UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION
Patent Owner.

Case IPR2017-01621
Patents 9,358,240

REBUTTAL DECLARATION OF JEFFERY A. STEC, Ph.D.

April 26, 2018

I, Jeffery A. Stec, Ph.D., declare as follows:

1. I have been retained as an expert in this case by counsel for United Therapeutics Corporation ("UTC" or "Patent Owner"). For this declaration, I have been asked to offer my opinions, based on my knowledge, experience, and analysis of information available in this case, about whether Tyvaso®, which is covered by U.S. Patent No. 9,358,240 ("the '240 patent"), has achieved commercial success. I have also been asked to review and evaluate the Declaration of DeForest McDuff, Ph.D.[1]

2. I understand that the commercial success of a product can be used as an "objective indicia" in demonstrating the non-obviousness of the underlying patented invention. The reason why commercial success shows non-obviousness is because, if a product is successful in the marketplace as demonstrated by objective factors, including substantial sales, then there are reasons to infer that such market success would have provided a significant incentive for others to pursue the patented invention. For the reasons set forth below, it is my opinion that Tyvaso® has demonstrated commercial success as reflected by, among other things, its sales and market share in the relevant market.

[1] *See* Ex. 1055 (Declaration of DeForest McDuff, Ph.D.)

I. Professional and Educational Background

3. I am a Managing Director with Berkeley Research Group, LLC ("BRG"). I am also a leader of its Intellectual Property practice and a co-leader of its Economics and Damages community. BRG is a leading global strategic advisory and expert consulting firm that provides independent advice, data analytics, valuation, authoritative studies, expert testimony, investigations, transaction advisory, restructuring services, and regulatory and dispute consulting to Fortune 500 corporations, financial institutions, government agencies, major law firms, and regulatory bodies around the world.

4. I have served as a consultant to a wide variety of clients on matters involving economic, financial, and statistical analysis and modeling for the purpose of interpreting and projecting data and evaluating the impact of business decisions, transactions, and economic events. I have also served as an expert witness or consultant in a wide range of litigation matters, including patent, copyright, and trademark infringement and trade secret misappropriation litigation. While the issues have varied from case to case, most included an analysis and evaluation of company-specific as well as industry-wide data for the purpose of determining the extent of economic damages. As part of these analyses, I have often examined the commercial success of products and the drivers of that success.

5. I received Ph.D. and Master's degrees in Economics from the Ohio State University. I received Bachelor's degrees in Philosophy and Psychology from Cornell University and in Economics with a Math Minor from the University of Illinois-Chicago. I am a member of various professional organizations, including the American Economic Association, the American Association of Public Opinion Research, and the Licensing Executives Society, among others.

6. My curriculum vitae, which includes all publications and presentations I have authored, is provided in Exhibit 2054. A list of the cases in which I have testified is also provided in Exhibit 2054. BRG is being compensated on a rate times hours basis for the work my staff and I perform. My current rate is $595 per hour. BRG's compensation does not depend in any way on the outcome of this litigation.

II. Background

A. Pulmonary Arterial Hypertension Market Overview

1. Disease Characterization and Classifications

7. PAH is a life-threatening medical condition that is characterized by increased blood pressure in the pulmonary arteries.[2] This increased pressure in the arteries strains the right side of the heart and can ultimately lead to right heart

[2] Ex. 1157, 7 (United Therapeutics 2015 10-K).

failure and death.[3] PAH is a rare disease which affects fewer than 50,000 people in the U.S., although only a fraction of those affected are treated due to the complexity of diagnosing the condition.[4]

8. The World Health Organization ("WHO") classifies pulmonary hypertension patients into groupings based on the cause of the condition.[5] The first group ("WHO Group 1") encompasses PAH patients.[6] The New York Heart Association (NYHA), Functional Classification system, is the most commonly used system to classify heart failure patients.[7] Under the NYHA classification system, patients are placed into one of the following four categories based on how limited they are during physical activity:[8]

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[3] *Id.*

[4] Ex. 2055, 10 (Tyvaso® (treprostinil) An Inhaled Prostacyclin Analogue presentation); Ex. 1157, 7 (United Therapeutics 2015 10-K).

[5] Ex. 1122 (Types of Pulmonary Hypertension, National Institute of Health website).

[6] *Id.*

[7] Ex. 2056 (Classes of Heart Failure, American Heart Association website).

[8] *Id.*

Table 1

NYHA Heart Failure Classifications

NYHA Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

2. PAH Treatments

9. Currently, there are three categories of FDA-approved therapies for PAH, each of which targets a different molecular pathway that is involved in the disease process.[9] These categories include: (1) prostacyclin analogues and IP prostacyclin receptor agonists, (2) PDE-5 inhibitors and guanylate cyclase

[9] Ex. 1157, 8 (United Therapeutics 2015 10-K).

stimulators, and (3) endothelin receptor antagonists (ETRAs).[10] One or more of these classes of drugs may be used simultaneously to treat patients with PAH.[11]

10. For patients with mild PAH symptoms (e.g., NYHA Class II), oral therapies such as PDE-5 inhibitors and ETRAs are commonly prescribed as first-line treatments.[12] As the disease progresses in severity (NYHA Class III and IV), non-oral therapies, such as inhaled or infused prostacyclin analogues, are commonly added.[13] As a result, not all PAH products directly compete with each other for the same patients because not all PAH products are able to treat effectively the various stages of the disease. In fact, the only PAH product that has the same indication as Tyvaso® is Ventavis® as they are the only two inhalable PAH treatments available on the market.

11. UTC currently markets four FDA approved PAH therapies. Three of these products, Remodulin® (infused therapy), Tyvaso® (inhaled therapy), and Orenitram® (oral therapy), share the same active pharmaceutical ingredient, a

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[10] *Id.*

[11] *Id.*

[12] *Id.*, 23.

[13] *Id.*

prostacyclin analogue known as treprostinil.[14] The fourth PAH therapy marketed by UTC, Adcirca®, is an oral PDE-5 inhibitor.[15]

12. The FDA approved PAH therapies are shown in the table below.

Table 2[16]

UTC PAH Therapy Alternatives

Name	Active Ingredient	Launch	Administration	Manufacturer
Flolan®	epoprostenol	1996	infused	GSK
Tracleer®	bosentan	2001	oral	Actelion
Ventavis®	iloprost	2004	inhaled	Actelion
Revatio®	sildenafil citrate	2005	oral	Pfizer
Letairis®	ambrisentan	2007	oral	Gilead
generic epoprostenol	epoprostenol	2008	infused	Teva
Veletri®	epoprostenol	2010	infused	Actelion
generic sildenafil citrate	sildenafil citrate	2012	oral	multiple
Adempas®	riociguat	2013	oral	Bayer
Opsumit®	macitentan	2013	oral	Actelion
Uptravi®	selexipag	2015	oral	Actelion

[14] *Id.*, 8, 11-12.

[15] *Id.*, 13.

[16] *Id.*, 22-23.

B. Tyvaso® Overview

13. The FDA approved Tyvaso® in July 2009, and the product was launched in September 2009.[17] When Tyvaso® entered the market, there were many approved PAH therapies, including Remodulin® and Adcirca®, first sold in 2002 and 2009, respectively,[18] as well as the six products shown in Table 2 that were launched between 1996 and 2008. Following Tyvaso®'s launch, a number of additional PAH therapies entered the market including Orenitram®, first sold in 2014,[19] and the five products shown in Table 2 that were launched between 2010 and 2015.

14. In June 2010, the FDA granted orphan drug designation to Tyvaso®.[20] This designation gave the drug exclusivity for the orphan indication through July 2016.[21] There are currently eight patents listed in the Orange Book for Tyvaso®.[22]

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[17] Ex. 2057 (*FDA Approves TYVASO (Treprostinil) Inhalation Solution for the Treatment of Pulmonary Arterial Hypertension,* July 30, 2009); Ex. 2058, 25-26 (2014 Fourth-Quarter and Annual Financial Results, Investor Conference Call Q&A); Ex. 1152, 9 (United Therapeutics 2010 10-K).

[18] Ex. 1158, 5 (United Therapeutics 2016 10-K).

[19] *Id*.

[20] Ex. 1157, 12 (United Therapeutics 2015 10-K).

C. The '240 Patent

15. U.S. Patent No. 9,358,240 is titled "Treprostinil administration by inhalation." The '240 patent issued on June 7, 2016, and expires on May 5, 2028.[23] I understand that claims 1-9 of the '240 patent are at issue in this case. The patent claims methods for treating pulmonary hypertension comprising administering treprostinil by inhalation with a nebulizer. I understand that the use of the Tyvaso® Inhalation System, in the intended manner and as taught in UTC's label and package insert, practices the asserted claims of the '240 patent.[24] It is my understanding that if a product embodies the claimed features of the patent, and the product and those features are coextensive, then a nexus is presumed.

D. Benefits of the '240 Patent

16. I understand that the '240 patent relates to methods of administering treprostinil via inhalation that includes a pulsed ultrasonic nebulizer with an opto-acoustical trigger that is used to deliver therapeutically effective amounts of the

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[21] *Id.*

[22] Ex. 2012 (Tyvaso®, FDA Orange Book).

[23] *Id.*; Ex. 1001 (The '240 patent).

[24] Ex. 2040, ¶74 (Declaration of Dr. Aaron Waxman).

drug.[25] As explained by Dr. Aaron Waxman, one of UTC's technical experts in this matter, the Tyvaso® Inhalation System and directions for use contains such a method.[26]

17. The Tyvaso® Inhalation System contains a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger. Furthermore, I understand from Dr. Waxman that:

> The Tyvaso® Prescribing Information explicitly describes the nebulizer as "an ultrasonic, pulsed delivery device." Pulsed indicates that the nebulizer intermittently generates aerosol rather than continuously generating aerosol. Ultrasonic indicates that the device uses vibration of a piezoelectric element to generate drug containing droplets.
>
> The device uses light and sound to trigger each time the patient must inhale through the mouthpiece in successive breaths, with the intent of triggering inhalation at the same time as a bolus of aerosol is being generated. The optical component takes the form of a green flashing inhalation indicator light and the acoustical component takes the form of a single short beep. This opto-acoustical trigger is the mechanism

[25] *Id.*, ¶11; Ex. 1001.

[26] *Id.*; Ex. 2040, ¶¶11, 74-75.

by which the patient is prompted to synchronize each inhalation to each pulse of aerosol generation.[27]

18. I also understand from Dr. Waxman that the unique features of the claimed method for using the nebulizer (e.g., the combination of visible and audible signals designed to prompt the correct number of inhalations, and inhalations coordinated with aerosol generation), together with its more convenient dosing regimen, are critical to the device's ability to deliver precise drug doses that balance safety and efficacy.[28] These features also help patient compliance.[29]

1. Inhaled Treprostinil

19. Intravenous treprostinil therapy is prone to catheter-related infections, drug tolerance, quality of life complications, and major systemic side effects.[30] Subcutaneous therapy avoids catheter infections but can cause local pain at the

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[27] *Id.*, ¶¶74-75.

[28] *Id.*, ¶76.

[29] *Id.*, Ex. 1163, 27-28 (Second Declaration of Dr. Roham T. Zamanian, '240 File History).

[30] Ex. 2059, 1 (Voswinckel, *et al.*, "Favorable Effects of Inhaled Treprostinil in Severe Pulmonary Hypertension: Results from Randomized Controlled Pilot Studies," J. Am. Coll. Cardiol., 48:1672-1681 (2006)).

infusion site and may limit effective dosing and long-term treatment.[31] The development of inhaled treprostinil therapy allows patients to avoid these issues.

20. The only other FDA approved inhaled PAH therapy is iloprost, a prostacyclin analogue.[32] In contrast to inhaled iloprost, inhaled treprostinil has an unexpectedly slower time to reach peak plasma concentration when administered by the inhalation route, making treprostinil surprisingly well suited to administrer with a pulsed ultrasonic nebulizer using the particular claimed dosing regimen.[33] I understand that the technology claimed by the '240 patent is essential to providing the unique benefits of Tyvaso®.[34]

2. Comparison of Tyvaso® Benefits to Ventavis®

21. Patients are administered Tyvaso® using the proprietary methods and nebulizer described above, from which they draw up to nine breaths four times daily.[35] Through this administration method, patients save on average 1.4 hours per

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[31] *Id.*

[32] Ex. 1158, 9 (United Therapeutics 2016 10-K).

[33] Ex. 2098, ¶¶13-14 (Second Declaration of Dr. Werner Seeger).

[34] Ex. 2040, ¶¶73-83 (Declaration of Aaron Waxman); Ex. 1162, 21-24. (Declaration of Dr. Roham T. Zamanian, '240 File History).

[35] Ex. 1157, 11 (United Therapeutics 2015 10-K).

day when using Tyvaso® compared to the only other FDA-approved inhaled prostacyclin analogue, Ventavis (iloprost).[36] Patients prescribed to Ventavis® need to inhale the drug six to nine times each day, with each session consisting of four to ten minutes of continuous inhalation via the nebulizer.[37] Also, the Tyvaso® Inhalation System uses a single ampule, once per day, so the system only needs to be cleaned once per day.[38] Ventavis®, on the other hand, uses an ampule each session and must be cleaned after each session.[39] In other words, Tyvaso® is more convenient and easier to use than Ventavis®. Additionally, Ventavis® can cause a decrease in systemic blood pressure if the patient is administered too high of a dose.[40]

III. Analysis

22. I understand that the commercial success of a product can be used as an "objective indicia" in demonstrating the non-obviousness of the underlying patented invention. Commercial success shows non-obviousness because if a

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[36] *Id.*

[37] *Id.*

[38] *Id.*

[39] Ex. 1160, 20-24.

