously unidentified adverse events that affect a drug’s common disease indication. Even though such concerns have never been documented by the Center for Drug Evaluation and Research (CDER) (personal communication with Dr Anne Pariser of CDER), the possibility of such adverse events is perceived to harm sales for the approved treatment of the common disease. It is likely that the repurposing of drugs with common disease approvals will attract the support of patient advocacy groups and emerge as an efficient way to support publicly funded clinical research.

**CONCLUSION**

While the data included in the database represent a re-configuration and cross-indexing of information
previously released by the FDA, the RDRD offers sponsors a new tool for finding special opportunities to develop niche therapies that have clear advantages over novel compounds and may be able to move faster through development. The opportunities tabulated in the RDRD database may provide a short cut for drug developers that hesitate to start from scratch with an untested new therapy compound.

**Key Points**
- Patients with rare diseases need targeted effective therapies.
- Like all drugs, orphan-designated products must be proven effective and safe before FDA will approve them for marketing.
- Repurposing FDA-approved products has practical advantages over novel compounds that are as yet unapproved for use in treating any human disease.
- Rare Disease Repurposing Database offers sponsors a new tool for finding special opportunities to develop niche therapies for rare disease patients.

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**References**