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Competition and Relevant Markets in the Pharmaceutical Industry: The Case of PAH Drugs

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Abstract
The nature and extent of competition between different therapies for a given medical condition often is a critical and controversial issue in both antitrust cases and in general strategic analysis in the pharmaceutical industry. The market for pulmonary arterial hypertension (“PAH”) therapies provides an interesting case study for analyzing these issues. An event study analyzing how the stock prices of PAH therapy providers respond to competitive developments sheds light on the nature of competition among different types of therapies. The results support the view that not all drugs for a given medical condition should necessarily be included in the same relevant market. In particular, the strength of competition between any two drugs can vary greatly depending on factors such as the mode of delivery, the mechanism of action, convenience/ease of use, and other characteristics.

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I. Relevant Product Markets in the Pharmaceutical Industry

Market definition can often be a critical issue in antitrust cases in the pharmaceutical industry. U.S. antitrust authorities and the courts have used a variety of approaches to defining the relevant market. In some cases they have advocated relatively broad markets, encompassing all drugs for treating a given medical condition. For example, in its 2003 challenge to the merger of Pfizer Inc. and Pharmacia Corporation, the FTC alleged a market of “research and development, and the manufacture and sale of prescription drugs for the treatment of ED” or erectile dysfunction. Similarly, in challenging Glaxo Wellcome plc’s merger with Smith-Kline Beecham plc, the FTC alleged relevant markets of “drugs for the treatment of irritable bowel syndrome” and “prophylactic herpes vaccines.” In some cases, the government has also included in the market not only currently marketed drugs for a given medical condition, but also new drugs under development for the condition.

In other cases, antitrust authorities sometimes have advocated much narrower relevant markets, including markets comprised of a single drug. For example, in many cases where the maker of a branded drug is accused of preventing or delaying the entry of generic competition, the relevant market has been limited to a single chemical compound. Similarly, in other cases the market has been defined even more narrowly, to include only generic versions of a particular drug. There have also been a number of cases where the relevant market definition was broader than a single drug, but narrower than all drugs for a given condition. In these cases, the market definition analysis has differentiated among therapies based on a variety of criteria such as:

- whether drugs treat a disease by interacting with the body in the same manner (i.e., whether they have the same “mechanism of action”);
- whether drugs have the same chemical compounds;
- whether drugs have the same dosage form (e.g. injectable, liquid, tablets, etc.);
- whether drugs have the same frequency of dosage, such as once a-day or extended release;
- whether drugs have the same strength of dosage;
- whether drugs are branded or generic;
- whether drugs require a prescription or are sold over-the-counter;

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• whether drugs are currently marketed or are in development.

An informative summary of these cases and the issues involved in using different approaches can be found in Morse.⁴

II. Relevant Product Markets for PAH Drugs

The market for drug therapies to treat pulmonary arterial hypertension (PAH) provides insight into the nature of competition in pharmaceutical markets. PAH is a serious medical condition characterized by continuous high blood pressure in the pulmonary arteries, the blood vessels that carry oxygen-poor blood from the right ventricle in the heart to the small arteries in the lungs. PAH is a serious condition for which there are several different types of treatments that benefit many patients, but no cure is currently available.⁵

The different types of therapies for PAH are summarized in Figure 1. PAH therapies differ from one another in several dimensions including mode of delivery, mechanism of action, actual and perceived efficacy, side effect profile, convenience/ease of use, and others. One of the important ways that PAH drug products differ is the manner in which they are delivered to patients. The drug delivery methods are: oral; subcutaneous; intravenous; and inhaled. In terms of ease of use and lack of impact on day to day life, patients generally prefer to have their drugs administered in oral form, followed perhaps by the inhaled form and then the subcutaneous and intravenous forms.

Oral treatment is the most convenient for the patient since it consists of a pill which can be easily ingested by the patient. Subcutaneous and intravenous drugs are considerably more cumbersome for the patient with the intravenous drug requiring the patient to have a central catheter while the subcutaneous product requires the patient to have a device implanted in their abdomen which slowly meters out the required medication. From the patient’s perspective, the inhaled product would fall between the oral and the subcutaneous and intravenous products. The inhaled products are administered using a nebulizer that requires the patient to breathe through

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⁵ In many PAH patients, the heart muscle weakens gradually over time and loses its ability to pump enough blood for the body’s needs, often resulting in heart failure.

an apparatus for several minutes. Currently marketed inhaled products require as many as 6 to 9
doses daily. While the oral products are clearly preferred from a cost and ease of use
perspectives, the other modes of delivery often become necessary for many patients as their
disease progresses.