[40] Ex. 1157, 11 (United Therapeutics 2015 10-K).

product is successful in the marketplace, then there are reasons to infer that such market success would have provided a significant incentive for others to pursue the patented invention.

23. In examining commercial success, financial metrics such as the product's sales, profits, and market share are computed and evaluated. This evaluation often includes how the product has performed in the relevant market relative to its competitors.[41] Other indications of commercial success include whether the drug is able to command a price premium relative to other competing drugs while still making substantial sales and widespread diffusion of the drug in the marketplace.

24. Here, the commercial success of Tyvaso® is demonstrated in a number of ways, including the substantial sales and market share of the product despite marketplace challenges, as well as the acceptance of Tyvaso® by doctors

[41] For example, the Federal Circuit has indicated that "the most probative evidence of commercial success is not overall sales, but whether those sales represent 'a substantial quantity in th[e] market.'" *See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1356 n.5 (Fed. Cir. 2013) (citing *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012)). *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

and patients. I have also considered whether the sales are driven by economic factors other than the patented invention, including marketing or pricing.

A. Factors Demonstrating Commercial Success of the Patented Product

25. There are many factors that indicate the commercial success of Tyvaso® and the underlying patents at issue in this case. These include: substantial sales of the product; profitability of the product; significant market share achieved by the product, despite marketplace challenges; and consistent price increases for Tyvaso® compared to other treatments. I discuss each of these more fully below.

1. Sales of Tyvaso®

26. The significant sales of Tyvaso® provide evidence indicating commercial success of the product. The process by which a consumer (patient) purchases Tyvaso® is fairly complex. First, a physician who wishes to prescribe Tyvaso® to a patient fills out a referral form.[42] Next, a specialty pharmacy takes over case management for the patient, checking the data provided by the physician to confirm that the patient has PAH and falls within the Tyvaso® indication.[43] Finally, if the patient is determined to have PAH and be appropriate for Tyvaso®,

[42] Ex. 2060.

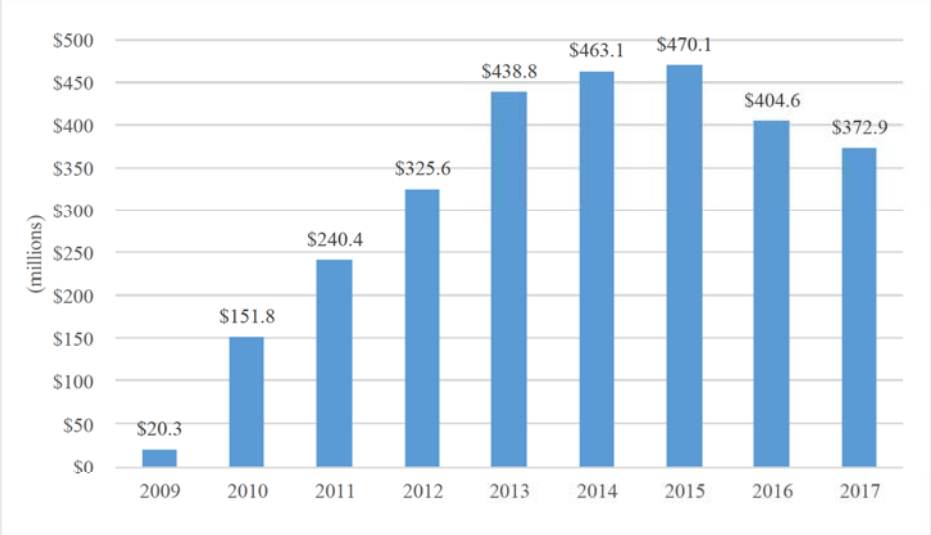
[43] *Id.*

the specialty pharmacy will deliver the medication and train the patient to use the inhaler.[44] This process makes it clear that sales of the product reflect demand for the particular features and benefits of Tyvaso®.

27. Tyvaso® sales since its launch are therefore compelling evidence of the product's commercial success. Figure 1 below shows the rapid growth in Tyvaso® sales revenue during the period September 2009 through 2017.

Figure 1

Net Sales of Tyvaso® September 2009 through 2017[45]



28. Comparing Tyvaso®'s first eight years of revenue to the first years of revenue available for each of the other drugs in PAH therapy market, shows that

[44] *Id.*

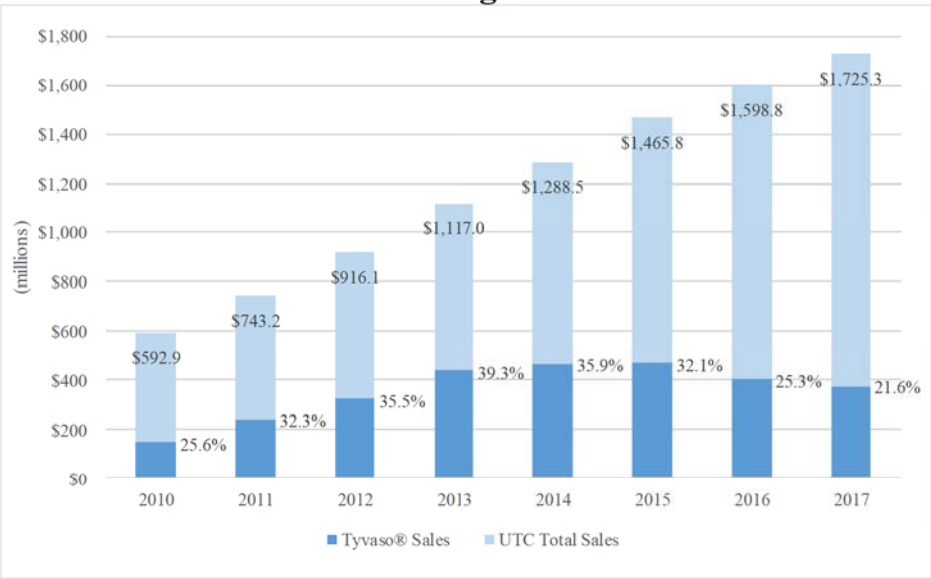
[45] Appendix 1.

Tyvaso® had at least the third largest revenue every year after the first year of launch, with having the second largest revenue in the 2nd through 4th, 6th, and 7th years after launch and the largest revenue in the 5th year after launch.[46]

29. Additionally, from 2010, the first full year that Tyvaso® was on the market, through 2017, Tyvaso® has accounted for between 22% and 40% of UTC's total revenues as shown in Figure 2 below.

Figure 2

Net Sales of Tyvaso® as a Percentage of UTC's Total Revenue – 2010 through 2017[47]



[46] Appendix 7.

[47] Appendix 4.

30. The demand for and commercial success of Tyvaso® is demonstrated by the billions of dollars in revenues generated since the launch of the product. Total annual net sales of Tyvaso® grew from $151.8 million in 2010, the first full year the product was on the market, to over $370 million in 2017, reflecting a compound annual growth rate of 14%.[48] As discussed in more detail below, the fact that these sales have been significant despite a number of marketplace challenges is further evidence of the demand for, and success of, Tyvaso®.

31. I also note that UTC was recognized by Forbes as the #12 best small company in the U.S. in 2012 based on factors such as its return on equity, sales growth, earnings growth, and stock performance compared to similar companies.[49] The following year UTC was recognized on Fortune's list of the 100 fastest growing companies.[50] These awards indicate that the market considered UTC to be a particularly valuable and fast-growing company as Tyvaso® sales continued to grow and made up more than a third of UTC total revenue. Similarly, in the years since Tyvaso® was launched, UTC's market capitalization has grown from

[48] Appendix 1.

[49] Ex. 2061 (The World's Biggest Public Companies – United Therapeutics, Forbes); Ex. 2062 (America's Best Small Public Companies, Forbes).

[50] Ex. 2063 (Fastest-Growing Companies, Forbes).

approximately $2.9 billion in 2009 to $6.1 billion in 2016.[51] These data correlate with Tyvaso®'s growing importance as a source of revenue to UTC during the same time period and provide further evidence of commercial success.

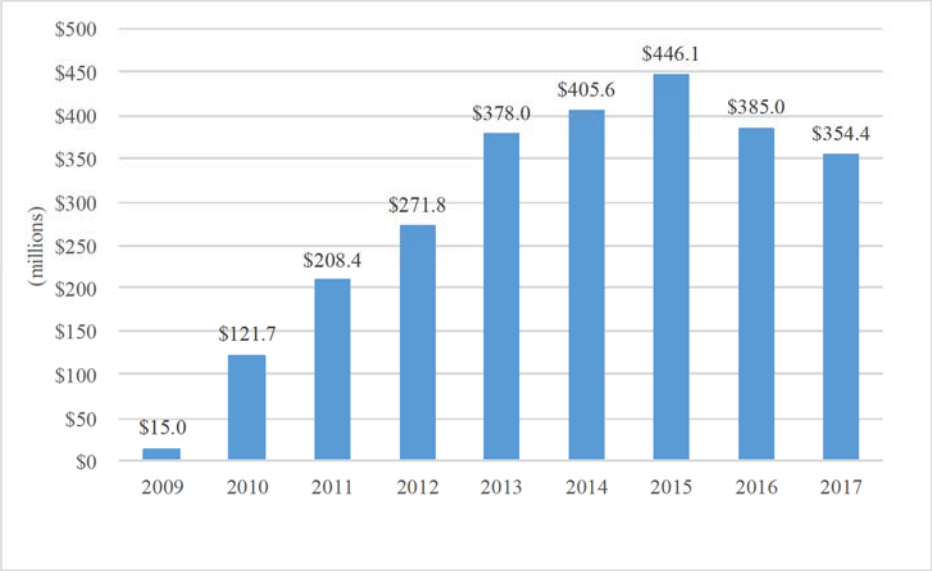
2. Profitability of Tyvaso®

32. Tyvaso®'s high profitability also shows the demand for and commercial success of the product. UTC has enjoyed positive gross profitability from the sale of Tyvaso® since launch. Figure 3 below summarizes the gross profits of Tyvaso®.

[51] Ex. 2064 (United Therapeutics Corp., Morningstar).

Figure 3

Gross Profits of Tyvaso® September 2009 through 2017[52]



33. As this figure shows, UTC was able to earn profits on Tyvaso® quickly, with billions of dollars in gross profits earned since the product was launched. Total gross profits earned from the sale of Tyvaso® grew from $121.7 million in 2010, the first full year the product was on the market, to $354 million in 2017, reflecting a compound annual growth rate of 17%.[53] Furthermore, Tyvaso®'s gross profit margin has been steadily increasing since launch.[54]

[52] Appendix 2.

[53] *Id.*

[54] *Id.*

3. Tyvaso® Market Share

34. As noted above, Tyvaso®'s sales and profit growth demonstrate that it is a commercial success. Tyvaso®'s market share also shows the demand for the product, in spite of marketplace challenges that UTC has faced, which is further evidence supporting Tyvaso®'s commercial success. It is my understanding that the target market for Tyvaso® includes patients on Ventavis®, the only other inhaled PAH product on the market, and patients on oral PAH therapies.[55]

35. As previously mentioned, there were at least eight other PAH therapies on the market when Tyvaso® was launched in September 2009.[56] Additionally, at least six other PAH therapies entered the market after Tyvaso®.[57] Despite this crowded market, Tyvaso®'s estimated share of the overall PAH

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[55] Exhibit 1142, 4 (UTC, "Q2 2010 United Therapeutics Earnings Conference Call," 7/28/2010).

[56] The eight PAH therapies on the market prior to Tyvaso® included Remodulin® and Adcirca® as well as the six products shown in Table 2 that were launched between 1996 and 2008.

[57] The six PAH therapies that were launched after Tyvaso® included Orenitram® and the five products shown in Table 2 that were launched between 2010 and 2015.

market grew from 1.2% in 2009 to 10.0% by 2016.[58] Tyvaso® has held the fourth largest share in this market from 2012 through 2016.[59] However, as explained above, Tyvaso® competes primarily with oral and inhaled therapies. Within this market segment, Tyvaso®'s estimated share grew from 1.7% in 2009 to 22.0% in 2013, declining to 11.9% by 2016.[60] Since 2012, Tyvaso® has held the third largest share in this market.[61] These data demonstrate that Tyvaso® has been able to gain a substantial portion of the market in spite of the numerous competitors that were launched both before and after Tyvaso®. In other words, as the market became even more competitive with additional entrants launching, Tyvaso® continued to increase its market share.

36. Between the time that Tyvaso® was launched in 2009 and 2013, the percentage of PAH patients on inhaled therapy doubled.[62] Within the inhaled

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[58] Appendix 6.4.

[59] *Id*. There were nine drugs in the market in 2012, 11 between 2013 and 2015, and 12 in 2016.

[60] Appendices 6.0 and 6.1.

[61] Appendix 6.0. There were six drugs in the market in 2012, eight in 2014, nine in 2014 and 2015, and 10 in 2016.

[62] Ex. 2065, 5 (Tyvaso 2014 Brand Plan).

therapy market segment, Tyvaso® became the inhaled market leader within seven months after the product launched.[63] This is particularly notable given the fact that Ventavis®, the only other FDA approved inhaled PAH therapy, was a well-established product that had been on the market since 2004. Additionally, the number of active users of Tyvaso® grew from approximately 850 in Q1 2010 to 3,199 in Q4 2015.[64] By 2015, Tyvaso® had approximately an 85% share of the patients on inhaled therapy.[65] The following figure compares the change in Tyvaso® and Ventavis® shares of the inhaled PAH therapy market between 2009 and 2016.

