

## **Innovator or Generic, All Roads Lead to the 505(b)(2)**

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Faced with decreasing R&D output, billions of dollars in patent expirations and increasing generic competition, innovators are forced to reevaluate traditional business models. At the same time, generic manufacturers face more competition than ever before. The result has been pressure on pharmaceutical companies across the board to adapt their strategies and transform their organizations to maintain income while developing new revenue streams.

### **Innovators**

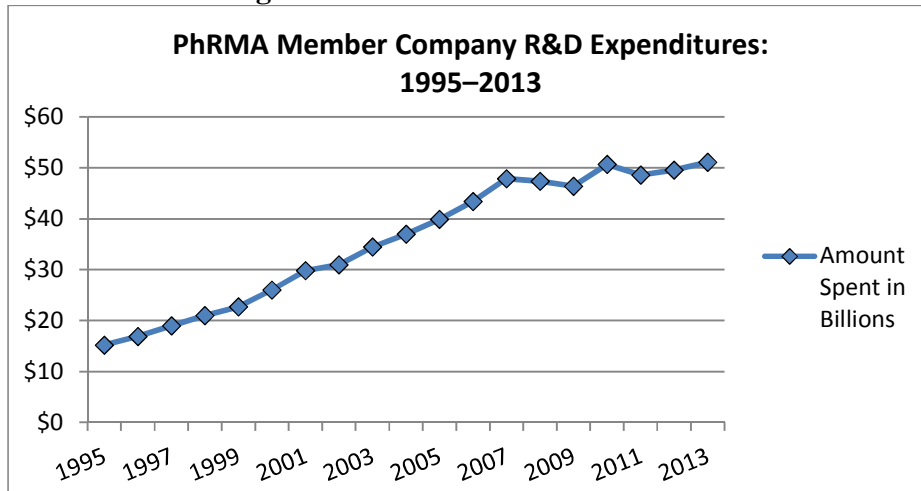
Profitable and continuous participation in the U.S. pharmaceutical market is fraught with challenge. The barriers to entry are considerable and sustained growth is always in question. Innovators operate in an environment where for every one blockbuster drug-product, multitudes of compounds are eliminated from consideration in the preclinical phase or, if they make it that far, fail in clinical trials. For every drug approval, millions are spent on pharmaceuticals that never make it to market. Those that do launch generally do not achieve blockbusters status, yet their sponsors must still address challenges such as patent expiries, generic competition, and increasingly stringent regulatory guidelines.

The challenges faced by innovators have been compounded by marked decreases in productivity in R&D, and consequently the number of new molecules introduced to the market. Despite scientific advances that have expanded the universe of plausible therapeutic targets for the development of innovative compounds, and decades of increased R&D investments, there has not been any corresponding increase in the output of new drug approvals<sup>1</sup> (See Tables 1 and 2).

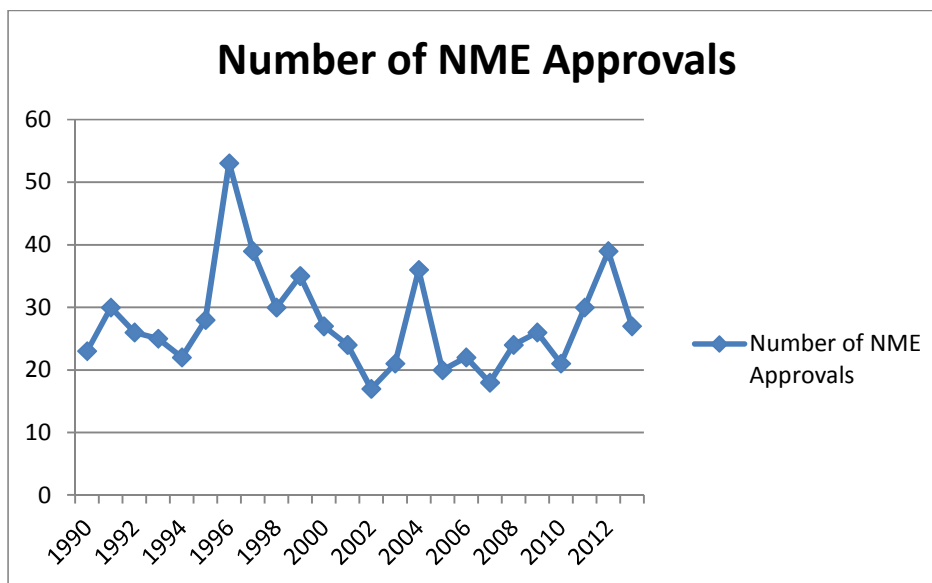
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<sup>1</sup> Pammolli, F; Magazzini, L; Riccaboni, M. Nature Reviews: Drug Discovery, June 2011, Vol 10, 428-438.