The difference in delivery methods is related to the type of drug treatment that is
prescribed. Currently there are four general categories of PAH drugs: Endothelin Receptor
Antagonists (ERAs) like Tracleer; Prostacyclins like Flolan and Remodulin; PDE-5 Inhibitors
like Revatio/Viagra, and calcium channel blockers. Each of these products addresses the
symptoms of PAH using different methods and generally are associated with specific delivery
methods. ERAs and PDE-5 Inhibitors are taken orally, while prostacyclins are administered
subcutaneously, intravenously or by inhaling using a nebulizer. In addition, some different types
of PAH drugs may be used in combination with each other to create a broader range of treatment
options for PAH patients.

Conceptually, the relevant product market is the smallest group of products which, if sold
by a hypothetical monopolist, could profitably be sold at prices that exceed the current pre-
merger levels by a small but significant amount. Factors considered in defining the relevant
market include substitutability (as reflected in product characteristics and perceptions of
producers, customers, government agencies, and the industry), cross-price elasticities between
product categories, price levels and trends, profit margins, and the ability to price discriminate.
These factors also indicate whether more than one relevant market exists.

In analyzing the relationships among different PAH drugs for defining relevant markets,
the key factors are what economists call the cross-price elasticities of demand between the
different drugs. For example, if a hypothetical monopolist of oral drugs for PAH attempted to
raise the price of such drugs, to what extent would they lose sales to suppliers of other categories
such as IV, subcutaneous or inhaled drugs? If the amount of sales they would lose would not be
sufficient to make such a price increase unprofitable, oral drugs can be considered a separate
relevant market. Similarly, if a hypothetical monopolist of IV and subcutaneous drugs would
find it profitable to raise prices on these drugs, these categories would also constitute a separate

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6 Calcium channel blockers are appropriate for only a third of patients who are vasoreactive.
7 “Horizontal Merger Guidelines,” U.S. Department of Justice and Federal Trade Commission, April 2, 1992,
Sections 1.0, 1.1.
relevant market. Obviously, if there were no potential for substitution between categories at all, each category would comprise a separate relevant market.

Given the background information on PAH drugs summarized above, it is plausible that a more complete economic analysis would show that oral PAH drugs are a separate relevant product market from subcutaneous and intravenous PAH drug products (and possibly inhaled PAH drug products.) As discussed above, the oral form of treatment generally is strongly preferred by both the patient and physician, especially in the early stages of treatment of PAH. This preference leads to a lack of significant substitution between oral and other drug categories for the large majority of early stage patients. In addition, oral PAH drug treatments are substantially cheaper on a yearly basis than subcutaneous/intravenous PAH drug treatments. For example, it has been estimated that the current market leader Tracleer costs approximately $35,000-40,000 a year per patient while I.V. Flolan and I.V. Remodulin cost about $100,000 and $120,000 a year per patient, respectively. Accordingly, we would expect relatively little direct competition on price between the oral PAH drug treatments and the subcutaneous/intravenous PAH drug treatments.

Additional information on cross elasticities can also be obtained from business documents that reveal how market participants and industry analysts view competition among different types of drugs. For example, the limited substitution between oral PAH drugs and other categories is consistent with the projections of industry analysts. It appears that the entry and future growth of Remodulin (at least in its IV and sub-cutaneous forms) is not expected to significantly impact on the future sales of oral drugs such as Tracleer. In contrast, entry and growth of oral competitors Revatio and Thelin are expected to significantly reduce the sales of Tracleer below where they would otherwise have been. Similarly, the projected growth of Remodulin is expected to substantially reduce the sales of Flolan, the pre-existing IV prostacyclin competitor.

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9 As some patients’ symptoms worsen, there may become a stage where there is more therapeutic substitution between drugs – e.g. adding Revatio and/or an inhaled prostacyclin to a pre-existing Tracleer regimen may delay the point where it is necessary to begin IV or sub-cutaneous treatment.