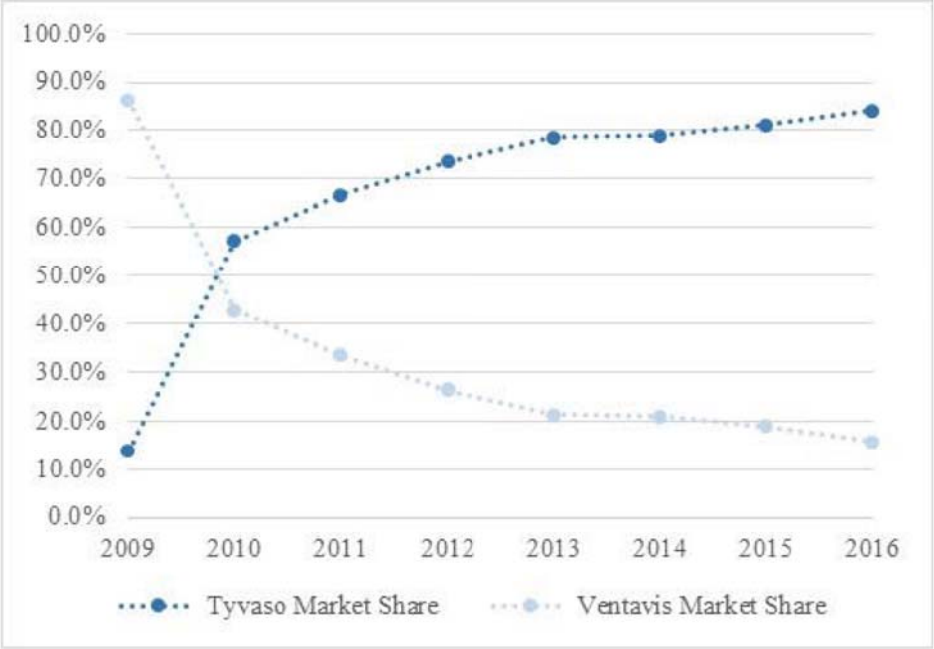
[63] Ex. 2066, 3 (2013 Marketing Plan).

[64] Appendix 5.

[65] Ex. 2067, 33 (Tyvaso Marketing Overview, August 19, 2015).

Figure 4

Inhaled PAH Therapy Market Shares, 2009-2016[66]



37. Given that the patented features and benefits of Tyvaso® contribute to its ease of use and efficacy, there is a nexus between Tyvaso®'s success and the '240 patent.[67] It is also important to recognize that while the inhaled therapy

[66] Appendix 6.2. Over this same time, the inhaled PAH therapy grew from $147 million in 2009 to almost $590 million in 2014; ending at $481 million in 2016. *See* Appendix 6.3.

[67] Ex. 2040, ¶84 (Declaration of Dr. Aaron Waxman); Ex. 1163, 26-28 (Second Declaration of Dr. Roham T. Zamanian, '240 File History).

market began to contract after 2013,[68] the number of active users of Tyvaso® has remained relatively constant.[69] Tyvaso®'s ability to gain or maintain market share in a declining market provides further evidence of the commercial success of the product.

4. Price Premium of Tyvaso® Versus Other Treatments

38. UTC has recognized in its SEC filings that its prostacyclin analogue products, including Tyvaso®, are expensive therapies.[70] The average annual cost of PAH therapy in 2011 was [redacted].[71] In contrast, according to a review article published in 2012, "the average cost per claim for inhaled treprostinil in early 2011 represented an annual expense of approximately $142,000."[72] Additionally, a study published in 2014 which compared the costs of oral and inhaled PAH therapies

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[68] Ex. 2074, 15 (Pulmonary Arterial Hypertension Market Surveillance ATU: Wave 5 (Q2 '15) – Final Report, Fielded July 2015).

[69] Appendix 5.

[70] Ex. 1158, 38 (United Therapeutics 2016 10-K).

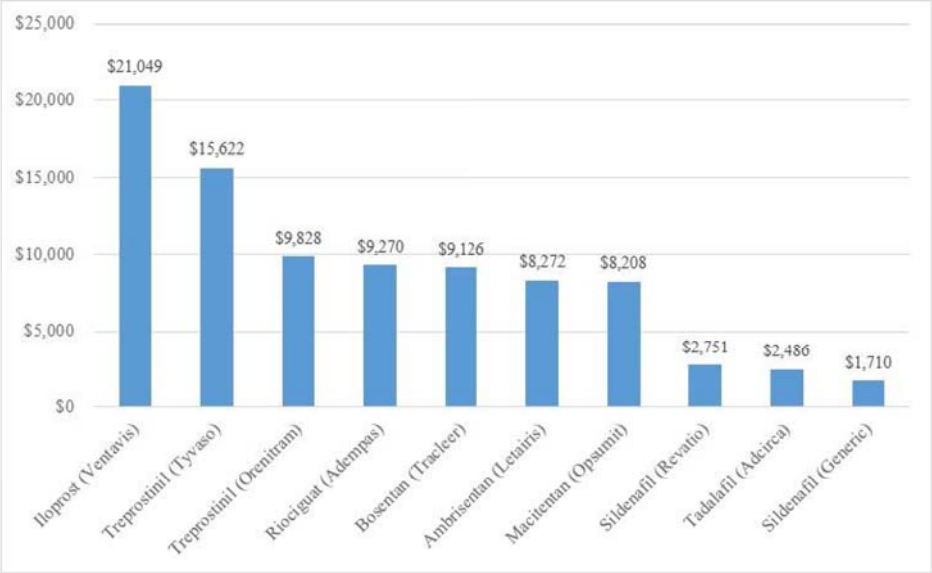
[71] Ex. 2068, 53 (Pulmonary Arterial Hypertension (PAH) Therapeutics – Global Drug Forecasts and Treatment Analysis to 2020).

[72] Ex. 2069, 13 (Frumkin, L.R., "The Pharmacological Treatment of Pulmonary Arterial Hypertension," Pharmacological Reviews, 64(3):583-620 (2012)).

found that while a one month supply of Tyvaso® was less expensive than an equivalent supply of Ventavis®, it was substantially more expensive than all of the approved PAH oral therapies.[73] The following figure compares the costs of a one month supply of the approved oral and inhaled PAH therapies as of 2014.

Figure 5

2014 Average Wholesale Price For 1 Month Supply of Inhaled and Oral PAH Therapies[74]



[73] Ex. 2070, 6 (Khaybullina, *et al.*, "Riociguat (Adempas): a Novel Agent For the Treatment of Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension," Pharmacy and Therapeutics, 39(11):749-758 (Nov. 2014)).

[74] *Id.*

39. The above figure demonstrates that Tyvaso® is one of the most expensive therapies amongst the products that compete with it.[75] Additionally, although Ventavis® was more expensive than Tyvaso® in 2014, this is due in part to a steep price increase for Ventavis®.[76]

5. Positive Return on Investment to Develop Patented Technologies

40. Another particularly relevant measure of commercial success is whether the patented inventions earn a positive net return on the investment required to develop those technologies.[77] In economic terms, an invention is a

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[75] As noted above, the only other inhaled treatment for PAH is Ventavis®, however, for this comparison, other PAH treatments were considered.

[76] Ex. 2071, 41 (Project Clock Discussion Materials, February 3, 2016); Ex. 2072 (Actelion Delivers Outstanding 2014 Results, Actelion website).

[77] Ex. 2078, 3-4 (McDuff , *et al.*, "Thinking Economically about Commercial Success," Landslide Magazine, 9(4) (2017)). *See also*, Ex, 2079, 2 (David, J. & M.B. Stewart. "Commercial Success: Economic Principles Applied to Patent Litigation." Economic Approaches to Intellectual Property: Policy, Litigation, and Management (Leonard & Stiroh eds., National Economic Research Associates Inc. New York) 196-207).

commercial success if it generates a positive net present value, i.e., if the present value of the profits from the invention exceed the upfront costs of developing the invention. Determining whether the patented invention has earned a positive net present value then involves measuring the present value of sales and profits that the invention generates and comparing that to the investment required to develop the patented technology.

41. I have calculated the estimated operating profits generated from the sale of Tyvaso®. The total estimated operating profits from September 2009 through 2017 for Tyvaso® was about $1.3 billion.[78] This cumulative operating profit compares to the total of $260.4 million which UTC invested in research and development between 2004, the earliest year in which UTC reported working on the development of inhaled treprostinil,[79] and 2009, the year Tyvaso® was launched.[80]

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[78] Appendix 8.

[79] In the Second Declaration of Werner Seeger, Dr. Seeger indicated that he began collaboration with Drs. Rubin and Olschewski for the development program for treprostinil inhalation in late 2003. (*See* Ex. 2098, ¶¶10-11 (Second Declaration of Dr. Werner Seeger)). Conservatively, including all of the UTC R&D expenses for its cardiopulmonary segment for 2003, does not significantly impact the net

42. I have also performed a net present value (NPV) calculation using UTC's cost of capital to determine the present value of profits and R&D investments. For the purposes of this calculation, I have calculated the NPV as of 2004. I have discounted Tyvaso® operating profits at a discount rate of 8.2%.[81] Total NPV of Tyvaso® including research and development expenses and

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present value that UTC earned on its development and sale of Tyvaso®. (*See* Appendix 8.1).

[80] Appendix 8; UTC's 2004 10-K states that "During 2004, independent clinical investigators performed small uncontrolled trials of inhaled treprostinil. United Therapeutics is now planning a controlled trial in patients with pulmonary arterial hypertension using treprostinil, in an inhaled formulation known as TRIUMPH (Treprostinil Inhalation Used in the Management of Pulmonary Hypertension). Such a trial, if allowed by the FDA and European authorities, is expected to commence in 2005." Ex. 1146, 10 (United Therapeutics 2004 10-K). Additionally, UTC's 2003 10-K describes "Major Research and Development Projects" but does not mention inhaled treprostinil. Ex. 1145, 34 (United Therapeutics 2003 10-K).

[81] UTC's weighted average cost of capital in 2004 was 8.2%. Ex. 2073 (Bloomberg L.P. WACC Report for UTHR).

operating profit through 2017 is $365.4 million.[82] Tyvaso® has therefore generated significant positive profits above and beyond the costs associated with research, development, and operating expenses related to the product.

43. Importantly, this calculation shows that the inventions claimed in the '240 patent have already generated profits significantly exceeding development costs without considering future profits. It is highly likely that UTC will continue to earn additional operating profits into the future, and these future profits will further increase the NPV of UTC's investment. Thus, my calculation of the NPV of the '240 patent is conservative since 1) I consider the R&D expenses for at least the entirety of UTC's cardiopulmonary segment, and 2) I do not attempt to estimate future Tyvaso® profits.

B. Marketplace Challenges

44. As previously explained, oral therapies are commonly prescribed as first-line treatments for PAH patients with less severe symptoms (NYHA Class II) and as these patients progress in severity, therapies with less convenient methods of administration, such as inhaled or infused therapies, are added.[83] UTC has noted that "the availability of oral therapies effects demand for our inhaled and infused

[82] Appendix 8.

[83] Ex. 1158, 22 (United Therapeutics 2016 10-K).

products."[84] This observation is consistent with a 2016 analysis performed for UTC, which stated that the launch of new oral therapies caused the total inhaled therapy market to contract.[85] In fact, a UTC presentation from July 2015 indicated that inhaled therapies had [redacted] of the market in 2013 but had [redacted] by 2015.[86] In an investor conference call discussing 2014 financial results, UTC specifically identified three recently launched oral therapies (Orenitram, Adempas, and Opsumit) as contributing to the decline in Tyvaso® revenue growth.[87]

45. However, despite the fact that there were at least eight other PAH therapies on the market when Tyvaso® was launched, Tyvaso®'s market share grew from 1.2% in 2009 to 17.2% by 2013.[88] And, although at least six additional

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[84] *Id.*

[85] Ex. 2071, 41 (Project Clock Discussion Materials, February 3, 2016).

[86] Ex. 2074, 15 (Pulmonary Arterial Hypertension Market Surveillance ATU: Wave 5 (Q2 '15) – Final Report, Fielded July 2015).

[87] Ex. 2075, 9 (2014 Fourth-Quarter and Annual Financial Results, Investor Conference Call Q&A).

[88] The eight PAH therapies on the market prior to Tyvaso® included Remodulin® and Adcirca® as well as the six products shown in Table 2 that were launched between 1996 and 2008; Appendix 6.5.

PAH therapies entered the market after Tyvaso®, Tyvaso® has been able to maintain an approximate 10% market share.[89] This is particularly notable given that the inhaled therapy market has been contracting over the past few years. These data demonstrate that not only was Tyvaso® able to compete successfully with PAH therapies that had been on the market for years; it has been able to maintain that success in the face of increasing competition and a contracting market.

46. Despite the substantial competition Tyvaso® has faced from a number of recently launched oral therapies, Tyvaso® has nevertheless been able to achieve substantial sales and profits. This is further evidence of Tyvaso®'s commercial success.

