

# Press Release



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## 2016 Annual Report – DTR 6.3.5 Disclosure

**March 23, 2017** - Shire plc (LSE: SHP, NASDAQ: SHPG) (the “Company”) announces that the following documents have today been posted or otherwise will be made available to shareholders:

- > 2016 Annual Report
- > Notice of the 2017 Annual General Meeting
- > Form of Proxy

In accordance with Listing Rule 9.6.1R, a copy of each of these documents will be uploaded to the National Storage Mechanism and will be available for viewing shortly.

The 2016 Annual Report and Notice of the 2017 Annual General Meeting are also available on Shire’s website: [www.shire.com](http://www.shire.com)

Disclosure & Transparency Rule (“DTR”) 6.3.5R requires the Company to disclose to the media certain information from its Annual Report if that information is of a type that would be required to be disseminated in a half-yearly report. The information contained in the Appendix to this announcement, together with the Company’s unaudited full year results for the year ended December 31, 2016, issued on February 16, 2017, constitute the materials required by DTR 6.3.5R to be communicated to the media in unedited full text through a Regulatory Information Service. This material is not a substitute for reading the full 2016 Annual Report.

The information included in the Appendix is extracted from the 2016 Annual Report which was approved by the Board of Directors on February 22, 2017. Defined terms used in the Appendix refer to terms as defined in the 2016 Annual Report, unless the context otherwise requires.

Stephen Williams  
Deputy Company Secretary

### For further information please contact:

#### Investor Relations

Ian Karp	<a href="mailto:ikarp@shire.com">ikarp@shire.com</a>	+1 781 482 9018
Robert Coates	<a href="mailto:rcoates@shire.com">rcoates@shire.com</a>	+44 1256 894874

### NOTES TO EDITORS

#### About Shire

Shire is the leading global biotechnology company focused on serving people with rare diseases. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including Hematology, Immunology, Neuroscience, Ophthalmics, Lysosomal Storage Disorders, Gastrointestinal / Internal Medicine / Endocrine and Hereditary Angioedema; and a growing franchise in Oncology.

Our employees come to work every day with a shared mission: to develop and deliver breakthrough therapies for the hundreds of millions of people in the world affected by rare diseases and other high-need conditions, and who lack effective therapies to live their lives to the fullest.

[www.shire.com](http://www.shire.com)

## Forward-Looking Statements

Statements included herein that are not historical facts, including without limitation statements concerning future strategy, plans, objectives, expectations and intentions, the anticipated timing of clinical trials and approvals for, and the commercial potential of, In-line or pipeline products, are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, the following:

- > Shire's products may not be a commercial success;
- > increased pricing pressures and limits on patient access as a result of governmental regulations and market developments may affect Shire's future revenues, financial condition and results of operations;
- > Shire conducts its own manufacturing operations for certain of its products and is reliant on third-party contract manufacturers to manufacture other products and to provide goods and services. Some of Shire's products or ingredients are only available from a single approved source for manufacture. Any disruption to the supply chain for any of Shire's products may result in Shire being unable to continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis for some period of time;
- > the manufacture of Shire's products is subject to extensive oversight by various regulatory agencies. Regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- > certain of Shire's therapies involve lengthy and complex processes, which may prevent Shire from timely responding to market forces and effectively managing its production capacity;
- > Shire has a portfolio of products in various stages of research and development. The successful development of these products is highly uncertain and requires significant expenditures and time, and there is no guarantee that these products will receive regulatory approval;
- > the actions of certain customers could affect Shire's ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely affect Shire's revenues, financial conditions or results of operations;
- > Shire's products and product candidates face substantial competition in the product markets in which it operates, including competition from generics;
- > adverse outcomes in legal matters, tax audits and other disputes, including Shire's ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on the combined company's revenues, financial condition or results of operations;
- > inability to successfully compete for highly qualified personnel from other companies and organizations;
- > failure to achieve the strategic objectives with respect to Shire's acquisition of NPS Pharmaceuticals, Inc., Dyax Corp. ("Dyax") or Baxalta Inc. ("Baxalta") may adversely affect Shire's financial condition and results of operations;
- > Shire's growth strategy depends in part upon its ability to expand its product portfolio through external collaborations, which, if unsuccessful, may adversely affect the development and sale of its products;
- > a slowdown of global economic growth, or economic instability of countries in which Shire does business, as well as changes in foreign currency exchange rates and interest rates, that adversely impact the availability and cost of credit and customer purchasing and payment patterns, including the collectability of customer accounts receivable;
- > failure of a marketed product to work effectively or if such a product is the cause of adverse side effects could result in damage to the Shire's reputation, the withdrawal of the product and legal action against Shire;