**Table 1: R&D budgets have been on the rise for decades.<sup>2</sup>**



**Table 2: Despite steadily increasing R&D investments, FDA approvals of new chemical entities have been relatively flat.<sup>3,4,5</sup>**



At the same time, the pharmaceutical industry has experienced the results of a patent cliff. The patent cliff has been described as roughly a five-year period when a majority of U.S. blockbusters have gone off patent. The cliff emerged in 2009, peaked by 2012, and has continued

<sup>2</sup> PhRMA 2014 Profile

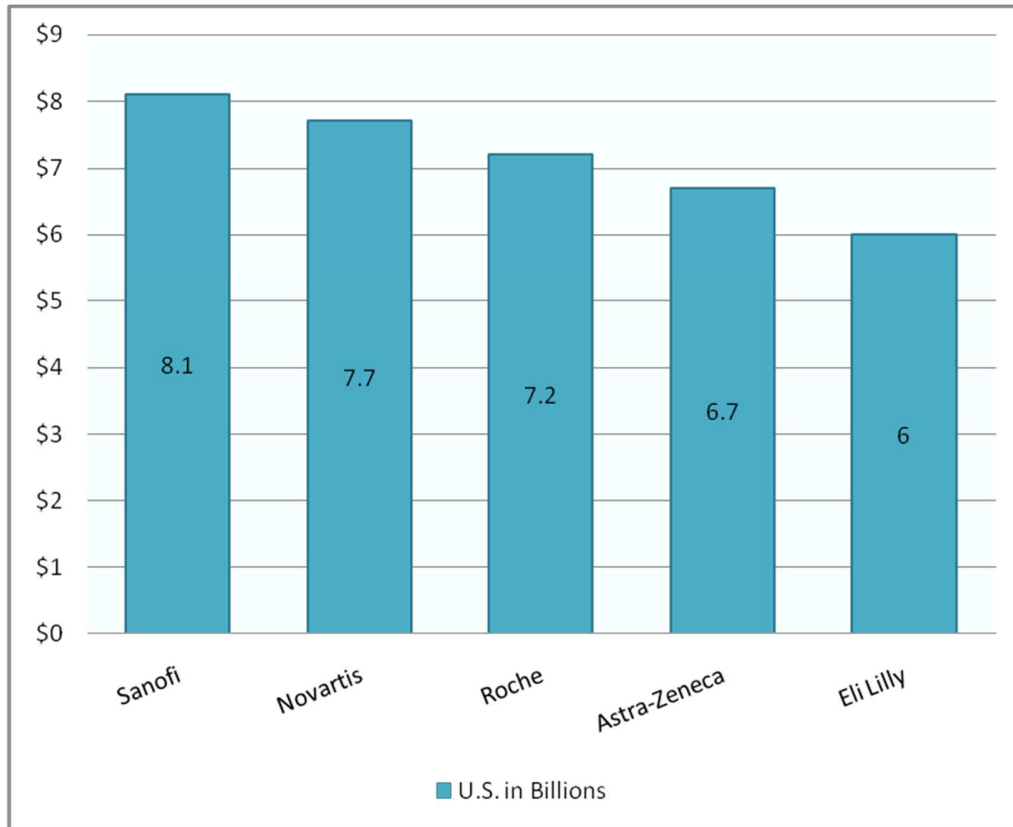
<sup>3</sup> FDA Summary of NDA Approvals & Receipts, 1938 to the present

<sup>4</sup> FDA Novel New Drugs Summary 2012

<sup>5</sup> FDA Novel New Drugs Summary 2013

through 2014. Some of the brands that have or will lose patent protection include Lipitor® and Zyprexa® in 2011; Diovan®, Plavix®, Seroquel®, Lexapro®, Actos®, and Singulair® in 2012; Oxycontin® and Cymbalta® in 2013; and Nexium® and Celebrex® in 2014.<sup>6</sup>

**Table 3: Companies losing at least \$6 billion each in revenues as a result of patent expiries between 2009 and 2014.<sup>7</sup>**