IV. Rebuttal of Dr. McDuff

47. I have reviewed Dr. McDuff's declarations and his evaluation of the commercial success of Tyvaso® as it relates to the '240 patent. For purposes of my review and rebuttal of Dr. McDuff's declaration, I have summarized portions of his declaration below. Additionally, I have provided rebuttal comments to his declaration in what follows.

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[89] The six PAH therapies that were launched after Tyvaso® included Orenitram® and the five products shown in Table 2 that were launched between 2010 and 2015; *See* Appendix 6.4.

A. Dr. McDuff's Skewed Market Definition

48. Dr. McDuff believes the relevant market to consider when evaluating the commercial success of Tyvaso® is the worldwide market for all therapies in the PAH market. This definition of the market ignores the facts of this case. It is my understanding that Tyvaso® is almost entirely sold in the U.S., with only minimal sales in one foreign country.[90] Therefore comparing worldwide sales of other drugs with significant markets outside the U.S. is not a fair comparison to sales of Tyvaso® where sales have almost entirely been within the U.S. Employing a worldwide market for therapies where different regulatory schemes in different regions largely affect approval and availability is also improper. As discussed in Dr. McDuff's declarations, using his flawed assumption, Tyvaso®'s share ranged from 0.7% to a peak of 10.4% in 2013 and declined to 7.3% in 2016.[91] When considering only the U.S. market, Tyvaso® peak market share in 2013 increases by

[90] UTC withdrew its application for sales of Tyvaso® in Europe (for reasons not related to safety or efficacy) and is only approved in Israel outside the U.S. *See*, Ex. 2086, (February 17, 2010 Withdrawal Letter); *see also* Ex. 2075, 12 ("Tyvaso is approved in Israel, but not yet commercialized outside the US.").

[91] Ex. 1055, 13.

almost 70% to 17.3%.[92] Dr. McDuff also points out that about 20% of the patients, maybe a little bit more than 20%, switch to Tyvaso® from Ventavis, and then the majority, the large majority, around 70%, switch to Tyvaso® after not really achieving the results desired with either oral or more commonly dual oral therapies.[93]

49. This means that more than 90% of the patients that use Tyvaso® either come from existing Ventavis® users or else choose Tyvaso® over Ventavis® (and other options) after progressing from a single or dual oral therapy. As discussed above, considering the U.S. market for oral and inhaled therapies, Tyvaso®'s peak market share in 2013 reached 22.0%, which is more than double the "modest" 10.4% market share considered by Dr. McDuff.[94] Dr. McDuff also dismisses any comparison of Tyvaso®'s sales to Ventavis® as being "overstated and unrepresentative of competition in th[e] market."[95] This statement ignores the fact that these two products are the only two inhalation products on the market and both treat patients at the same point in the disease progression. If a doctor decides

[92] Appendix 6.4.

[93] Ex. 1142, 4.

[94] Appendix 6.0.

[95] Ex. 1055, 9.

that an inhalation product is appropriate for their patient, then Tyvaso® and Ventavis® are the only two competing products in the market.

B. Dr. McDuff's Improperly Assumes Sales Were Impacted by Marketing

50. Dr. McDuff asserts that Tyvaso®'s sales were impacted by marketing rather than the clinical properties that result from the patented inventions at issue. His basis for this assumption is the flawed assertion that "Tyvaso's purported 25.0% share of sales representatives compared to a peak market share of just 10.4% indicates above average marketing relative to competition." This is improper as the 25.0% share of sales representatives is for UTC and not only Tyvaso®. These sales representatives could be marketing any one of UTC's four therapies. While the exact breakdown is not available, assuming 25% is related to Tyvaso®, this indicates a below average marketing effort relative to competition contrary to Dr. McDuff's conclusion. Moreover, unlike many other pharmaceutical products, these are not products that can be advertised directly to consumers – these are specialty products available only in specialty pharmacies.[96]

51. I have reviewed various Tyvaso® promotional documents and the majority of the marketing documents I reviewed appear to be targeted at physicians

[96] *See* ¶26 above.

and are educational or informative in nature, focusing on the results of the clinical studies for Tyvaso® and the product's ease of use. Thus, it is reasonable to conclude that, even if there was a significant amount of advertising and promotion of Tyvaso®, any growth in sales following such promotion is related to the product benefits and clinical characteristics of Tyvaso®. To the extent that these promotional efforts result in increased sales, it is not the promotional expenditures in and of themselves that have driven Tyvaso®'s sales, but the increased awareness of and the resulting demand for characteristics of the product claimed by the '240 patent.

52. In order to put the promotional expenditures in perspective, it is useful to consider the ratio of promotional expenditures to sales. It is my understanding that it is not possible to determine how much of UTC's sales and marketing expenses are attributable to Tyvaso®. However, even if one were to assume that all of UTC's sales and marketing expenses were attributable to Tyvaso® – which is clearly not the case and would substantially overstate the actual amount attributable to Tyvaso® – it is clear that Tyvaso® promotion was not unusual in the context of the pharmaceutical industry. Industry studies have shown that pharmaceutical companies spend on average between 22.5% and 33% of revenue

on promotional spending and that some firms spend as much as 50%.[97] Between September 2009 and 2017, UTC's total spend on sales and marketing averaged to about 21.5% of Tyvaso®'s revenue.[98] Even if all of UTC's sales and marketing expenses were solely attributable to Tyvaso®, which is clearly not the case, there would be no indication that UTC had been any more aggressive in promoting Tyvaso® than is typical in the pharmaceutical industry.

C. Dr. McDuff's Evaluation of the Nexus is Flawed

53. Dr. McDuff's assertion that the differences between Ventavis® and Tyvaso® are only due to the known half-life differences between treprostinil and iloprost and not the innovative aspects of the '240 patent is incorrect.[99] As described above, the unexpected slow time to peak plasma concentration when treprostinil is administered by inhalation along with the unique features of the claimed methods of using the nebulizer are critical to the device's ability to deliver

[97] Ex. 2077, 4 (Gagnon, M-A & J. Lexchin, J., "The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States," PLoS Medicine, 5(1):29-33 (Jan. 2008)).

[98] Appendix 3.

[99] Ex. 1055, 14.

precise drug doses.[100] The '240 patent provides for single event dosing and the limited number of breaths that it takes to administer the dose.[101] Both of these innovative aspects contribute to the commercial performance of the product through patient compliance and ease of use.[102] Ventavis® uses an adaptive aerosol delivery nebulizer which adjusts the dose amount to the volume of the patient's breath.[103] This leads to longer engagement times required by the patient than what is required by Tyvaso®.[104] Once the Ventavis® dose is delivered, the patient is required to take the device apart and remove the mesh from within the device and the patient could potentially clean that single mesh after each use.[105] The Tyvaso® nebulizer is filled once and is not cleaned or disassembled until the end of the

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[100] Ex. 2040, ¶76 (Declaration of Dr. Aaron Waxman); Ex. 2098, ¶¶13-14 (Second Declaration of Dr. Werner Seeger).

[101] Ex. 1163, 26 (Second Declaration of Dr. Roham T. Zamanian, '240 File History).

[102] *Id*. 27-28.

[103] Ex. 1162, 24 (Declaration of Dr. Roham T. Zamanian, '240 File History).

[104] *Id*.

[105] *Id*.

day.[106] The innovative features described in the claims of the '240 patent contribute to the benefits of Tyvaso® over Ventavis®.[107]

D. Dr. McDuff's Flawed Analysis of Commercial Performance

54. According to Dr. McDuff, Tyvaso®'s "sales show only modest commercial performance."[108] Dr. McDuff believes that this is "evidenced by: (1) comparisons to pharmaceutical products generally, and (2) comparisons to competitor PAH products."[109]

1. Dr. McDuff's Comparison to Pharmaceutical Products is Flawed

55. When considering pharmaceutical products in general, Dr. McDuff finds it appropriate to compare Tyvaso®'s peak sales to what he considers the 1st and 2nd decile of all products in the pharmaceutical industry.[110] This comparison

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[106] *Id.*

[107] *Id.*; Ex. 2040, ¶¶77-83 (Declaration of Dr. Aaron Waxman).

[108] Ex. 1055, 15.

[109] *Id.*

[110] *Id.*, 15-16.

alone, suggests that 80% or 90% of approved drugs would fail to achieve commercial success.[111]

56. In order to make these comparisons, Dr. McDuff relies on a 2002 paper that attempts to analyze the returns and research and development on new drug introductions.[112] Dr. McDuff's reliance on this study is flawed. This study analyzes drugs launched between 1990 and 1994, and the actual sales that those products made through 2000.[113] This means that the study only had between seven and 11 years of actual data. Instead of relying on this actual data, Dr. McDuff instead chooses either to rely purely on the projections made in the study or some combination of actual sales and projected sales to create his comparisons.[114] This

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[111] *Id.*

[112] Ex. 1113.

[113] *Id.*, 2, 6.

[114] Since the study had between seven and 11 years of actual data, the only year in which it had actual data for all of the drugs is at year seven. Any years between 8 and 11 would be a combination of actual sales and projected sales and years after Year 11 would be purely based on projections made by the authors of the study. Dr. McDuff relied on Year 13 data for his 1st decile drugs, which is based purely of

study is also based on the worldwide sales of these products.[115] This is an improper comparison. Two of the same authors, using the same methodology in the study relied upon by Dr. McDuff, also analyzed the U.S. sales of drugs launched between 1988 and 1992.[116] This study also separated U.S. sales between orphan status drugs and non-orphan status drugs. Using this approach is more accurate because it takes into account orphan status drugs vs. non-orphan status drugs. Using the same methodology employed by Dr. McDuff, I have recreated his comparison using this data in the table below.

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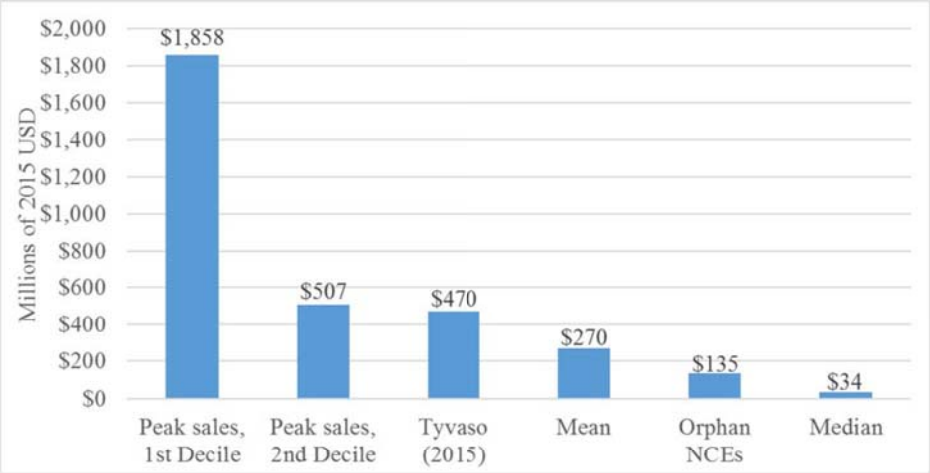
projected data, Year 9 for his 2nd decile and Year 10 for his average, both are based on combination of actual and projected data.

[115] Dr. McDuff did not consider U.S.-only data for his analysis, but he believed his conclusions would be the same without providing any further evidence of this point. Ex. 2035, 167:3-169:3 (McDuff Deposition Transcript).

[116] Ex. 2080, 1 (Grabowski, H.G. & J. Vernon, "The Distribution of Sales Revenue from Pharmaceutical Innovation," Pharmacoeconomics, 18(Suppl.1):21-32 (2000)).

Figure 6

2015 Peak U.S. Sales for Pharmaceutical Drugs[117]



57. As this graph shows, Tyvaso®'s sales are just below the 2nd decile of sales. Tyvaso®'s sales are more than three times greater than the peak average U.S. sales of other orphan drugs and almost double the peak average U.S. sales of all drugs considered. This data shows that Tyvaso®'s sales are both above average and exceptional, contrary to Dr. McDuff's statement that Tyvaso®'s sales "are not exceptional or even above average."[118] Based on this analysis, Tyvaso®'s sales are just outside the top 20% of pharmaceutical drugs, and far above other orphan drugs. This is exceptional given that many of the drugs included in this analysis

[117] Appendix 9.

[118] Ex. 1055, 15.

compete in larger markets with greater potential patient populations (e.g., drugs for depression, cancer, and cholesterol).[119]

58. Based on the worldwide data Dr. McDuff reaches the conclusion that, "average drugs tend be about break even in terms of profitability, and so when thinking about a commercially successful drug product, the fact that Tyvaso is below average indicates that it's likely not profitable."[120] The following facts: (1) Tyvaso® is almost in the 2nd decile of products in the U.S.; (2) Tyvaso® has earned almost $2.6 billion in gross profit and $1.3 billion in operating profit; and, (3) Tyvaso® has earned a net present value of over $365.4 million, clearly contradict Dr. McDuff's belief that Tyvaso® is likely not profitable.[121]

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[119] Ex. 2080, 8 (Grabowski, H.G. & J. Vernon, "The Distribution of Sales Revenue from Pharmaceutical Innovation," Pharmacoeconomics, 18(Suppl.1):21-32 (2000)).

[120] Ex. 2035, 174:4-20. *See also,* Ex. 2078, 3. Dr. McDuff was unable to analyze Tyvaso® gross profits because he was unaware of the data being available. Ex. 2035, 154:24-155:7. Tyvaso®'s gross profit margin is presented in UTC's 10-Ks and can be found in Appendix 2.