- > investigations or enforcement action by regulatory authorities or law enforcement agencies relating to Shire's activities in the highly regulated markets in which it operates may result in significant legal costs and the payment of substantial compensation or fines;
- > Shire is dependent on information technology and its systems and infrastructure face certain risks, including from service disruptions, the loss of sensitive or confidential information, cyber-attacks and other security breaches or data leakages that could have a material adverse effect on Shire's revenues, financial condition or results of operations;
- > Shire incurred substantial additional indebtedness to finance the Baxalta acquisition, which may decrease its business flexibility and increase borrowing costs;
- > difficulties in integrating Dyax or Baxalta into Shire may lead to the combined company not being able to realize the expected operating efficiencies, cost savings, revenue enhancements, synergies, or other benefits at the time anticipated or at all; and
- > a further list and description of risks, uncertainties and other matters can be found on pages 55 to 65 of this Annual Report.

All forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by this cautionary statement. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Except to the extent otherwise required by applicable law, we do not undertake any obligation to update or revise forward-looking statements, whether as a result of new information, future events or otherwise.

## **APPENDIX**

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## 1. Chairman's Review

This year has been one of transformation for Shire — one where we are now recognized as the world leader in the treatment of rare diseases.

With the acquisitions of Dyax and Baxalta, we have grown from 6,000 employees at the start of 2016 to approximately 24,000 today, and have expanded the reach of our global sales from 72 to over 100 countries. During this time, Shire launched four new drugs, including XIIDRA®, the first and only product approved in the U.S. to treat both the signs and symptoms of dry eye disease. We also expanded and progressed our pipeline so we now have roughly 40 programs in the clinic with about 20 in the later stages of development. These accomplishments set the stage for Shire's continued growth and are just a few examples of the many achievements highlighted in this Annual Report.

The patient is at the center of everything we do at Shire. This drives how we discover, develop and deliver new medicines, and guides how we interact and support our patient communities. During 2016, Shire provided a multi-year grant to the SeriousFun Children's Network to enable young people with rare illnesses to have a life-changing experience at summer camp and to help their families bond through Family Weekend programs. Many families have told us about the extraordinary impact of these experiences, a sentiment echoed by our employees who volunteered with SeriousFun.

Shire is also a leader in responsibility and sustainability. The company was recognized by Scrip's Pharma as "Company of the Year" in 2016. We were once again included in the FTSE4Good Index, which measures globally recognized standards for corporate responsibility. Newsweek ranked Shire as the number one greenest company in its 2016 Green Rankings. Our commitment to transparency was recognized by AllTrials, as Shire was the only company to have published results for all clinical trials completed during the past 10 years.

Our business is not without its challenges. We operate in an environment with significant political and market volatility. Shire's strategy is to deliver products that are innovative and differentiated, enabling us to provide value to patients and payers, while creating value for shareholders.

I would like to thank Flemming Ornskov, Shire's CEO, and his leadership team for their vision, passion and exceptional performance. We are now a global industry leader and forward-thinking organization. This is driven by the company's focus on innovation and high performance. I would also like to acknowledge Shire employees for their commitment to the company, and to patients, especially during a time of major transformation. I particularly want to recognize the thousands of Shire employees who participated in Shire's Global Day of Service, helping to improve local communities.

During the year, the Board played an important role, especially as the company completed the Baxalta acquisition, the largest in our history. My sincerest thanks to fellow Board members for their many contributions. In 2016, Gail Fosler and Albert Stroucken, formerly Baxalta Directors, joined our Board as Non-Executive Directors. In early 2017, Ian Clark, former CEO of Genentech, also joined the Shire Board. You can read more about the Board in the Governance section, beginning on page 66.

Looking forward, our priorities are to progress revenue growth, further develop the product pipeline, and continue to integrate the Baxalta business while reducing the associated debt. We will continue to be responsible and responsive to our communities while remaining focused on delivering long-term value to shareholders. I am confident we have the right team, the right strategy and the right resources in place to accomplish these goals. It is my privilege to be a part of this organization.

Susan Kilsby

Chairman

## 2. Chief Executive Officer's Review

### A game changing year

2016 was a transformational year for Shire. We took a big step forward in serving people with rare diseases with the acquisition of Baxalta, which added three new therapeutic areas including category leadership in hematology and immunology and a growing franchise in oncology. As a result of the acquisition and strong performance across our combined portfolio, we achieved record revenue of \$11.4 billion, almost double 2015's \$6.4 billion.

Since successfully navigating and finalizing the Baxalta acquisition, we are ahead of plan on the massive task of integration and delivering promised synergies. We are now approximately 24,000 people strong and are bringing our products to patients in over 100 countries.

We also completed the \$6 billion acquisition of Dyax to expand our industry leading portfolio in Hereditary Angioedema ("HAE") and we in-licensed from Pfizer a very promising candidate for Crohn's disease and ulcerative colitis.