**Generics**

ANDA sponsors describe a time when entry or participation in the U.S. market with generics was a significantly lower risk proposition. Those days appear to be on the wane. In 1984, on the eve of the passage of Hatch-Waxman only 12% of all dispensed prescriptions were generic. By 2000, that number had reached 44% yet represented only 8% of prescription drug revenue.<sup>8</sup> Today, 84% of the prescriptions dispensed in the United States are generic.<sup>9</sup> IMS reports that the value of the generic market averaged \$23 billion annually between the years 2008 and 2012 but could sink as low as \$13.1 billion in the aggregate for the period 2013 to 2019.<sup>10</sup>

<sup>6</sup> Jumping Off the Patent Cliff...and Surviving. Angelo Giambone Senior Vice President for Industry & Network Relations Prescription Solutions by OptumRx. 2014.

<sup>7</sup> This Patent Cliff 2014 Chart Shows How Much Revenue Big Pharma Will Lose. Kyle Anderson, Associate Editor, Money Morning. February 18, 2014.

<sup>8</sup> OGD 2007: The FDA Process for Approving Generic Drugs.

<sup>9</sup> Mylan's generic drug development illustrates challenges of industry. Alex Nixon. TribLive Business. Jan. 4, 2014.

<sup>10</sup> The Right Path. Samedan Ltd. Pharmaceutical Publishers. Summer 2014.

Compounding this concern, the field is becoming increasingly crowded with competitors as ANDA review times continue to rise. In 2013, there were 968 ANDAs submitted<sup>11</sup> and the median time for generic drug approval jumped to 36 months (in 2009, the average review time was approximately 26 months).<sup>12</sup> By the end of fiscal year 2014, there were 1,473 ANDAs submitted to FDA<sup>13</sup> and median time for approval was projected to be as high as 43 months.<sup>14</sup> While review times are projected to improve given the recent passage of GDUFA, the issue of a market crowded with competitors remains.

Business leaders in the Indian pharmaceutical industry, long a bellwether for global generics, recently stated: “Till a few years ago, Para IV filing opportunities in the US had leading Indian companies excited. A successful filing entitled a generic drug maker to 180 days of exclusive marketing rights in the US. Today, that option is no longer as attractive... moreover, with newer entrants in the U.S. generics market, the small opportunities are getting excessively crowded.”<sup>15</sup>

It is well known that generic drug prices fall with a significant increase in competition. However, a lesser known theory holds that prices tend to remain above long-run marginal cost until eight or more competitors enter the market.<sup>16</sup>

Today, it is not unusual to see ten or more competitors enter within in a very short time.<sup>17</sup> Despite their abbreviated development process, generic manufacturers still make significant investments before knowing when or how much competition will await, or when or if their efforts will be profitable.

Current events suggest that the pharmaceutical industry is undergoing a substantial transformation. The decrease in innovative output by industry giants poses a threat to their short and long-term economic performance. This has been exacerbated by such factors as the patent cliff, price concession demands of public payers, and ever-increasing regulatory requirements.<sup>18</sup> On the generic side of the ledger, it is likely that available revenues will continue to shrink, the field will remain crowded and the opportunity to capitalize on blockbusters going off patent will diminish.

In short, it appears that we may experience a decrease in the development and launch of blockbusters and continued crowding in a shrinking generic market. The result has placed pressure on pharmaceutical companies across the board to adapt their strategies and transform their organizations to extend the value of existing products, develop niche products and create new sources of revenue. The 505(b)(2) NDA represents a useful regulatory pathway for industry to enhance and stabilize revenues.

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<sup>11</sup> Activities Report of the Generic Drug Program (FY 2013)

<sup>12</sup> FDA Public Meeting September 17, 2010 on Generic Drug User Fees

<sup>13</sup> Activities Report of the Generic Drug Program (FY 2014)

<sup>14</sup> GDUFA Policy Development Hearing, September 17, 2014

<sup>15</sup> Mathew, J.C.; Jayakumar, P.B. Business World: 10 February 2014

<sup>16</sup> Reiffen, D.; Ward, M.R. Generic Drug Industry Dynamics, February, 2002

<sup>17</sup> [www.fda.gov/Drugs](http://www.fda.gov/Drugs) @ FDA

<sup>18</sup> <http://www.strategie-aims.com/events/conferences/23-xxieme-conference-de-l-aims/communications/2840-on-the-road-towards-new-r-d-based-business-models-to-sustain-value-creation-in-big-pharmaceutical-companies-exploring-the-case-of-roche/download> accessed on January 15, 2015