10 See, e.g. Wachovia, pp. 25-26.

11 Ibid.
The lack of a significant projected effect of non-oral drugs like Remodulin or Flolan on prices or sales of oral drugs such as Tracleer may seem somewhat counter-intuitive in light of the historical development of PAH therapies. When Actelion introduced Tracleer in 2001, the only existing approved therapy for PAH was Flolan. In growing its sales from its entry to the present, Actelion undoubtedly made sales to many patients that would otherwise have become Flolan (or more recently Remodulin) patients. Similarly, Actelion may have considered the prices of existing IV and subcutaneous products in deciding how to price Tracleer when it entered in a way that would substantially expand the potential market for PAH therapy and maximize its profits. However, the key question for evaluating competition and relevant markets in the current market environment is what the relevant cross-price elasticities between the different types of drugs are going forward in the environment that prevails today and in the foreseeable future. Even if the prices of intravenous and subcutaneous drugs may have had some impact on Tracleer’s prices and sales in the past when Tracleer faced no direct oral vs. oral competition, this does not imply that they would have a significant impact in the future when oral competition exists.

There are currently many more patients taking oral medications than there are taking prostacyclins. Moreover, the number taking oral meds is expected to grow much more rapidly. For example, one source estimates that there are currently 8,896 US patients on oral meds and 3,231 on prostacyclins.\textsuperscript{12} By 2009 the same source projects 16,059 patients on oral meds and 3,886 on prostacyclins.\textsuperscript{13} This reinforces the conclusion that competing successfully against other suppliers of oral products is much more important for Tracleer and other oral products than any possible competitive efforts to take additional patients from prostacyclins.

The pricing strategies adopted by different firms in the industry also supports the proposition that competition within a category is much more important than competition across categories. Market analysts expect Myogen to price Ambrisentan similarly to Tracleer.\textsuperscript{14} Similarly, United Therapeutics appears to have priced Remodulin at somewhat of a premium to Flolan (e.g. $120,000 per year vs. $100,000), reflecting Remodulin’s advantages in ease of administration and other factors. This approach suggests that optimizing pricing relative to other

\textsuperscript{12} Wachovia, p. 25-26
\textsuperscript{13} Ibid
\textsuperscript{14} Ibid, p. 20.
infused prostacyclins is perceived as more important for Remodulin than pricing to try to expand usage of prostacyclins at the expense of oral drugs. Moreover, as mentioned above, market analysts expect Remodulin to gain its sales primarily at the expense of Flolan.

Inhaled forms of prostacyclins such as Remodulin and Ventavis appear to fall somewhere in between oral drugs and IV/subcutaneous drugs in terms of both price and the potential for therapeutic substitution. Some analysts project that inhaled products may become useful on an “as needed” basis for some patients to complement oral meds and potentially delay the transition to infused prostacyclins. The expected growth for such drugs appears to be relatively gradual in the near term unless more convenient dosing methods can be developed. Market analysts estimate that Ventavis is currently priced at roughly $50,000 per year. Moreover, inhaled Remodulin appears to be more of a complement to oral meds in delaying the transition to IV prostacyclin than a direct substitute for oral.

Another factor that is relevant to the relevant market inquiry is the effect of entry by new oral drugs Revatio and Thelin on the pricing of incumbents like Tracleer. To the extent that the availability of these drugs caused Actelion to reduce the level and/or rate of change in Tracleer prices below what it would otherwise have been, this entry will reinforce the conclusion that oral drugs are a separate relevant market.