Our employees did an outstanding job staying focused and delivering for patients during a time of significant change. In 2016, we also launched truly innovative products to address high unmet medical needs.

- > The launch of XIIDRA, the only prescription eye drop approved in the U.S. for the treatment of signs and symptoms of Dry eye disease, was another big success. We had an exceptional new drug launch, demonstrating our strength in commercial excellence and capturing 19 percent of market share within four months. This marks an outstanding entry into ophthalmics and we aim to further build a leadership position in this therapeutic area.
- > We launched CUVITRU™ in the U.S., a convenient at-home, subcutaneous treatment for primary immunodeficiency. Convenience is important to our patients and their families because many of our medicines are given as infusions or injections, through various devices and delivery methods.
- > Outside the U.S., we gained EU Marketing Authorization of ONIVYDE® for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have had gemcitabinebased therapy. ONIVYDE is the first and only approved treatment option for this patient population.

These new therapies exemplify our commitment to new-to-class, potentially best-in-class, or novel treatments for rare diseases.

All in all, 2016 was a standout year where we achieved our goal of becoming the leading biotech company focused on rare diseases. Today, 75 percent of our pipeline and 65 percent of our sales are in rare diseases.

### A unique need — and model — for biotech innovation

Rare diseases, most of which are genetic and are present throughout a person's entire life, pose a significant medical and economic burden for patients, communities and healthcare systems. There are more than 7,000 known rare diseases impacting 350 million people worldwide. Millions more have specialized conditions. What these figures do not reflect are the untold number of mothers, fathers, friends and family who watch a loved one struggle with health challenges that, in many cases, cannot be adequately addressed today. Nearly 50 percent of the time these loved ones are children.

What's more, delays to diagnosis are commonly experienced by patients with rare diseases, and can lead to serious consequences for their health, as well as the wider healthcare system.

These facts are what drive our unique model for biotech innovation. It is a mix of internal knowledge, capabilities and research, combined with collaborations with external partners, and supplemented by business development and M&A. We are very flexible in our approach, combining internal and external to create the best routes to innovation.

At the same time, we are extremely focused on growing and leading in our chosen therapeutic areas. We see our patient communities as key partners in innovation. Close, long-term relationships with patients, their

doctors and caregivers make all the difference in finding solutions for the challenges of their often-lifetime conditions. We have also significantly expanded our support services in helping patient's gain access to and stay on our medicines.

### **An exciting late-stage clinical portfolio**

Our pipeline has transformed in recent years, and now includes compounds with potential rare disease indications at all stages of development. Most of the products are new-to-class, potentially best-in-class or novel. We have 17 Phase 3 programs and most are expected to launch by the end of 2020, if approved. These include:

- > SHP465, the first new treatment in almost a decade for Attention Deficit Hyperactivity Disorder ("ADHD").
- > SHP621, recently granted breakthrough therapy designation by the U.S. FDA for eosinophilic esophagitis, a serious, chronic rare disease.
- > SHP643, recently granted breakthrough therapy designation by the U.S. FDA for hereditary angioedema ("HAE"). If we are able to replicate the clinical data we saw in earlier trials and if SHP643 is approved, we believe this product has the potential to be an advancement in the way HAE patients are treated, offer significant benefit to patients, and serve as a key growth driver for Shire's business.
- > SHP607, our treatment for neonatal complications, has had positive Phase 2 results and is now going into Phase 3, with the potential to significantly impact the health of premature infants.

With approximately 40 programs in the clinic and about 20 in the later stages of development, we now have the deepest, and most innovative, pipeline in our 30-year history.

### **A commitment to doing the right thing**

Our employees lead the way in ensuring we have a positive impact on society. In addition to their day-to-day focus on patients and a commitment to doing the right thing at work, they are also involved in our communities. In 2016, approximately 6,500 employees participated in our Global Day of Service in 150 locations around the world. Together, they donated over 25,000 hours of their time. This was for one event. We know our people and teams are dedicated to helping others throughout the year and also to using our resources in a responsible way. In fact, the company has received awards and recognition for our responsibility efforts and I encourage you to read on in this report to learn more.

It is an honor to work alongside our talented and dedicated employees and I'm thrilled that Shire is a place where people like to work, where we not only attract the best at all levels but also invest in their ongoing education and development. We saw a surge in job applications in 2016, also mirroring the greater recognition we have gained in our industry as a biotech leader.

### **Building on our leading position**

We have a strong track record of excellent commercial execution and delivering on short and medium-term financial promises to our shareholders. We like to set stretch goals and the integration of Baxalta has not distracted us from this focus.

As we grow, we want to retain the touch and feel of a small biotech so we have the benefits both of scale and agility. It's about very simple, very flat and rapid decision-making. We support this through innovation and operational excellence, through the interplay between our key strategic centers in Zug, Boston and Dublin, and through our In-line, Pipeline and Corporate Committees.