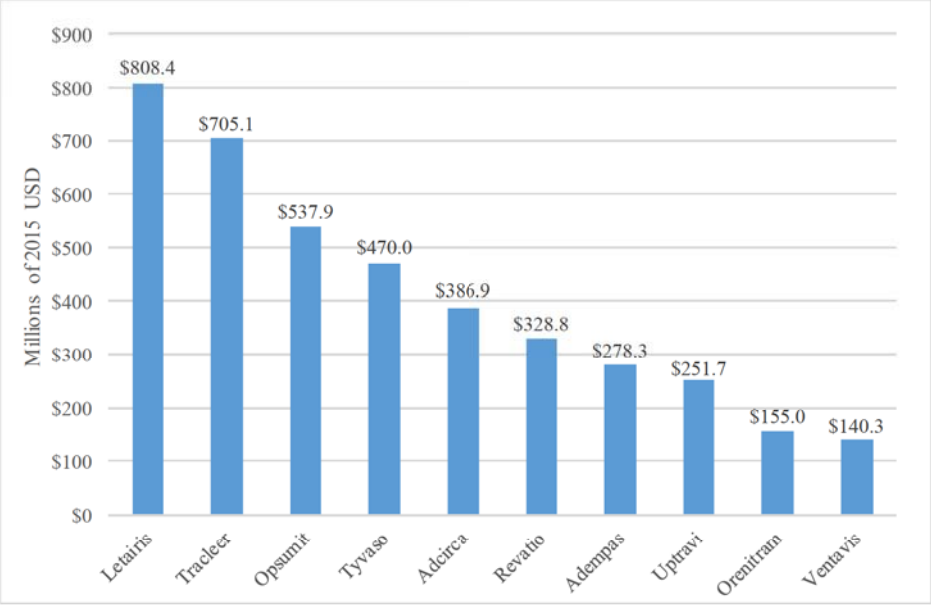
[121] Appendices 2 and 8.

2. Dr. McDuff's Comparison to Other PAH Products is Flawed

59. Dr. McDuff compares Tyvaso®'s peak sales to the peak worldwide sales of all other therapies in the PAH market. This comparison is improper. As discussed above, Tyvaso® primarily competes in the U.S. with the other inhalation therapy and oral therapies in the PAH market. The graph below shows that Tyvaso® has the 5th highest peak sales in the U.S. oral and inhalation PAH market over the 2009 to 2016 period.

Figure 7

2015 Peak U.S. Sales PAH Therapies[122]



[122] Appendix 10.

60. As the above graph shows when compared directly to the only other inhalation therapy on the market, Tyvaso® peak sales are more than three times greater than Ventavis®'s sale ever were.[123] Once again, Ventavis® is the only other inhalation product in the PAH market, and it also treats the same stage of the disease progression.

E. Dr. McDuff's Blocking Patents and Regulatory Exclusivity Assertions Are Improper

61. Dr. McDuff believes that even if Tyvaso® was determined to be a commercial success, that "success would not be economically relevant to obviousness of the patent-at-issue since other companies would have been blocked from commercializing those technologies."[124] However, Dr. McDuff acknowledged that none of these patents or exclusivities were blocking Tyvaso®'s most direct competitor for market share, Ventavis®, which uses a different drug and was already on the market when Tyvaso® launched as explained more fully below. Specifically, Dr. McDuff lists U.S. Patent Nos. 4,306,075 ("the '075 patent"); 5,143,222 ("the '222 patent"); 6,521,212 ("the '212 patent"); and

[123] Appendix 10.

[124] Ex. 1055, 21.

6,756,033 ("the '033 patent") as also covering Tyvaso® from the Orange Book.[125] With respect to the '212 patent and '033 patents, Dr. McDuff fails to provide any analysis or reasoning as to why the '212 patent or the '033 patent would be blocking patents to the '240 patent in his Declaration and admitted he did not analyze whether the '212 patent or '033 patent disclosed the technology used to administer an inhaled form of treprostinil.[126]

62. With respect to the '075 patent, Dr. McDuff admitted that the '075 patent would not have blocked any treprostinil product after its expiration date in 1999, yet the '240 patent was not even filed until 2006.[127]

63. Dr. McDuff also mistakenly claims that the importance of the '240 patent to the sale of Tyvaso® cannot be due to this patent because of these preceding patents. Under Dr. McDuff's theory, since there are preceding patents on treprostinil any success contributed by the '240 patent are economically irrelevant. This theory ignores the fact that the active ingredient; the nebulizer; and the kits

[125] *Id*. at 19-20.

[126] Ex. 2035, 228:5-229:25.

[127] *Id*. at 206:4-11.

are used to administer the therapy, and all three contribute to the commercial success of the product.

64. Dr. McDuff also failed to consider whether the allegedly blocking patents did indeed block others from developing treprostinil products. For example, U.S. Patent No. 8,410,121 ("the '121 patent") was filed on July 11, 2007 and claims methods of treating pulmonary hypertension with treprostinil and another drug substance.[128] The '121 patent is assigned to Lexicon Pharmaceuticals, not UTC. Similarly, U.S. Patent No. 9,550,716 is entitled "Process for treprostinil salt preparation" and was filed on December 30, 2010 and claims a process for preparing treprostinil salt.[129] The '716 patent is assigned to Eon Labs, not UTC. The '716 patent and '121 patent demonstrate that others such as Eon Labs, Inc. and Lexicon Pharmaceuticals were developing treprostinil technologies despite the alleged blocking patents listed by Dr. McDuff. There must be an economic incentive to obtain a patent and Dr. McDuff agrees.[130] Thus the economic incentive

[128] Ex. 2081 ('121 patent), claims 12-13.

[129] Ex. 2082 ('716 patent), claim 1.

[130] Ex. 2035, 222:19-223:2.

existed for both Eon Labs and Lexicon Pharmaceuticals to pursue treprostinil-based products even in the presence of these so-called blocking patents.

65. In sum, Dr. McDuff fails to provide any evidence that the '222 patent, '075 patent, '212 patent, or '033 patent actually blocked others from developing further treprostinil technologies.

F. Dr. McDuff's Limited Market Interest is Unsupported

66. Dr. McDuff asserts that since UTC had unique specialization in PAH and the fact that PAH is an orphan drug, there would be limited commercial opportunity and a lack of market-wide interest in developing an inhaled treprostinil product.[131] These assertions completely ignore the fact that with an inhaled treprostinil product UTC has earned $2.9 billion in revenue, $2.6 billion in gross profits, and $1.3 billion in operating profit.[132] This also ignores the fact that Tyvaso®'s peak sales outperformed the average of other orphan drugs by more than three times. Under Dr. McDuff's theory, there would be very little competition in markets if companies did not attempt to challenge market

[131] Ex. 1055, 21-23.

[132] Appendices 2 and 8.2.

incumbents or were unwilling to enter markets with the opportunity to earn significant revenues and profits.

G. Dr. McDuff Improperly Assesses the Contributions of the '240 Patent

67. Dr. McDuff asserts that "Tyvaso's commercial performance would [not] be any different if it used a different (nonclaimed type of nebulizer or a different (nonclaimed) dosing regimen."[133] Dr. McDuff makes this assertion without evidence, and this assertion is contrary to evidence in this matter. As discussed above, the unique features of the method of using the claimed nebulizer (e.g., the combination of visible and audible signals designed to prompt the correct number of inhalations, and inhalations coordinated with aerosol generation) are critical to the device's ability to deliver precise drug doses.[134] Indeed, Tyvaso® is not approved by the FDA as a stand-alone drug product but as a drug-device combination. But for the development of the methods of using the nebulizer approved and used with Tyvaso® it would not be approved by the FDA and available to patients. And patients must use the specific nebulizer and are not free to use Tyvaso® with a different device, making Tyvaso®'s commercial success

[133] Ex. 1055, 24.

[134] Ex. 2040 ¶77 (Declaration of Dr. Aaron Waxman).

inextricably tied to the combination of inhaled treprostinil in the claimed dosage, concentration, and with the claimed device.

V. Conclusion

68. It is my opinion that Tyvaso® has been a commercial success by several measures since its launch in September 2009. Sales of Tyvaso® have been significant, as indicated by U.S. net sales revenues of over $2.9 billion from September 2009 through 2017 and gross profits over $2.6 billion during the same period.[135] Tyvaso® also captured the majority of the inhaled therapy market segment within seven months after launch and, although Ventavis®'s share was declining, the inhaled therapy segment doubled in size between 2009 and 2013.[136] Additionally, Tyvaso® has generated at least $365.4 million in profits above and beyond the costs associated with the operating expenses related to the product and the research and development expenses required to develop the technologies covered by the '240 patent.[137]

69. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true;

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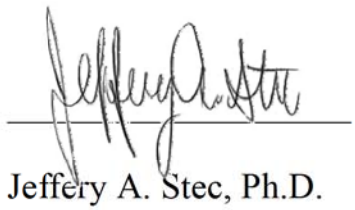
[135] Appendices 2 and 3.

[136] Ex. 2065, 5 (Tyvaso 2014 Brand Plan).

[137] Appendix 8.

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Date: April 26, 2018



Jeffery A. Stec, Ph.D.
Managing Director
Berkeley Research Group

Appendix 1

IPR2017-01621

Appendix 1

Tyvaso Net Product Sales [1]

$ in thousands	**2009 [2]**	**2010 [3]**	**2011 [4]**	**2012 [5]**	**2013 [6]**	**2014 [7]**	**2015 [8]**	**2016 [9]**	**2017 [10]**	**Total**	**CAGR (2010-2017)**
Tyvaso Net Product Sales	$20,268	$151,797	$240,382	$325,614	$438,793	$463,067	$470,069	$404,600	$372,900	$2,887,490	14%
Growth %		*649%*	*58%*	*35%*	*35%*	*6%*	*2%*	*-14%*	*-8%*		

Notes:

(1) I understand that ex-U.S. sales are covered by the patents-in-suit since Tyvaso is manufactured within the United States. As such, there is a nexus between the ex-U.S. sales of Tyvaso and the patents-in-suit. Tyvaso has been commercialized in the U.S. (since 2009) and Israel (since mid-2015), however it appears that sales in Israel have been negligible to this point. *See* Ex. 1158 at 6, 9, 21, 58, 111 (United Therapeutics Corporation 2016 10-K).

(2) Ex. 1151 at 9, 52 (United Therapeutics Corporation 2009 10-K). Tyvaso was first commercialized in September 2009.

(3) Ex. 1152 at 62 (United Therapeutics Corporation 2010 10-K).

(4) Ex. 1153 at 72 (United Therapeutics Corporation 2011 10-K).

(5) Ex. 1154 at 77 (United Therapeutics Corporation 2012 10-K).

(6) Ex. 1155 at 73 (United Therapeutics Corporation 2013 10-K).

(7) Ex. 1156 at 72 (United Therapeutics Corporation 2014 10-K).

(8) Ex. 1157 at 71 (United Therapeutics Corporation 2015 10-K).

(9) Ex. 1158 at 57 (United Therapeutics Corporation 2016 10-K).

(10) Ex. 2087 at 118 (United Therapeutics Corporation 2017 10-K).

Appendix 2

IPR2017-01621

Appendix 2
Tyvaso Gross Profits

$ in thousands	**2009** [2]	**2010** [3]	**2011** [4]	**2012** [5]	**2013** [6]	**2014** [6]	**2015** [6]	**2016** [7]	**2017** [8]	**Total**	
Tyvaso Net Product Sales[1]	$20,268	$151,797	$240,382	$325,614	$438,793	$463,067	$470,069	$404,600	$372,900	$2,887,490	**CAGR**
Tyvaso Cost of Goods Sold	5,318	30,131	31,934	53,825	60,831	57,442	23,925	19,600	18,500	301,506	**(2010-2017)**
Tyvaso Gross Profits	**$14,950**	**$121,666**	**$208,448**	**$271,789**	**$377,962**	**$405,625**	**$446,144**	**$385,000**	**$354,400**	**$2,585,984**	**17%**
% of Net Product Sales	*73.8%*	*80.2%*	*86.7%*	*83.5%*	*86.1%*	*87.6%*	*94.9%*	*95.2%*	*95.0%*	*89.6%*	

Notes:

(1) Appendix 1.
(2) Ex. 1153 at 133 (United Therapeutics Corporation 2011 10-K).
(3) Ex. 1154 at 142 (United Therapeutics Corporation 2012 10-K).
(4) Ex. 1155 at 136 (United Therapeutics Corporation 2013 10-K).
(5) Ex. 1156 at 134 (United Therapeutics Corporation 2014 10-K).
(6) Ex. 1157 at 129 (United Therapeutics Corporation 2015 10-K).
(7) Ex. 1158 at 111 (United Therapeutics Corporation 2016 10-K).
(8) Ex. 2087 at 118 (United Therapeutics Corporation 2017 10-K).