III. Using Event Studies to Analyze Market Definition for PAH Drugs

Economists have used event studies of stock market prices to study competition and the effects of mergers for many years. For example, Eckbo and Stillman conducted seminal studies

15 Ibid, pp. 25-26
16 This is consistent with the fact that the Ventavis clinical trials were designed to show that adding Ventavis to current Tracleer patients produced clinical improvements.
17 However, it is theoretically possible that new entry by very low priced competitors could actually have the effect of leading an incumbent such as Tracleer to raise its prices. To the extent that Revatio’s (and/or Cialis) anticipated low prices caused Tracleer to essentially concede the price elastic segments of the market to Revatio, it could lower the elasticity of demand faced by Tracleer sufficiently so that it becomes profitable to raise prices. This would be analogous to the situation many brand name drugs face when generics enter the market. One factor that differentiates Tracleer/Revatio competition from the generic case is the fact that both drugs are branded and they are significantly differentiated products. Rather than being chemically equivalent, Tracleer and Revatio (and Thelin) differ in their mechanisms of action, potential side effects, potential differences in perceived efficacy in both the short and long term, and length and outcomes of clinical experience. However, the fact that Pfizer is constrained to set relatively low prices for Revatio due to pricing of Viagra as an ED drug gives it one characteristic similar to generic entry.
18 Economic literature indicates that new entry can have varying impacts on the prices of existing drugs depending on such factors as how close a substitute the drugs are and the nature of competition in the industry. See, e.g. Perloff, Suslow and Seguin, “Higher Prices from Entry: Pricing of Brand Name Drugs.”
of the effect of merger announcements on the stock prices of merging firms and their rivals. In general, these studies find that the stock prices of rival firms respond positively to announcements of mergers among their competitors, but do not respond negatively to announcements that the mergers will be challenged by antitrust authorities. This evidence is generally believed to indicate that the gain experienced by the rival firms is not due to expectations of post-merger collusive pricing. Rather, it reflects the market’s expectations that the rival firms may be able to take advantage of similar efficiencies as the merging firms.

The market for PAH therapies provides an interesting case study for analyzing relevant market issues in pharmaceuticals. Several of the key providers of PAH therapies that specialize in different types of therapies are publicly traded companies. In addition, they are relatively “pure play” companies in the sense that a large portion of their present and expected future income is expected to come from their PAH therapies. Finally, these companies made a number of announcements that revealed substantial new information to the market regarding their PAH drugs. Accordingly, analyzing how their stock prices respond to particular competitive developments in the market for PAH therapies can shed light on the nature of competition among different types of therapies for a given condition and the appropriate definition of the relevant market for merger analysis.

A sample of major announcements regarding clinical trials and/or FDA approvals for PAH drugs is listed in Table 1. These events represent all announcements we could identify from 2004 to the present that had a substantial effect on the stock price of the announcing firm. We confine the analysis to announcements that had a significant impact on the announcing firm to isolate those that conveyed substantial new information to the marketplace. The announcement with the largest impact on firm values is Myogen’s announcement of positive clinical data in the phase 3 trial of its oral PAH drug Ambrisentan on December 12, 2005. The announcement was widely received as extremely positive news for Myogen. For example, one source reported the results as follows:

- **AMBRISENTAN BLOWS PAST PRIMARY ENDPOINT IN ARIES-2 PAH TRIAL.** The drug produced a 59m placebo-adjusted 6-minute walk improvement

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(p=0.0002), well ahead of our expectations of 30-35m (based on the response seen in the Phase II trial). …

- **AMBRISENTAN APPEARS TO BE THE MOST ATTRACTION ENDOTHELIN ANTAGONIST FOR PAH, EXPECT MAJORITY OF PAH MARKET SHARE TO ULTIMATELY FALL TO MYOGEN.** With its once daily dosing, apparently superior 6-minute walk benefit, low liver toxicity, and lack of significant drug-drug interactions, we expect ambrisentan to become PAH clinicians preferred endothelin antagonist.

These positive expectations for Ambrisentan were immediately reflected in Myogen’s stock price, which increased by a market adjusted 40.5 percent on the day of the announcement. Based on Myogen’s market capitalization, this represented a gain in equity value of $327.3 million. In contrast to the large positive effect on Myogen, the announcement had widely varying effects on other suppliers of PAH therapies. The largest percentage effect was the 33 percent market adjusted decline in Encysive, the supplier of competing oral drug Thelin. The t-statistic for this decline was a highly significant -15. Actelion, the supplier of the only currently marketed oral drug Tracleer also experienced a large decline of -16.7 percent with a t-statistic of -9.2. Accordingly, the positive news about Myogen’s new oral drug was seen as very negative news for other suppliers of oral PAH drugs.

