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It is Good to Be an Orphan

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One can expect more companies to be developing safe new orphan drugs soon. Orphan drugs can be obtained from compounds in the food supply. The push for personalized medicine and pharma's growing interest in orphan drug development for patients with rare diseases generated by the Orphan Drug Act [1] are converging to help both patient's and supplement/pharmaceutical companies. Orphan drugs are essential for the small segment of the population suffering from a disease that has few if any treatment options. Orphan drugs also offer financial benefits to companies looking at diminishing pipelines and impending biosimilars and generic competition to blockbusters.

In the United States, orphan drugs are defined as therapies that treat fewer than 200,000 patients [2]. The National Institutes of Health lists approximately 6,000 rare diseases [3]. Approximately 83% of these disorders affect fewer than 6,000 patients. Therefore a large portion of the orphan marketplace is really made up of small, different patient populations. This is an important distinction because markets of a few hundred to a few thousand patients are very different from larger markets of 50,000 to 200,000 and they require a different approach to clinical trials, manufacturing, and marketing.

Orphan drug development provides several advantages to developers:

1. On average it requires slightly less than 5 years for an orphan drug to move from Phase 2 clinical trial to market, in contrast to 6 to 8 years required for traditional drug approval

2. Drugs with orphan designations have better odds of approval, with an 82% success rate (Phase 2 forward) in contrast to 35% for traditional drugs

3. Orphan products offer attractive profitability given the smaller patient populations, which drive premium pricing and reduce the cost of sales

4. Orphan products often experience ongoing revenue growth due to steady increase in use after launch by chronic, lifetime customers

5. Orphan products benefit from a significant competitive advantage in being first to market

6. Some orphan products (e.g., for tropical and perhaps pediatric diseases pending congressional renewal) may be eligible for FDA priority review vouchers [4,5]

The orphan drug industry has seen impressive growth in recent years, with global sales of $84.9 billion in 2009, for example. As a result, enormous attention is now being paid to the orphan market. In FY 2011, the FDA approved 35 innovative new drugs, almost one-third (10) for orphan disorders. A total of 41 new molecular entities and biologics were approved by the FDA in 2014. Orphan drug approvals increased to 41% (17 out 41) of the new drug approvals by 2014 [6].

Many dietary supplements have become orphan drugs. The FDA encourages sponsors to test such compounds as drugs, and offers orphan drug exclusivity as an incentive for sponsors to invest in the necessary studies to prove safety and efficacy. Some dietary supplements and their orphan drug designations and approvals include:

- Glucosamine-N-acetylglucoseamine thiazoline. Used for treatment of adult Tay-Sachs disease. Orphan drug designation 2-06-06.
- Omega-3 Fatty Acids - L-amino acids, vitamins and minerals combined with omega-3 fatty acids. Used for treatment of patients with pediatric Crohn's disease. Orphan drug designation 1-12-11. Omega-3 fatty acids also became a blockbuster drug in Lovaza.
- Levomefolate calcium [7] - Used by Virtus for treatment of megaloblastic anemia caused by folate deficiency. Orphan drug designation 2-10-15.
- Calcium acetate - formerly developed by Pharmedic and used for treatment of hyperphosphatemia in end stage renal failure and disease. Orphan drug designation 12-22-88 and 6-27-89.
- Calcium carbonate - developed by R & D Laboratories [8] for treatment of hyperphosphatemia in patients with end stage renal disease. Orphan drug designation 6-06-90.
- Calcium gluconate - developed by Calgonate [9] for
  - Use as a wash for hydrofluoric acid spills on human skin. Orphan drug designation 11-20-97.
  - Calcium gluconate gel, for use in the emergency topical treatment of hydrogen fluoride (hydrofluoric acid) burns. Orphan drug designation 5-21-91, and calcium gluconate gel 2.5%, for emergency topical treatment of hydrogen fluoride (hydrofluoric acid) burns. Orphan drug designation 5-10-90.
- Coenzyme Q10 - developed by Integrative Therapeutics [10] for treatment of
  - Huntington's disease. Orphan drug designation 3-05-01, and
  - Coenzyme Q10 and d-alpha-tocopherol, developed for treatment of Friedreich's Ataxia. Orphan drug designation 3-14-11.
- Ubiquinol - coenzyme Q10, ubiquinone, developed by Gel-Tec division of Tishcon Corporation [11] for treatment of pediatric congestive heart failure. Orphan drug designation 4-12-04.
- Melatonin - developed by Neurim Pharmaceuticals, Ltd [12] and currently marketed in Europe, Asia-Pacific and the Middle East for
  - Treatment of non-24-hour sleep-wake disorder in blind individuals without light perception. Orphan drug designation 7-09-04.

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- Treatment of circadian rhythm sleep disorders in blind people with no light perception. Orphan drug designation 11-15-93.
- Treatment of neonatal hypoxic ischemic encephalopathy. Orphan drug designation 4-12-13.

- Leucovorin calcium.
  - Leucovorin - For use in combination with 5-fluorouracil for the treatment of metastatic colorectal cancer. Orphan drug designation 12-08-86.
  - Leucovorin - For rescue use after high dose methotrexate therapy in the treatment of osteosarcoma. Orphan drug designation 8-17-88.
  - Leucovorin calcium, developed as Wellcovorin by Glaxo Well come [13] for use in combination with 5-fluorouracil in the treatment of metastatic colorectal cancer. Orphan drug designation 6-23-88.

Orphan products constitute most of the new drug approvals in oncology. Compared with pivotal trials used to approve nonorphan cancer drugs, pivotal trials for recently approved orphan drugs for cancer are more likely to be smaller and to use nonrandomized, unblinded trial designs and surrogate endpoints to assess efficacy. The same philosophy that enables such simplified trials in oncology also enables similar trials for dietary supplements repurposed for orphan drug indications. Companies that specialize in helping small sponsors over the various scientific and regulatory hurdles to converting dietary supplements into orphan drugs are now available [14]. These companies bring on board scientific, engineering, clinical, and regulatory expertise from both the food and drug industries. Safety and efficacy may be more easily established in these compounds, which usually have a longer history of use than NMEs (new molecular entities). The repurposing of dietary supplements as orphan drugs is only beginning to be explored.

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