### **The 505(b)(2) Opportunity**

Pharmaceutical firms that seek to develop differentiated products without investing tens of millions of dollars will find the 505(b)(2) NDA to be an indispensable competitive mechanism. The 505(b)(2) is a powerful weapon in the regulatory arsenals of those firms in need of niche products and revenue streams pursued by fewer competitors in the short-term. Indeed, a recent publication reports of the 96 non-ANDA approvals issued by FDA in 2013, two-thirds were new combinations, dosage forms and active ingredients, or other type 505(b)(2) approvals.<sup>19</sup>

Most basically, the 505(b)(2) pathway involves changing an already approved product to create a new drug with either a new indication, formulation, target population or other differences requiring clinical evidence for approval. One of the major advantages of the 505(b)(2) is that sponsors may rely in part upon previous FDA findings of safety and efficacy, as well as data from the scientific literature or otherwise available in the public domain. Because approval may rely upon data previously accepted by FDA, and in most cases the active moiety has already been approved, study requirements may be of lesser scope. Therefore, costs, risk and time to market are reduced. A major incentive is the potential for three to five years of marketing exclusivity (seven for orphan products) depending on the extent of change to the product and clinical studies required for approval by FDA.

There are a number of changes to approved drugs/reasons for which 505(b)(2) applications can be submitted, including dosage form, strength, route of administration, substitution of an active ingredient in a combination product, formulation, dosing regimen, active ingredient, combination product, indication, Rx-to-OTC switch, nonprescription product outside the OTC monograph, or bioequivalence. The balance of this discussion will describe the opportunities associated with combination drugs, orphan drugs and the Rx-to-OTC switch.

### **Fixed Dose Combinations (FDCs)**

FDCs represent lucrative lifecycle extension strategies, with worldwide sales topping \$30 billion in 2009.<sup>20</sup> FDA added to the appeal of FDCs in October 2014 with a newly finalized policy, which will for the first time allow new fixed-dose combinations consisting of at least one new drug product to be eligible for five years of new chemical entity exclusivity. Under the eligibility clause, a drug is eligible for five-year NCE exclusivity if it is 'a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [505(b)] application'.<sup>21</sup> This would seem to indicate that five-year exclusivities will be available for certain grandfathered drugs.

There are a number of high profile examples of FDC successes (Advair<sup>®</sup>, Caduet<sup>®</sup>, and Vytarin<sup>®</sup> to name a few). However, Horizon Pharma offers a more apt example to those pharmaceutical firms who seek niche markets. On April 23 2011, Horizon Pharma won approval for Duexis<sup>®</sup>, its FDC of proprietary single-tablet combination of ibuprofen (800mg) and famotidine (26.6mg).

Duexis<sup>®</sup> is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers. With the

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<sup>19</sup> Ibid. @ 15

<sup>20</sup> Kappe, Eelco (2014), "Pharmaceutical Lifecycle Extension Strategies," in Innovation and Marketing in the Pharmaceutical Industry, Min Ding, Jehoshua Eliashberg, and Stefan Stremersch, Eds., Springer, forthcoming

<sup>21</sup> FDA Guidance, New Chemical Entity Exclusivity Determinations for Certain Fixed-Dose Combination Drug Products, October 2014

launch of Duexis<sup>®</sup>, the indicated population who may also be at risk for developing upper gastrointestinal ulcers from NSAID use, became the beneficiaries of a new treatment option. Upon launch, Horizon stated that they expected broad managed care access while ensuring availability to patients at a reasonable out of pocket cost.<sup>22</sup> The first full-year gross sales for Duexis<sup>®</sup> (2013) were \$85.5 million yielding a net of \$59.0 million.<sup>23</sup>

### **Orphan Drugs**

Orphan drug use comprises approximately 6% of total pharmaceutical sales. As of 2012, it was estimated that 25 million people in the US were afflicted with an orphan disease.<sup>24</sup> Although relatively small numbers of individuals have specific orphan disorders, the size of the overall population and high levels of reimbursement make this an attractive option for industry.

In general, orphan drugs that meet the criteria described above would qualify for 505(b)(2) reviews. Once approved, the further opportunity lies in the repositioning of these drugs to treat other rare diseases. Surprisingly, there have been a number of orphan drug blockbusters.