Appendix 3

IPR2017-01621

Appendix 3
UTC Sales and Marketing Expense as a Percentage of Tyvaso Net Product Sales

$ in thousands	**2009** [2]	**2010** [3]	**2011** [4]	**2012** [5]	**2013** [6]	**2014** [6]	**2015** [6]	**2016** [7]	**2017** [8]	**Total**
Tyvaso Net Product Sales[1]	$20,268	$151,797	$240,382	$325,614	$438,793	$463,067	$470,069	$404,600	$372,900	$2,887,490
UTC Sales and Marketing Expense	40,745	46,123	66,405	67,220	73,871	82,000	94,297	84,600	64,300	619,561
UTC Sales and Marketing Expense as a Percentage of Tyvaso Net Product Sales	**201.0%**	**30.4%**	**27.6%**	**20.6%**	**16.8%**	**17.7%**	**20.1%**	**20.9%**	**17.2%**	**21.5%**

Notes:

(1) Appendix 1.
(2) Ex. 1153 at 10, 76 (United Therapeutics Corporation 2011 10-K). Represents Sales and Marketing Expense for full year 2009. Tyvaso was first sold in September 2009.
(3) Ex. 1154 at 82 (United Therapeutics Corporation 2012 10-K).
(4) Ex. 1155 at 78 (United Therapeutics Corporation 2013 10-K).
(5) Ex. 1156 at 77 (United Therapeutics Corporation 2014 10-K).
(6) Ex. 1157 at 72, 76 (United Therapeutics Corporation 2015 10-K).
(7) Ex. 1158 at 60 (United Therapeutics Corporation 2016 10-K).
(8) Ex. 2087 at 64 (United Therapeutics Corporation 2017 10-K).

Appendix 4

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Appendix 4
Tyvaso Revenue as a Percentage of UTC Total Revenue

$ in thousands	**2009 [2]**	**2010 [3]**	**2011 [4]**	**2012 [5]**	**2013 [6]**	**2014 [7]**	**2015 [7]**	**2016 [8]**	**2017 [9]**	**Total**
Tyvaso Revenue[1]	$20,268	$151,797	$240,382	$325,614	$438,793	$463,067	$470,069	$404,600	$372,900	$2,887,490
UTC Total Revenue	369,848	592,899	743,183	916,076	1,116,984	1,288,519	1,465,761	1,598,800	1,725,300	9,817,370
Tyvaso Revenue as a Percentage of UTC's Total Revenue	**5.5%**	**25.6%**	**32.3%**	**35.5%**	**39.3%**	**35.9%**	**32.1%**	**25.3%**	**21.6%**	**29.4%**

Notes:

(1) Appendix 1.
(2) Ex. 1152 at 62 (United Therapeutics Corporation 2010 10-K).
(3) Ex. 1153 at 72 (United Therapeutics Corporation 2011 10-K).
(4) Ex. 1154 at 77 (United Therapeutics Corporation 2012 10-K).
(5) Ex. 1155 at 73 (United Therapeutics Corporation 2013 10-K).
(6) Ex. 1156 at 72 (United Therapeutics Corporation 2014 10-K).
(7) Ex. 1157 at 71 (United Therapeutics Corporation 2015 10-K).
(8) Ex. 1158 at 57 (United Therapeutics Corporation 2016 10-K).
(9) Ex. 2087 at 80 (United Therapeutics Corporation 2017 10-K).

Appendix 5

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Appendix 5
Tyvaso Active Users

	Tyvaso Active Users	Source
2010 Q1	[redacted]	[A]
2010 Q2		[A]
2010 Q3		[A]
2010 Q4		[B]
2011 Q1		[C]
2011 Q2		[C]
2011 Q3		[C]
2011 Q4		[D]
2012 Q1		[D]
2012 Q2		[D]
2012 Q3		[D]
2012 Q4		[D]
2013 Q1		[E]
2013 Q2		[E]
2013 Q3		[E]
2013 Q4		[E]
2014 Q1		[E]
2014 Q2		[E]
2014 Q3		[E]
2014 Q4		[E]
2015 Q1		[E]
2015 Q2		[E]
2015 Q3		[E]
2015 Q4		[E]

Notes:

[A] Ex. 2089.
[B] Ex. 2088 at 5. January 2011 figure used as proxy.
[C] *Id*.
[D] Ex. 2066 at 6.
[E] Ex. 2071 at 44.

Appendix 6

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Appendix 6.0

Market Share – U.S. Oral and Inhaled PAH Therapy Market [1]

	U.S. Oral and Inhaled PAH Therapy Market							
Product	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tracleer	46.2%	42.2%	39.2%	32.2%	32.2%	25.7%	17.3%	11.3%
Opsumit					0.3%	6.1%	13.3%	16.0%
Letairis	15.7%	16.6%	17.2%	21.3%	26.1%	24.9%	24.8%	24.0%
Tyvaso	1.7%	10.5%	14.1%	16.9%	22.0%	19.4%	16.6%	11.9%
Adcirca	0.5%	2.5%	4.2%	7.4%	9.9%	10.1%	10.6%	11.5%
Revatio	25.0%	20.3%	18.3%	16.2%	3.4%	2.1%	2.3%	2.9%
Adempas [2]					0.2%	4.9%	7.1%	8.3%
Uptravi [2]								7.5%
Orenitram						1.7%	4.2%	4.6%
Ventavis	10.8%	7.9%	7.0%	6.1%	6.0%	5.1%	3.9%	2.2%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Notes:

(1) Appendix 6.5.
(2) Adempas and Uptravi sales are not reported on a geographic basis.

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Appendix 6.1

U.S. Oral and Inhaled PAH Therapy Market [1]

$ in millions

		U.S. Oral and Inhaled PAH Therapy Market							
Product		**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tracleer		$541.0	$610.0	$669.0	$622.0	$642.0	$615.0	$489.0	$385.0
Opsumit		-	-	-	-	5.0	145.0	376.0	545.0
Letairis		184.0	240.0	293.0	410.0	520.0	595.0	700.0	819.0
Tyvaso		20.0	152.0	240.0	326.0	439.0	463.0	470.0	405.0
Adcirca		6.0	36.0	71.0	142.0	197.0	241.0	300.0	392.0
Revatio		293.0	293.0	312.0	312.0	67.0	51.0	65.0	98.0
Adempas	[2]	-	-	-	-	4.0	118.0	201.0	282.0
Uptravi	[2]	-	-	-	-	-	-	-	255.0
Orenitram		-	-	-	-	-	41.0	118.0	157.0
Ventavis		127.0	114.0	120.0	117.0	119.0	123.0	109.0	76.0
Total		$1,171	$1,445	$1,705	$1,929	$1,993	$2,392	$2,828	$3,414

Notes:

(1) Appendix 6.5.
(2) Adempas and Uptravi sales are not reported on a geographic basis.

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Appendix 6.2

Market Share – U.S. Inhaled PAH Therapy Market [1]

	U.S. Inhaled PAH Therapy Market Shares							
Product	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tyvaso	13.6%	57.1%	66.7%	73.6%	78.7%	79.0%	81.2%	84.2%
Ventavis	86.4%	42.9%	33.3%	26.4%	21.3%	21.0%	18.8%	15.8%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Note:

(1) Appendix 6.5.

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Appendix 6.3

U.S. Inhaled PAH Therapy Market [1]

$ in millions	**U.S. Inhaled PAH Therapy Market**							
Product	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tyvaso	$20.0	$152.0	$240.0	$326.0	$439.0	$463.0	$470.0	$405.0
Ventavis	127.0	114.0	120.0	117.0	119.0	123.0	109.0	76.0
Total	$147	$266	$360	$443	$558	$586	$579	$481

Note:

(1) Appendix 6.5.

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Appendix 6.4

Market Shares - Overall PAH Therapy Market [1]

		Overall U.S. PAH Therapy Market Shares										
Product		**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tracleer		64.7%	49.1%	40.3%	36.0%	33.0%	30.1%	25.3%	25.1%	20.6%	14.2%	9.5%
Opsumit		-	-	-	-	-	-	-	0.2%	4.9%	10.9%	13.4%
Letairis		-	-	9.8%	12.2%	13.0%	13.2%	16.7%	20.4%	19.9%	20.3%	20.2%
Remodulin	[2]	35.3%	25.8%	23.4%	22.1%	21.8%	19.4%	18.6%	19.2%	18.6%	16.6%	14.8%
Tyvaso		-	-	-	1.3%	8.2%	10.8%	13.3%	17.2%	15.5%	13.7%	10.0%
Adcirca		0.0%	0.0%	0.0%	0.4%	1.9%	3.2%	5.8%	7.7%	8.1%	8.7%	9.7%
Revatio		-	16.7%	18.8%	19.5%	15.8%	14.1%	12.7%	2.6%	1.7%	1.9%	2.4%
Adempas	[2]	-	-	-	-	-	-	-	0.2%	4.0%	5.8%	7.0%
Uptravi	[2]	-	-	-	-	-	-	-	-	-	-	6.3%
Orenitram		-	-	-	-	-	-	-	-	1.4%	3.4%	3.9%
Veletri		-	-	-	-	0.1%	0.6%	0.8%	1.3%	1.2%	1.2%	1.0%
Ventavis		-	8.4%	7.6%	8.4%	6.2%	5.4%	4.8%	4.7%	4.1%	3.2%	1.9%
Flolan		-	-	-	-	-	3.2%	2.1%	1.5%	-	-	-
Total		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Notes:

(1) Appendix 6.5.

(2) Remodulin, Adempas, and Uptravi sales are not reported on a geographic basis.

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Appendix 6.5
Overall U.S. PAH Therapy Market Revenues [1]

$ in millions

		Overall U.S. PAH Therapy Market										
Product		**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Tracleer		$279.0	$382.0	$464.0	$541.0	$610.0	$669.0	$622.0	$642.0	$615.0	$489.0	$385.0
Opsumit		-	-	-	-	-	-	-	5.0	145.0	376.0	545.0
Letairis		-	-	113.0	184.0	240.0	293.0	410.0	520.0	595.0	700.0	819.0
Remodulin	[2]	152.0	201.0	270.0	332.0	404.0	430.0	458.0	491.0	554.0	573.0	602.0
Tyvaso		-	-	-	20.0	152.0	240.0	326.0	439.0	463.0	470.0	405.0
Adcirca		0.0	0.0	0.0	6.0	36.0	71.0	142.0	197.0	241.0	300.0	392.0
Revatio		-	130.0	217.0	293.0	293.0	312.0	312.0	67.0	51.0	65.0	98.0
Adempas	[2]	-	-	-	-	-	-	-	4.0	118.0	201.0	282.0
Uptravi	[2]	-	-	-	-	-	-	-	-	-	-	255.0
Orenitram		-	-	-	-	-	-	-	-	41.0	118.0	157.0
Veletri		-	-	-	-	2.0	14.0	20.0	32.0	37.0	41.0	41.0
Ventavis		-	65.0	88.0	127.0	114.0	120.0	117.0	119.0	123.0	109.0	76.0
Flolan		-	-	-	-	-	71.0	52.0	39.0	-	-	-
Total		$431	$778	$1,152	$1,503	$1,851	$2,220	$2,459	$2,555	$2,983	$3,442	$4,057

Notes:

(1) Ex. 2090 at 1. Reflects U.S.-only sales when possible. *See* Footnote 2.
(2) Remodulin, Adempas, and Uptravi sales are not reported on a geographic basis.

Appendix 7

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Appendix 7

U.S. PAH Therapy Revenues First Seven Years After Launch [1]

$ in millions

Product		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Tracleer							$279.0	$382.0	$464.0
Opsumit		$5.0	$145.0	$376.0	$545.0				
Letairis		$113.0	$184.0	$240.0	$293.0	$410.0	$520.0	$595.0	$700.0
Remodulin	[2]					$152.0	$201.0	$270.0	$332.0
Tyvaso		$20.0	$152.0	$240.0	$326.0	$439.0	$463.0	$470.0	$405.0
Adcirca		$6.0	$36.0	$71.0	$142.0	$197.0	$241.0	$300.0	$392.0
Revatio				$130.0	$217.0	$293.0	$293.0	$312.0	$312.0
Adempas	[2]	$4.0	$118.0	$201.0	$282.0				
Uptravi	[2]	$255.0							
Orenitram		$41.0	$118.0	$157.0					
Veletri		$2.0	$14.0	$20.0	$32.0	$37.0	$41.0	$41.0	
Ventavis				$65.0	$88.0	$127.0	$114.0	$120.0	$117.0
Total		$446	$767	$1,500	$1,925	$1,655	$2,152	$2,490	$2,722
Tyvaso®'s Rank		4	2	2	2	1	2	2	3
Number of Competing Therapies		8	7	9	8	7	8	8	7

Notes:

(1) Ex. 2089. Reflects U.S.-only sales when possible. *See* Footnote 2.

(2) Remodulin, Adempas, and Uptravi sales are not reported on a geographic basis.

Appendix 8

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Appendix 8.0
Estimated Net Present Value of Tyvaso Development and Commercialization 2004 - 2017

$ in thousands	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Nominal Values															
R&D [1]	$30,713	$36,052	$33,005	$38,459	$60,549	$61,574									$260,352
Operating Profit [2]						$1,455	$43,860	$102,786	$149,872	$114,905	$193,636	$224,163	$268,679	$176,129	$1,275,485
Present Value Factor (2004) [3]	1.000	0.924	0.854	0.789	0.730	0.674	0.623	0.576	0.532	0.492	0.455	0.420	0.388	0.359	
Present Values															
PV of R&D	$30,713	$33,320	$28,192	$30,361	$44,177	$41,520									$208,283
PV of Operating Profit						$981	$27,334	$59,203	$79,781	$56,532	$88,047	$94,203	$104,353	$63,223	$573,658
Net Present Value															**$365,375**

Notes:

(1) The first clinical trials involving inhaled formulations of treprostinil occurred in 2004 and 2005. Ex. 1146 at 10 (UTC 2004 10-K); Ex. 1147 at 9 (UTC 2005 10-K).
2004-2005: Ex. 1148 at 49, 73 (United Therapeutics Corporation 2006 10-K). UTC reported total R&D expenses of $30.7 million and $36.0 million in 2004 and 2005, respectively. UTC also reported its R&D expenses related to Remodulin, cancer pharmaceuticals, and infectious disease pharmaceuticals totaled $26.8 million and $32.0 million over the same respective periods.
2006-2007: Ex. 1149 at 54, 57 (United Therapeutics Corporation 2007 10-K). UTC reported Cardiovascular R&D expenses of $33.0 million and $38.5 million in 2006 and 2007, respectively. UTC also reported its R&D expenses related to Remodulin were $33.0 million and $35.0 million over the same respective periods.
2008: Ex. 1151 at 54 (United Therapeutics Corporation 2009 10-K). R&D expense related to cardiovascular projects specifically reported.
2009: Ex. 1152 at 63 (United Therapeutics Corporation 2010 10-K). R&D expense related to cardiopulmonary projects specifically reported.
(2) Appendix 8.2.
(3) Calculated as 1/(1+.082)^(Respective Year - 2004). UTC's 2004 weighted average cost of capital (8.2%) sourced from Bloomberg L.P. *See* Ex. 2073.