It also is interesting to compare the changes in the dollar value of the equity for each company. While Myogen’s equity value increased by $327.3 million, the declines for Actelion and Encysive were $383.1 million and $216.4 million respectively, for a total decline of $599.5 million. Accordingly, the large increase in Myogen’s equity value appears to have been more than offset by the declines in its oral drug competitors. This appears to reflect the market’s expectation that strong competition from Ambrisentan would substantially reduce the overall expected profitability of oral PAH drugs as a group. This overall decline in equity value for the three oral drug suppliers as a group is consistent with an expectation that the entry of Ambrisentan will cause much of the benefits of aggressive competition among the oral drug suppliers to redound to consumers, rather than drug suppliers.

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In contrast to the large declines experienced by the competing oral therapies, the Myogen announcement had no measurable effect on the stock prices of the suppliers of other types of PAH therapies. In particular, United Therapeutics, the marketer of subcutaneous and intravenous versions of Remodulin experienced a statistically insignificant return of -0.8 percent. Similarly, CoTherix, the marketer of Ventavis, an inhaled form of prostacyclin therapy, experienced a statistically insignificant positive return of 1.3 percent. Accordingly, the stock market appears to believe that oral PAH drugs compete much more strongly with one another than they do with other forms of PAH therapies.

A similar pattern of stock price reactions followed a series of announcements by Encysive, developer of the oral drug Thelin. After some initial positive clinical results that raised high expectations for Thelin, the company has repeatedly been denied approval by the FDA. Its stock price has suffered large declines each time that these failures were publicly announced: 3/24/06: -51.3 percent, 7/25/06: -40.3 percent, and 12/28/06: -28.4 percent. After the second failure to obtain FDA approval in July of 2006, the trade press reported that:

“The Houston-based biotech company has now failed twice to secure a blessing from the Food and Drug Administration to sell Thelin, … Investors, who had been counting on outright approval, once again sent the company's shares plummeting. …

Now, despite management’s continued optimism, many experts foresee additional trial work as inevitable and the hit to Thelin's sales as significant. Notably, they believe that Thelin could actually trail Myogen's (MYOG) supposed "best-in-class" PAH drug to the market and miss out on the competitive advantages that it would have enjoyed by winning that fierce race.”

Based on Encysive’s market capitalization, these three announcements resulted in a combined loss in equity value of $547.5 million. In contrast to the large negative effect on Encysive, the announcements generally appear to have had positive impacts on the other oral drug suppliers. The combined effect of the three announcements was 16.5 percent for Myogen and 8.9 percent for Actelion, for a combined increase in equity value was $232.1 million. Once again, the Encysive announcements had much smaller impacts on the suppliers of non-oral therapies.

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URL: http://www.thestreet.com/newsanalysis/biotech/10299181.html
These examples suggest that major announcements of clinical trial results for oral PAH drugs generally caused substantial valuation effects in the opposite direction for competing oral drugs. In contrast, they have much less effect on other types of PAH drugs. These results support the widely expressed view in the trade and business press that oral PAH drugs are perceived to be direct and significant competitors to one another. Accordingly, these stock price responses support an approach to market definition and competitive analysis which is much more nuanced than including all drugs for a given condition in a single relevant market. As discussed above, a detailed analysis of the actual therapeutic and economic choices facing PAH patients suggested that oral PAH drugs would be much stronger competitors for one another at this stage of the market’s development than competition between oral drugs and other drug types such as subcutaneous or intravenous.

Another interesting finding is the different pattern of results for announcements by the non-oral drug suppliers. There are three major announcements by non-oral drug suppliers in the sample listed in Table 1. In November 2004, United Therapeutics announced that the FDA had approved intravenous use of its drug Remodulin for PAH. Shortly thereafter, in December 2004, CoTherix announced that Ventavis(R)(iloprost) Inhalation Solution has been approved by the FDA for the treatment of patients with relatively advanced (Class III or IV) symptoms. Finally, in November of 2007, United Therapeutics announced that a phase III trial of Viveta, an inhaled formulation of Remodulin had "robustly met" its anticipated benchmarks in clinical trials. As shown in Table 1, each of these announcements had large positive effects on the announcing firm’s stock price, indicating that the announcements conveyed significant new information to the market. However, in contrast to the oral drug announcements, these announcements did not have the large and opposite signed effects on their closest competitors in the PAH space. In fact, there appears to be little measurable effect of these announcements on any of the competing drug suppliers.