The following are examples of orphan successes:

- NebuPent (pentamidine – sponsor Lyphomed) has long been used for sleeping sickness.<sup>25</sup> However, further research yielded a new use, the IM/IV treatment and prophylaxis of AIDS-related pneumocystis pneumonia, an orphan indication eligible for seven years of market exclusivity.<sup>26 27</sup> The lifecycle of Pentamidine was again extended by reformulating an aerosolized dosage form that reduced side-effects and filing a 505(b)(2) for the new approval.<sup>28 29 30</sup> Shortly thereafter, Lyphomed sold for close to \$1 billion.<sup>31</sup>
- Glycopyrrolate was originally approved for intravenous administration to reduce gastric and other secretions before surgery and during anesthesia and intubation.<sup>32</sup>  
<sup>33</sup>Glycopyrrolate was later approved as a tablet to treat peptic ulcers.<sup>34 35</sup> Additional research led to yet more new indications and the 505(b)(2) development of a liquid formulation for cerebral palsy patients to reduce drooling.<sup>36</sup> The new drug was granted orphan<sup>37</sup> drug status and is currently being developed as a long-acting muscarinic antagonist for use by COPD patients in a multiple-dose inhaler, dry powder inhaler and

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<sup>22</sup> Horizon Pharma Announces Launch of DUEXIS® (Ibuprofen/Famotidine) 800mg/26.6 mg in the United States. Marketwired News Room - 12/05/11

<sup>23</sup> Horizon Pharma Reports 2013 Financial Results and Provides Business Update. Horizon Pharma Press Release 03/13/14

<sup>24</sup> Orphan Drugs: "Rare" Opportunities To Make Money. Forbes, Pharma & Healthcare, August 23, 2012

<sup>25</sup> [www.drugs.com](http://www.drugs.com) Pentamidine Isethionate

<sup>26</sup> [www.fda.gov](http://www.fda.gov) Drugs @ FDA Pentamidine

<sup>27</sup> Physicians Desk Reference 1994

<sup>28</sup> Ibid. @ 24, 25

<sup>29</sup> FDA Panel Backs Drug for AIDS-Related Pneumonia. LA Times May 2, 1989

<sup>30</sup> Thoene, J.G. Science, New Series, Vol. 251, No. 4998. (Mar. 8, 1991), pp. 1158-1159.

<sup>31</sup> Lyphomed Executives Step Down. April 4, 1990 Chicago Tribune, Steven Morris

<sup>32</sup> [www.fda.gov](http://www.fda.gov) Drugs @ FDA Glycopyrrolate

<sup>33</sup> Physicians Desk Reference 1978

<sup>34</sup> Ibid. @ 32

<sup>35</sup> Ibid. @ 33

<sup>36</sup> Ibid. @ 32

<sup>37</sup> Cuvposa Glycopyrrolate, NDA 022-571, FDA Review, Approval Date July 28, 2010

nebulized dosage forms. It has been reported that the value of these new indications exceeds \$1 billion.

### **Rx to OTC Switches**

Rx to OTC switches and the corresponding repositioning from the prescription marketplace to the retail space represents huge market potential. The global market for nonprescription drugs is expected to exceed \$70 billion by 2015.<sup>38</sup> Retail OTC sales in the US in 2013 have been reported to be \$33.1 billion.<sup>39</sup> Further, FDA's recent Non-prescription Safe Usage Regulatory Initiative (NSURE), is reviewing a number of disorders and drug classes that hold promise for conversion to nonprescription status.<sup>40</sup> Following are selected examples of successful Rx-to-OTC switches (see also Table 3).

In 2002 Adams Pharmaceutical received approval for 505(b)(2) nonprescription Mucinex<sup>®</sup>. Previously available by prescription only, Mucinex<sup>®</sup> became the only long-acting, single ingredient, guaifenesin product available nationwide when FDA removed all competing prescription products from the market. The 1951 Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act stipulates that a drug product cannot be marketed simultaneously both as a prescription and as a nonprescription product at the same strength and same dosage. It should also be noted that all other sponsors were marketing unapproved versions of the product and FDA regulations had long required an NDA for all long-acting drug products.<sup>41</sup> However, Adams' 505(b)(2) approval was evidently the catalyst for the widespread withdrawal of all competing products.