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Appendix 8.1
Estimated Net Present Value of Tyvaso Development and Commercialization 2003 - 2017

$ in thousands	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Nominal Values																
R&D [1]	$35,417	$30,713	$36,052	$33,005	$38,459	$60,549	$61,574									$295,769
Operating Profit [2]							$1,455	$43,860	$102,786	$149,872	$114,905	$193,636	$224,163	$268,679	$176,129	$1,275,485
Present Value Factor (2004) [3]	1.000	0.927	0.859	0.796	0.738	0.684	0.634	0.587	0.544	0.504	0.468	0.433	0.402	0.372	0.345	
Present Values																
PV of R&D	$35,417	$28,464	$30,966	$26,273	$28,373	$41,400	$39,018									$229,912
PV of Operating Profit							$922	$25,759	$55,945	$75,601	$53,718	$83,898	$90,013	$99,990	$60,748	$546,594
Net Present Value																**$316,681**

Notes:

(1) Dr. Seeger indicated that he began the development program for treprostinil inhalation in 2003. Ex. 2098 at ¶10-11.
2003: Ex. 1147 at 38, 41-42 (United Therapeutics Corporation 2005 10-K). UTC reported a total R&D expense of $35.4 million in 2013. UTC also reported its R&D expenses related to Remodulin, cancer pharmaceuticals, and infectious disease pharmaceuticals totaled $30.6 million
2004-2005: Ex. 1148 at 49, 73 (United Therapeutics Corporation 2006 10-K). UTC reported total R&D expenses of $30.7 million and $36.0 million in 2004 and 2005, respectively. UTC also reported its R&D expenses related to Remodulin, cancer pharmaceuticals, and infectious disease pharmaceuticals totaled $26.8 million and $32.0 million over the same respective periods.
2006-2007: Ex. 1149 at 54, 57 (United Therapeutics Corporation 2007 10-K). UTC reported Cardiovascular R&D expenses of $33.0 million and $38.5 million in 2006 and 2007, respectively. UTC also reported its R&D expenses related to Remodulin were $33.0 million and $35.0 million over the same respective periods.
2008: Ex. 1151 at 54 (United Therapeutics Corporation 2009 10-K). R&D expense related to cardiovascular projects specifically reported.
2009: Ex. 1152 at 63 (United Therapeutics Corporation 2010 10-K). R&D expense related to cardiopulmonary projects specifically reported.
(2) Appendix 8.2.
(3) Calculated as 1/(1+.079)^(Respective Year - 2003). UTC's 2003 weighted average cost of capital (7.9%) sourced from Bloomberg L.P. *See* Ex. 2104.

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Appendix 8.2
Estimated Tyvaso Operating Profits

$ in thousands	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Net Product Sales [(1)]	$20,268	$151,797	$240,382	$325,614	$438,793	$463,067	$470,069	$404,600	$372,900	$2,887,490
Operating Margin [(2)]	7.2%	28.9%	42.8%	46.0%	26.2%	41.8%	47.7%	66.4%	47.2%	
Estimated Operating Profits	$1,455	$43,860	$102,786	$149,872	$114,905	$193,636	$224,163	$268,679	$176,129	$1,275,485

Notes:

(1) Appendix 1.

(2) Tyvaso-specific operating profits cannot be ascertained from UTC regulatory filings. UTC's overall company operating margin is therefore used as a proxy.
2009: Ex. 1153 at 91 (United Therapeutics Corporation 2011 10-K).
2010: Ex. 1154 at 98 (United Therapeutics Corporation 2012 10-K).
2011: Ex. 1155 at 93 (United Therapeutics Corporation 2013 10-K).
2012: Ex. 1156 at 94 (United Therapeutics Corporation 2014 10-K).
2013: Ex. 1157 at 90 (United Therapeutics Corporation 2015 10-K).
2014: Ex. 1158 at 73 (United Therapeutics Corporation 2016 10-K).
2015-2017: Ex. 2087 at 80 (United Therapeutics Corporation 2017 10-K).

Appendix 9

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Appendix 9
Tyvaso Comparison to the U.S. Pharmaceutical Industry - McDuff Analysis

$ in millions	**U.S. Sales [1]**	**CPI Adjustment**	**Inflation-Adjusted (2015 USD)**
Peak sales, 1st Decile	$1,100	1.689	$1,858
Peak sales, 2nd Decile	$300	1.689	$507
Tyvaso (2015)	$470	1.000	$470
Mean	$160	1.689	$270
Orphan NCEs	$80	1.689	$135
Median	$20	1.689	$34

	1992	**2015**
Consumer Price Index: [2]	140.31	236.99
Adjustment Factor:	1.689	1.000

Notes:

(1) Ex. 2080 at 7.
(2) Ex. 2091.

Appendix 10

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Appendix 10

Tyvaso Comparison to U.S. Oral and Inhaled PAH Drug Revenues - McDuff Analysis [1]

$ in millions

	U.S. Oral and Inhaled PAH Therapy Market			
Product	**Peak Year**	**Sales**	**Inflation Adjustment [2]**	**Sales (2015 USD)**
Letairis	2016	$819.0	0.987	$808.4
Tracleer	2011	$669.0	1.054	$705.1
Opsumit	2016	$545.0	0.987	$537.9
Tyvaso	2015	$470.0	1.000	$470.0
Adcirca	2016	$392.0	0.987	$386.9
Revatio	2011	$312.0	1.054	$328.8
Adempas [2]	2016	$282.0	0.987	$278.3
Uptravi [2]	2016	$255.0	0.987	$251.7
Orenitram	2016	$157.0	0.987	$155.0
Ventavis	2009	$127.0	1.105	$140.3

Notes:

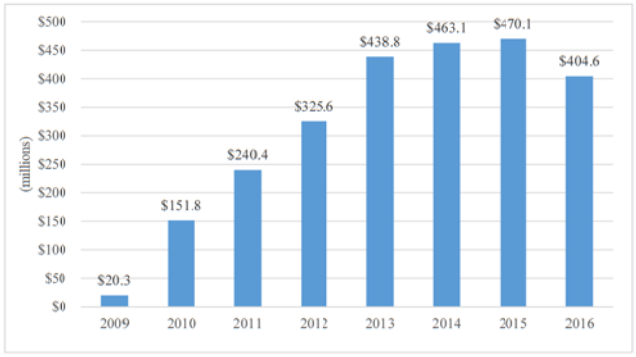
(1) Ex. 2090 at 2 Reflects U.S.-only sales when possible. *See* Footnote 2.

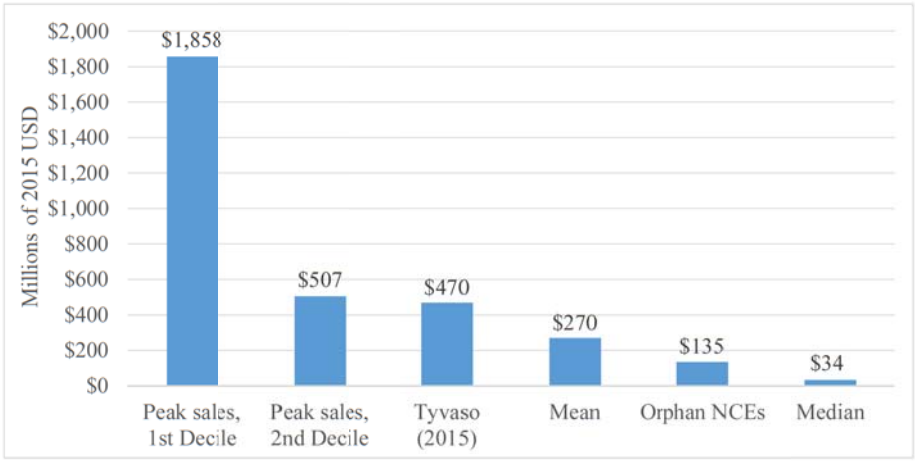
(2) Ex. 1055 at 39.

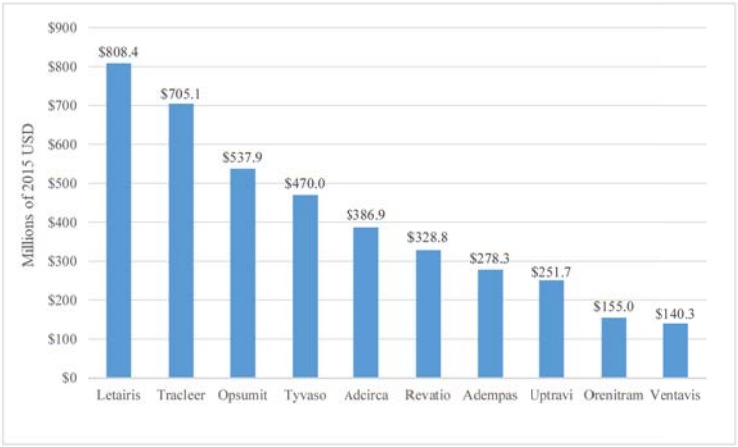
(3) Adempas and Uptravi are not reported on a geographic basis.

Name	Active Ingredient	Launch	Administration	Manufacturer
Flolan®	epoprostenol	1996	infused	GSK
Tracleer®	bosentan	2001	oral	Actelion
Ventavis®	iloprost	2004	inhaled	Actelion
Revatio®	sildenafil citrate	2005	oral	Pfizer
Letairis®	ambrisentan	2007	oral	Gilead
generic epoprostenol	epoprostenol	2008	infused	Teva
Veletri®	epoprostenol	2010	infused	Actelion
generic sildenafil citrate	sildenafil citrate	2012	oral	multiple
Adempas®	riociguat	2013	oral	Bayer
Opsumit®	macitentan	2013	oral	Actelion
Uptravi®	selexipag	2015	oral	Actelion

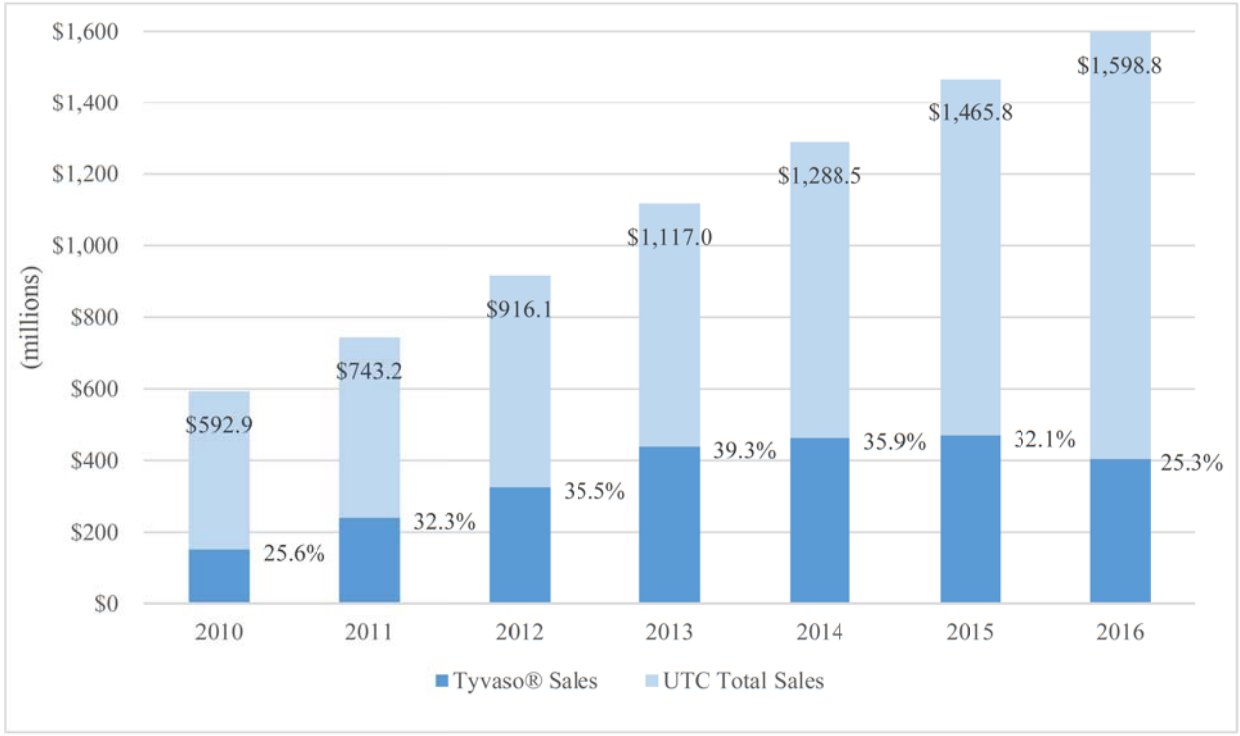
2009	2010	2011	2012	2013	2014	2015	2016	Total
$20.3	$151.8	$240.4	$325.6	$438.8	$463.1	$470.1	$404.6	**$2,514.6**