This different pattern of price changes may reflect the fact that these inhaled, subcutaneous and intravenous drugs are perceived to be more differentiated from one another, and from the oral drugs by patients and physicians. As discussed above, oral drugs are generally strongly preferred by both the patient and physician in the early stages of treatment of PAH. This preference leads to a lack of significant substitution between oral and other drug categories for the large majority of early stage patients and a lack of direct competition on price between
the oral PAH drug treatments and the subcutaneous/intravenous PAH drug treatments. Accordingly, the lack of a significant effect of these announcements on oral drugs is not surprising.

However, it is somewhat surprising that there is not more perceived substitution between the two different forms of prostacyclins (Ventavis and Remodulin). Given that these drugs are being prescribed when the disease is in a more advanced state, it could be that price competition is relatively less important. In other words, the willingness of physicians and patients to switch from one drug to another for a modest price reduction may decline when the patient’s condition is relatively advanced.

The lack of a negative effect on competing drugs for non-oral drug announcements could also reflect the fact that some PAH drugs can be used together in combination therapy. For example, in the clinical trials announced by United Therapeutics on November 1, 2007, the United Therapeutics drug Viveta was administered to patients that were also taking either Tracleer or Revatio oral drugs. Accordingly, the positive test results could indicate that some patients may be able to continue taking oral drugs (plus Viveta) for a longer period of time than they would otherwise have been able to before they would transition to an IV or subcutaneous drug. In economic terms, this implies that combination therapy may cause some drugs to become complements to some degree rather than substitutes. It also highlights the potential complexity of the economic forces that can arise in evaluating pharmaceutical competition issues. Sorting out these different types of effects for other categories of drugs would appear to be a fruitful avenue for further research.

IV. Conclusions

Antitrust enforcement agencies and the courts have employed a variety of approaches to determine relevant markets for pharmaceuticals, ranging from a single chemical compound to all drugs for a given condition. The market for PAH drugs provides an interesting opportunity to analyze some of the issues that arise in defining markets in this industry. The primary conclusion is that simplistic approaches to market definition, such as including all drugs for a given condition, without analyzing evidence of actual and potential substitution between different types of drugs, are likely to produce misleading answers in many cases. PAH drugs that share similar methods of administration and mechanism of action appear to be much closer economic substitutes than other types of PAH drugs. Relevant market analysis must take
account of the actual therapeutic and economic options facing patients and their physicians. The results also indicate that event studies of securities prices can play a significant role in relevant market analysis for some drugs.
Figure 1

Characteristics of PAH Drugs

<table>
<thead>
<tr>
<th></th>
<th>Remodulin (treprostinil)</th>
<th>Flolan (epoprostenol)</th>
<th>Tracleer (bosentan)</th>
<th>Ventavis (inhaled iloprost)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Prostacyclin</td>
<td>Prostacyclin</td>
<td>Dual ETRA</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Subcutaneous or IV infusion Dose-titrated</td>
<td>IV infusion Dose-titrated</td>
<td>Oral, twice daily</td>
<td>Inhaled, 6-9 times daily</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Marketed</td>
<td>Marketed</td>
<td>Marketed</td>
<td>Marketed</td>
</tr>
<tr>
<td><strong>Convenience</strong></td>
<td>Patient must carry pump at all times. Smaller pump being developed for IV Remodulin</td>
<td>Patient must carry pump with ice at all times and mix under sterile conditions</td>
<td>Twice-daily pill patients must undergo monthly liver monitoring</td>
<td>6-9 inhalation – each one taking 15-20 minutes. Cumbersome nebulizer.</td>
</tr>
<tr>
<td><strong>Approximate Ann. Price</strong></td>
<td>$100,000+</td>
<td>$50,000-150,000</td>
<td>$35,000</td>
<td>$50,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Thelin (sitaxsentan)</th>
<th>ambrisentan</th>
<th>Revatio (sildenafil)</th>
<th>Inhaled Remodulin (treprostinil)</th>
<th>Cialis (tadalafil)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Selective ETRA</td>
<td>Selective ETRA</td>
<td>PDE-5 inhibitor</td>
<td>Prostacyclin</td>
<td>PDE-5 inhibitor</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral, once daily</td>
<td>Oral, once daily</td>
<td>Oral, thrice daily</td>
<td>Inhaled</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>NDA preparation</td>
<td>Phase III enrolling (Data Mid-2005)</td>
<td>NDA pending approval</td>
<td>Entering Phase III</td>
<td>Entering Phase III</td>
</tr>
<tr>
<td><strong>Convenience</strong></td>
<td>Daily pill patients must undergo monthly liver monitoring</td>
<td>Daily pill. Patients must undergo monthly liver monitoring</td>
<td>Thrice daily pill</td>
<td>Four daily inhalations</td>
<td>Once daily pill</td>
</tr>
<tr>
<td><strong>Approximate Ann. Price</strong></td>
<td>$35,000</td>
<td>$35,000</td>
<td>$15,000-$20,000</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Source: Auster, Cohen and Bernstein, “Breathe Easy: PAH Therapeutic Overview and ATS Preview,” Wachovia Securities, 5/5/2005,
### Table 2