According to Adams in 2005 "We currently market two OTC products under our Mucinex brand... For the fiscal year ended June 30 2004, our revenues were \$61.3 million and our net income was \$35.8 million... representing a 337% growth in revenues over the fiscal year ended June 30, 2003. For the nine months ended March 31, 2005, our revenues were \$121.1 million and our net income was \$24.0 million, representing a 147% increase in revenues over the nine months ended March 31 2004."<sup>42</sup> Adams was later acquired by Reckitt Benckiser for \$2.3 billion.<sup>43</sup>

Additional examples of successful Rx to OTC switches are listed in Table 4.<sup>44</sup> Those products with sales data available ranged from \$38 million to \$300 million in annual sales for at least one year between 2007 and 2012. While the sponsors of the examples that follow are from big pharma, it is important to note that in general, any pharmaceutical company can submit a 505(b)(2) for an Rx to OTC switch of any drug whether pioneer or generic (subject to approvability, patent concerns, etc.).

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<sup>38</sup> Stone, Kathlyn. [www.about.com](http://www.about.com) The Over-The-Counter Drug Industry. Sales increase as consumers reduce number of doctor visits for minor ailments

<sup>39</sup> CHPA OTC Retail Sales 1964-2013

<sup>40</sup> Lauder, S.P. Successfully Making the Rx-to-OTC Switch. September 18, 2013

<sup>41</sup> Adams Laboratories Comments on Favorable FDA Regulatory Action In the Long-Acting Guaifenesin Market, PR Newswire Oct 21

<sup>42</sup> Adams Respiratory Therapeutics 424(b)(1), July 20, 2005

<sup>43</sup> Press Release - Adams Respiratory Therapeutics receives a \$2.3 billion investment, Dec 10, 2007

<sup>44</sup> Arnum, P.V. DCAT Connect. May 5, 2014. Novartis, GSK, Bayer and Merck Become Movers in the OTC Market

**Table 4: Snapshot of Rx to OTC Switches.**

Company	Product (Active)	Purpose	Year Approved	Sales (in Millions)	Year of Reported Sales
Merck	Claritin <sup>™</sup> (Loratadine)	Antihistamine	1993	\$300	2012
J & J	Zyrtec <sup>™</sup> (cetirizine)	Antihistamine	2007	\$160	2007
Novartis	Prevacid 24HR <sup>™</sup> (lansoprazole)**	Acid reducer; proton pump inhibitor	2009	\$98	2013
Merck & Co.	Zegerid <sup>™</sup> (omeprazole and sodium bicarbonate)**	Acid reducer; proton pump inhibitor	2009	\$38	2013
Sanofi	Allegra <sup>™</sup> (fexofenadine HCl)	Antihistamine	2011	\$203	2013
Sanofi	Allegra D 12-Hour <sup>™</sup> (fexofenadine HCl and pseudoephedrine HCl)	Antihistamine/decongestant	2011	NA	NA
Sanofi	Allegra D 24-Hour <sup>™</sup> (fexofenadine HCl and Pseudoephedrine HCl)	Antihistamine/decongestant	2011	NA	NA
Sanofi	Nasacort Allergy 24HR <sup>™</sup> (triamcinolone acetonide)	Allergice rhinitis	2013	NA	NA
Merck & Co.	Oxytrol for Women <sup>™</sup> (oxybutynin)	Overactive bladder	2013	NA	NA
Pfizer	Nexium 24HR <sup>™</sup> (esomeprazole magnesium)	Acid reducer to reduce frequent heartburn	2014	NA	NA

The key to successes such as those outlined above is the employment of strategic planning principles beginning at project conception. The engagement of a strategic pharmaceutical consultant with experience in 505(b)(2) submissions should be addressed at the earliest stages of development. Generic companies that have historically developed only bioequivalent versions of other drug products, often lack the competencies to evaluate the scientific, medical, regulatory, and commercial feasibility of differentiated drug products. Likewise, start-ups and mid-cap innovators do not always have access to all the resources necessary to strategically execute each facet of a 505(b)(2) program. Being continuously positioned to address such challenges is vital to marketing success and return on investment.

#### **About the Author**

Charles Jaap is Vice-President of Operations and Business Development for Pharmaceutical Development Group, Inc (PDG<sup>®</sup>). PDG is a global pharmaceutical consultant with extensive experience in the strategic development of 505(b)(2) drug products. From identification and choice of viable candidates through ensuring the existence of cost-effective commercialization strategies, PDG is unique in its ability to comprehensively and ideally integrate products, dosage forms, populations and FDA regulatory pathways. Please feel free to [contact us](#) for more information.

The opinions and statements in this paper are solely those of Charles Jaap and do not necessarily reflect those of PDG.