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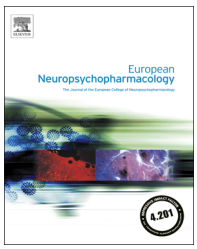

Lost interest for existing compounds: New boosts

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Abstract
Development of new drugs is typically thought of as a bottom-up endeavor where basic science identifies a target, various strategies are used to generate drugs that stimulate or inhibit the target, the drugs are first tested for safety and efficacy in animals and finally efficacy and safety are evaluated in a well defined clinical development process. However, this is not the only way that new drug products are developed. Many new products come from re-initiating development of discontinued drugs, finding new uses for existing drugs, creating a new product by obtaining marketing approval in expanded territories, obtaining approvals for new formulations or a single isomer of a previously approved racemic drug, converting products from prescription to over-the- counter use or converting folk medicines or vitamins to modern pharmaceuticals. Based on this long and successful history of contributions to modern therapeutics, these alternative sources of new products should not be neglected.

1. Introduction

The last decade has been characterized by a steep increase in cost per drug for new drug approvals (Pharmaceutical Research and Manufacturers of America Profile 2013). The number of new chemical entities submitted to the FDA has remained stable, but the consolidated industry investment in R&D has approximately doubled. No clear cause for this declining productivity has been identified. However, various efforts have been undertaken to address it. These include data sharing consortia (e.g. Critical Path Institute, c-path.org), clinical trial registries that require posting of results even from negative studies (e.g. clinicaltrials.gov), establishment of publically available databases of genetic information (e.g. NIH GenBank) to aid drug discovery, the establishment of the National Center for Advancing Translational Science by the US National Institutes of Health and the ECNP Medicines Chest program (Nutt et al., 2014).

These efforts to improve development productivity emphasize translation of basic research discoveries to commercial products. However, this is not the only way of inventing a new product. There is a long history of alternative approaches to developing new products including: re-initiating development of discontinued drugs, finding new uses for existing drugs, creating a new product by obtaining marketing approval in

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expanded territories, obtaining approvals for new formulations or single isomers of a previously approved drug, converting products from prescription to over-the-counter use or converting folk medicines or vitamins to modern pharmaceuticals.

Drugs derived from the pathways described above often have the advantage of reduced risk of expensive failure in advanced clinical trials because there is generally more safety and efficacy data available at the time such trials are initiated. On the other hand, such drugs are often not considered for development because they lack traditional intellectual property protection, e.g. a composition of matter patent. As shown by many examples below, products can be quite economically successful even without this particular kind of intellectual property protection.

A complete review of such products is beyond the scope of this article, the aim of which is to increase interest in these potential new approaches to finding innovative therapeutics by citing successful examples of new products they have generated.

2. Reinitiating development of discontinued drugs

Donepezil HCl, a cholinesterase inhibitor, is an example of a drug that had been discontinued from development following a few phase I studies. It had been rejected as a licensing candidate by many large pharmaceutical companies and discontinued by its commercial sponsor. One of the authors (LTF) identified it as an excellent development candidate based on a number of factors including a large unmet medical need for dementia treatments (no anti-dementia drugs were FDA approved in the US at the time) and evidence that the class had efficacy based on data available from another cholinesterase inhibitor, tacrine. Since tacrine had chemical alerts for various forms of toxicity and was associated with adverse effects on liver enzymes, it seemed unlikely to be a feasible product for most patients. Nonetheless, it provided evidence of efficacy for the class, which was ultimately confirmed when tacrine, donepezil and other cholinesterase inhibitors were approved for the treatment of Alzheimer's disease. Although tacrine was never widely prescribed, the other cholinesterase inhibitors achieved widespread use for the treatment of Alzheimer's disease and they are still widely used today (Alzheimer's Association, 2014). Another example, not from the CNS therapeutic field but nonetheless relevant to the issue of reviving discontinued drugs is rabeprazole a proton pump inhibitor. Rabeprazole was initially put through a few phase I trials and then discontinued because of safety concerns related to tumors in rats observed for another similar product, omeprazole. In this case as well, one of the authors (LTF) recognized that these tumors had a number of features that made them less worrisome than a superficial analysis might conclude. For example, the particular kind of tumors caused by proton pump inhibitors was almost never a cause of human disease, being most commonly found incidentally at autopsy after death from some other cause. Furthermore, the rats that developed these tumors survived longer than rats that did not, suggesting that in rats, as in humans, these tumors are not pathogenic but rather incidental changes without adverse consequences. As might be expected, it took some time and considerable basic research to verify the biochemical mechanism responsible, but omeprazole, rabeprazole and other proton pump inhibitors ultimately became widely used therapeutics that benefited millions of patients (International Foundation for Functional Gastrointestinal Disorders, 2014).

Iloperidone is an atypical antipsychotic originally developed by Hoechst Marion Roussel, Inc., which discontinued it from development and licensed it to Titan Pharmaceuticals, Inc., which in turn sold to Vanda Pharmaceuticals, Inc. Vanda eventually obtained FDA approval of iloperidone for treatment of schizophrenia, again showing that a product that was discontinued by one company may be successfully developed by another (Bender, 2009).

These are just a few of the examples that could likely be cited if the archives of pharmaceutical companies were more accessible.

3. New products derived by finding a new use for an existing product

Although it is quite common for a product to have multiple uses (approved indications), it is also possible to market the same or a very closely related chemical substance under a second brand name for a different indication. Examples among central nervous system therapeutics include: paroxetine, which was originally as Paxil® and approved for CNS disorders like depression and anxiety but later marketed by a different manufacturer as Brisdelle® for treatment of "moderate to severe vasomotor symptoms associated with menopause". A similar rebranding was done with antidepressant fluoxetine which rebranded as Sarafem® and marketed as a treatment for premenstrual dysphoric disorder.

Bevacizumab (Avastin®), (Genentech/Roche) is an angiogenesis inhibitor that slows the growth of new blood vessels. It was originally licensed to treat various cancers, including colorectal, lung, breast, glioblastoma, kidney and ovarian. Genentech later introduced a modified version of bevacizumab, ranibizumab (Lucentis®) as a treatment for wet macular degeneration. Introduction of ranibizumab treatment resulted in significant improvements in wet macular degeneration patient outcomes (Mitchell et al., 2014 l).

Perhaps the most unusual rebranding of a drug for a new use is the case of thalidomide. This drug was originally marketed as a treatment for various CNS disorders including anxiety and insomnia and was later marketed as a treatment for morning sickness in pregnant women. In the latter use, thalidomide produced terrible birth defects and was taken off the market for that reason (Botting, 2002). Today, thalidomide is being successfully marketed as a treatment for multiple myeloma and certain complications of leprosy with prominent warnings about the potential for birth defects (Thalomid Prescribing Information, 2014).

Another method for making a "new" product from an existing approved product is to obtain approval for non-prescription use of a formerly prescription product. There are a number of examples of such conversions including: ibuprofen, omeprazole and other proton pump inhibitors and H_2 blockers.

One interesting example of a new product generated from an old one is Rogaine® (minoxidil). Minoxidil was originally marketed as a systemic anti-hypertensive with