Stock Price Responses to Announcements About Clinical Trials and FDA Approvals for PAH Drugs

<table>
<thead>
<tr>
<th>Date</th>
<th>Oral Drugs</th>
<th>Non-Oral Drugs</th>
<th>United Therapeutics</th>
<th>CoTherix</th>
<th>Announcement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myogen</td>
<td>Actelion</td>
<td>Encysive</td>
<td>Announcements regarding Oral PAH Drugs</td>
<td></td>
</tr>
<tr>
<td>15-Feb-05</td>
<td>Return 0.5%</td>
<td>19.2%</td>
<td>-1.3%</td>
<td>4.3%</td>
<td>Encysive Pharmaceuticals announces topline data from Stride-2 clinical trials.</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Dec-05</td>
<td>Return 40.5%</td>
<td>-16.7%</td>
<td>-33.0%</td>
<td>-0.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Mar-06</td>
<td>Return 3.2%</td>
<td>4.9%</td>
<td>-51.3%</td>
<td>1.4%</td>
<td>-2.9%</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Apr-06</td>
<td>Return -12.3%</td>
<td>5.2%</td>
<td>-4.4%</td>
<td>-2.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-Jul-06</td>
<td>Return 13.3%</td>
<td>5.0%</td>
<td>-40.3%</td>
<td>1.7%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-Aug-06</td>
<td>Return -1.9%</td>
<td>-28.4%</td>
<td>0.6%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>15-Jun-07</td>
<td>Return 5.2%</td>
<td>-43.4%</td>
<td>-0.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Myogen</td>
<td>Actelion</td>
<td>Encysive</td>
<td>Therapeutics</td>
<td>CoTherix</td>
</tr>
<tr>
<td>26-Nov-04</td>
<td>Return 4.8%</td>
<td>1.0%</td>
<td>28.8%</td>
<td>-0.8%</td>
<td>United Therapeutics announces FDA approval for intravenous dosing of Remodulin.</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-Dec-04</td>
<td>Return 0.9%</td>
<td>-2.9%</td>
<td>-2.7%</td>
<td>19.4%</td>
<td>CoTherix announces FDA approval of Ventavis Inhalation solution for patients with Class III or IV symptoms.</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
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</tr>
<tr>
<td>2-Aug-05</td>
<td>Return 21.8%</td>
<td>0.8%</td>
<td>-0.1%</td>
<td>26.3%</td>
<td>-2.0%</td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Nov-07</td>
<td>Return -2.8%</td>
<td>50.3%</td>
<td>37.5</td>
<td>United Therapeutics announced that Vivora, an inhaled formulation of Remodulin, &quot;robustly met&quot; its primary endpoint in a phase III trial.</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>t-stat</td>
<td>$ Change</td>
<td></td>
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</tr>
</tbody>
</table>

**Notes:**
- The table includes stock price responses to announcements about clinical trials and FDA approvals for PAH drugs.
- The responses are categorized by whether the drug is oral or non-oral.
- The announcements are related to the performance or approval of various PAH drugs and their associated companies.
- The table highlights both positive and negative stock price movements in response to these announcements.