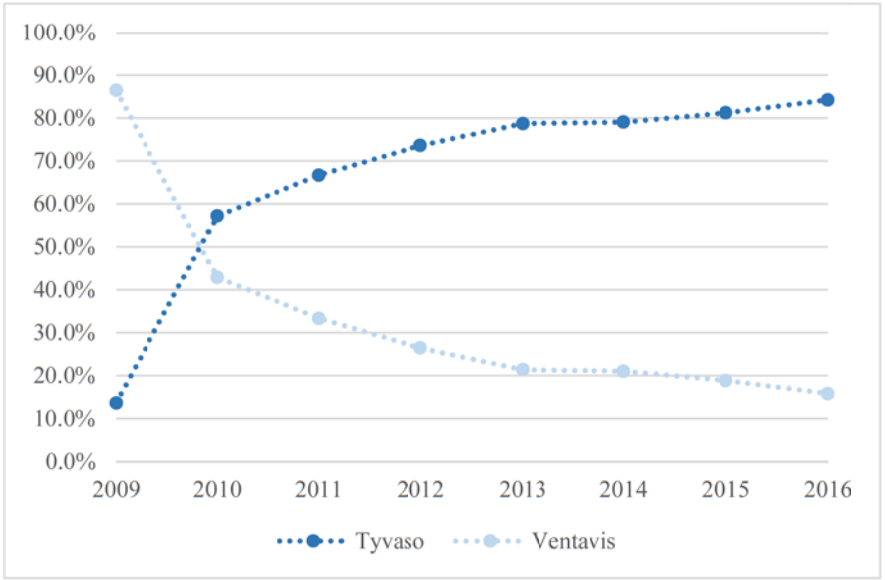


	2010	2011	2012	2013	2014	2015	2016	Total
Tyvaso ® Sales	$151.8	$240.4	$325.6	$438.8	$463.1	$470.1	$404.6	**$2,514.60**
UTC Total Sales	$441.1	$502.8	$590.5	$678.2	$825.4	$995.7	$1,194.2	
UTC Total	$592.9	$743.2	$916.1	$1,117.0	$1,288.5	$1,465.8	$1,598.8	**$8,092.10**
Tyvaso Sales as a % of Total	*25.6%*	*32.3%*	*35.5%*	*39.3%*	*35.9%*	*32.1%*	*25.3%*	**31.10%**

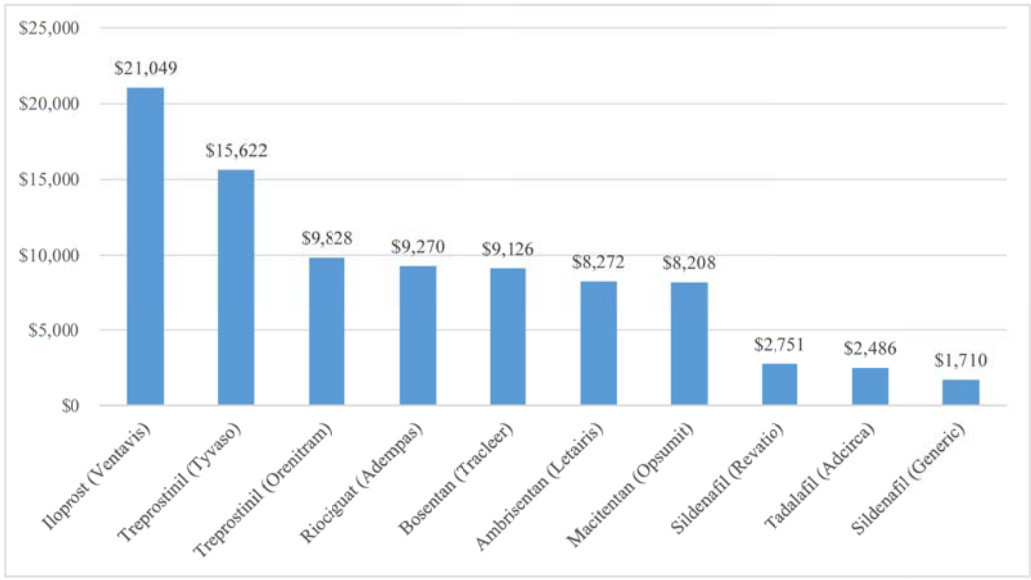


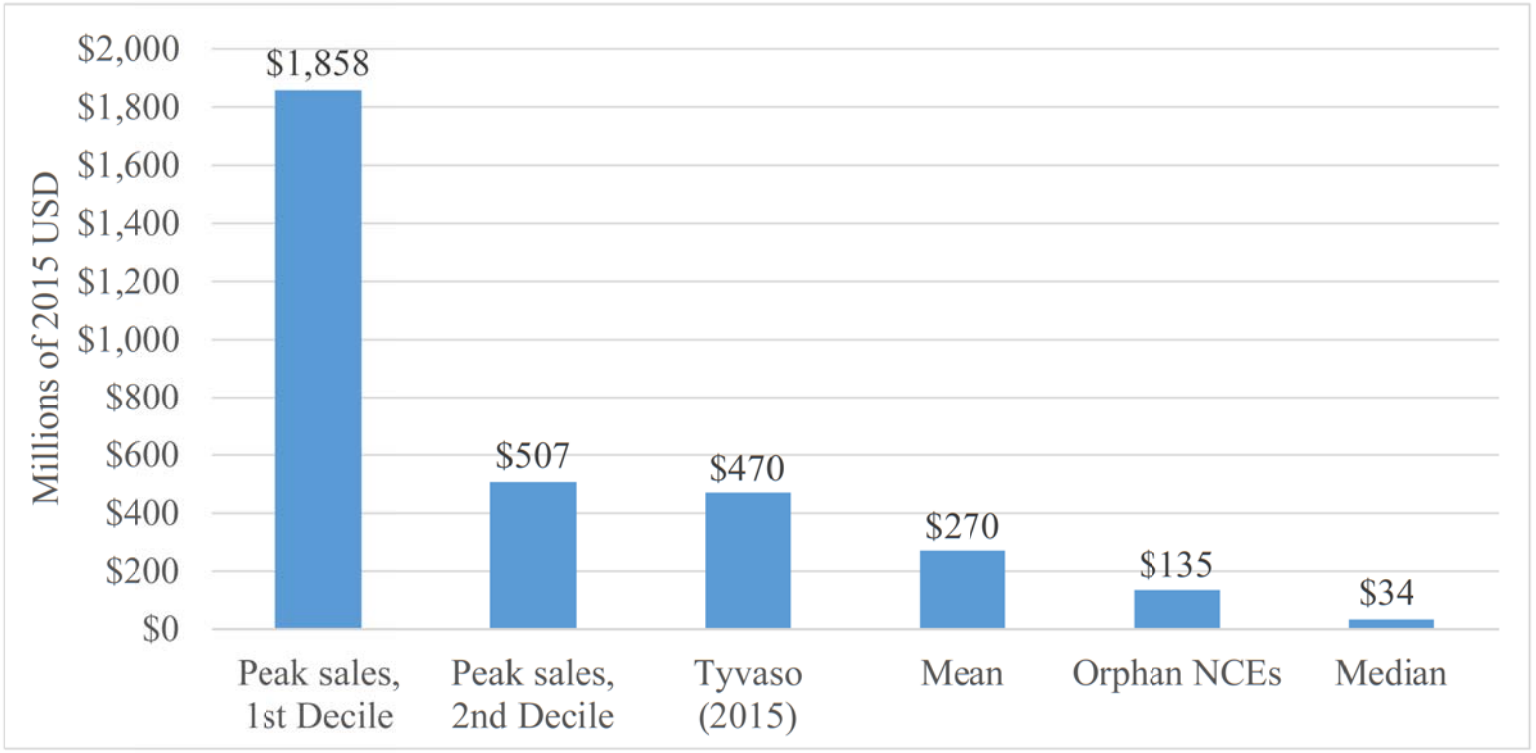
	2009	2010	2011	2012	2013	2014	2015	2016	Total
Gross Profit	$15.0	$121.7	$208.4	$271.8	$378.0	$405.6	$446.1	$385.0	**$2,231.6**
Gross Margin	*73.8%*	*80.2%*	*86.7%*	*83.5%*	*86.1%*	*87.6%*	*94.9%*	*95.2%*	***88.7%***

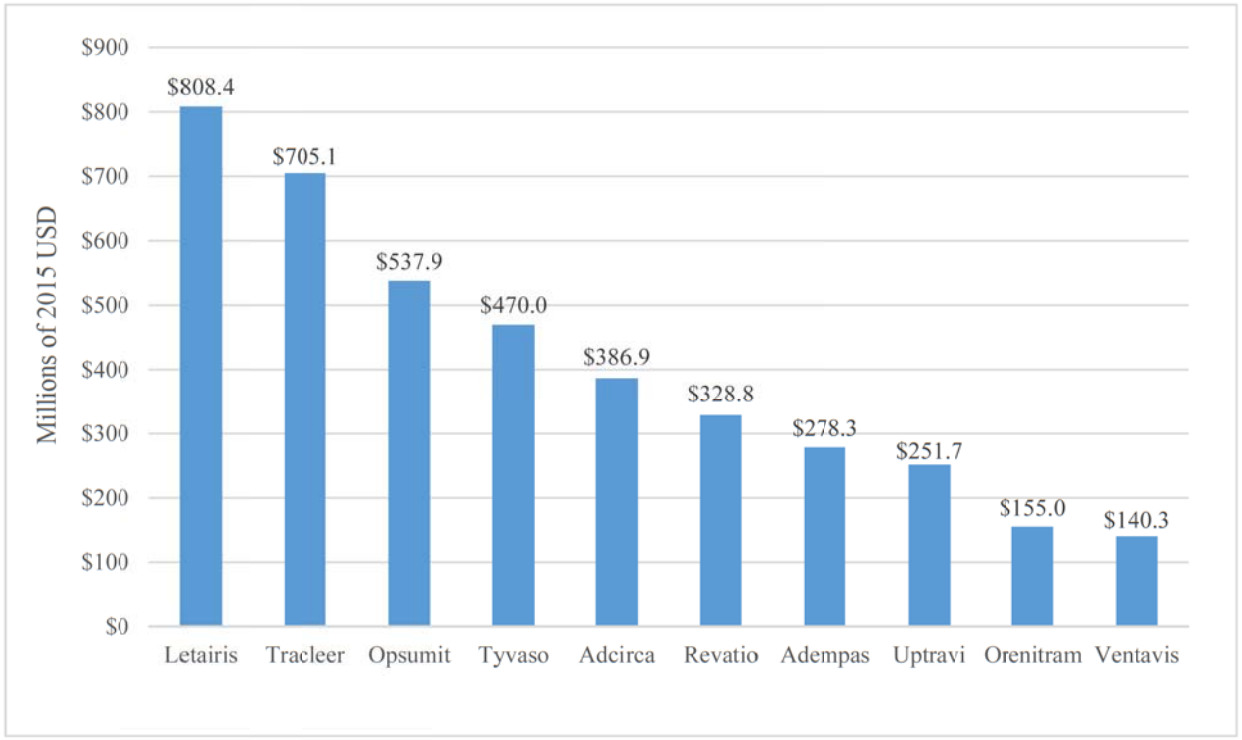
Product	2009	2010	2011	2012	2013	2014	2015	2016
Tyvaso	20	152	240	326	439	463	470	405
Ventavis	127	114	120	117	119	123	109	76
Total	**147**	**266**	**360**	**443**	**558**	**586**	**579**	**481**
Tyvaso	13.6%	57.1%	66.7%	73.6%	78.7%	79.0%	81.2%	84.2%
Ventavis	86.4%	42.9%	33.3%	26.4%	21.3%	21.0%	18.8%	15.8%



Cost of Therapy With Orally Administered Or Inhaled PAH-Approved	
Drug	Cost
Iloprost (Ventavis)	$21,049
Treprostinil (Tyvaso)	$15,622
Treprostinil (Orenitram)	$9,828
Riociguat (Adempas)	$9,270
Bosentan (Tracleer)	$9,126
Ambrisentan (Letairis)	$8,272
Macitentan (Opsumit)	$8,208
Sildenafil (Revatio)	$2,751
Tadalafil (Adcirca)	$2,486
Sildenafil (Generic)	$1,710




$2,000
$1,800
$1,600
$1,400
$1,200
$1,000
$800
$600
$400
$200
$0
Millions of 2015 USD
$1,858
$507
$470
$270
$135
$34
Peak sales, 1st Decile
Peak sales, 2nd Decile
Tyvaso (2015)
Mean
Orphan NCEs
Median


$900
$800
$700
$600
$500
$400
$300
$200
$100
$0
Millions of 2015 USD
$808.4
$705.1
$537.9
$470.0
$386.9
$328.8
$278.3
$251.7
$155.0
$140.3
Letairis
Tracleer
Opsumit
Tyvaso
Adcirca
Revatio
Adempas
Uptravi
Orenitram
Ventavis