Speed matters, especially to the patients who are waiting for treatments, and that's why we've built a fast-paced, entrepreneurial, international culture where we give people freedom and opportunity to excel while also setting a high bar for being ethical and responsible.

Our teams will continue to support people with rare diseases through every step of their journey. This includes targeted diagnostic approaches to help improve the pathway to diagnosis, assistance programs for those with limited financial resources and personalized life-long programs that support on-going treatment

and enhance quality of life. We also remain committed to working alongside partners, doctors, patient advocacy organizations, governments and payers to deliver value and meaningful outcomes that help ease the long-term economic burden of these diseases for patients, communities and healthcare systems.

While each rare disease community is small on its own; together they make one large rare disease population in need of solutions. Shire is in a leading position to provide these solutions on a global scale, enabling more patients and families around the world to live their lives to the fullest.

Thank you for your continued support.

Flemming Ornskoy, MD, MPH  
Chief Executive Officer

### 3. Financial Review

#### Overview

The Company has grown both organically and through acquisition, completing a series of major transactions that have brought therapeutic, geographic and pipeline growth and diversification. The Company will continue to conduct its own research and development, focused on rare diseases, as well as evaluate companies, products and pipeline opportunities that offer a strategic fit and have the potential to deliver value to all of the Company's stakeholders: patients, physicians, policy makers, payers, partners, investors and employees.

The Company's purpose is to enable people with life-altering conditions to lead better lives. The Company will execute on its purpose through its strategy and business model. For further details of Shire's strategy and business model, refer to pages 12 and 14.

Through deep understanding of patients' needs, the Company is able to:

- > serve patients with high unmet needs in select, commercially attractive specialty therapeutic areas;
- > drive optimum performance of its marketed products — to serve patients today; and
- > build its pipeline of innovative specialist treatments through both R&D and Corporate Development activities to enable the Company to serve patients in the future.

Shire's in-licensing and acquisition efforts are focused on products in specialist markets with strong intellectual property protection or other forms of market exclusivity and global rights. Shire believes that a carefully selected and balanced portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

Company revenues, expenditures and net assets are attributable to the R&D, manufacture, sale and distribution of pharmaceutical products within one reportable segment. The Company also earns royalties (where Shire has out-licensed products to third-parties) which are recorded as royalty revenues.

Revenues are derived primarily from two sources — sales of the Company's own products and royalties:

- > 95.5 percent (2015: 95.0 percent) of total revenues are derived from Product sales; and
- > 4.5 percent (2015: 5.0 percent) of total revenues are derived from royalties.

The markets in which the Company conducts its business are intensely competitive and highly regulated.

The healthcare industry is also experiencing:

- > pressure from governments and healthcare providers to keep prices low while increasing access to drugs;
- > increased discounts, which reduce revenue, due to the population of "baby boomers" covered under Medicare, specifically those beneficiaries receiving drug cost offset through the Medicare Part D Coverage Gap (the "Donut Hole");
- > increasing challenges from third-party payers for products to have demonstrable clinical benefit, with pricing and reimbursement approval becoming increasingly linked to a product's clinical effectiveness and impact on overall costs of patient care;

- > increased R&D costs, because development programs are typically larger and take longer to get approval from regulators;
- > challenges to existing patents from generic manufacturers;
- > governments and healthcare systems favoring earlier entry of low cost generic drugs; and
- > higher marketing costs, due to increased competition for market share.

Shire's strategy has been developed to address these industry-wide competitive pressures. This strategy has resulted in a series of initiatives in the following areas:

### Markets

Shire's current portfolio of approved products spans seven key therapeutic areas ("TAs"): Hematology, Genetic Diseases (HAE/LSD), Neuroscience, Immunology, Internal Medicine, Oncology and Ophthalmology. In addition, Shire has a number of marketed products for other TAs from which it generates Product sales or royalties. In 2016, the contribution of each TA to overall Product sales was as follows:

	Product sales	Percentage
	\$'M	%
Hematology	2,240.8	20.6
Genetic Disease	2,698.0	24.8
Neuroscience	2,490.5	22.9
Immunology	1,516.1	13.9
Internal Medicine	1,755.5	16.1
Oncology	130.5	1.2
Ophthalmology	54.4	0.5
	10,885.8	100.0

Shire has grown in part through acquisition which has brought therapeutic, geographic and pipeline growth and diversification.

The acquisition of Baxalta in 2016 added the Hematology, Immunology and Oncology franchises and enabled Shire to become the global leader in rare diseases and highly specialized conditions.

The acquisition of Dyax in January 2016, with their lead pipeline product, SHP643, and marketed product KALBITOR, expanded and extended Shire's industry-leading HAE portfolio (FIRAZYR and CINRYZE).

In July 2016, Shire licensed the global rights to all indications for SHP647 from Pfizer Inc. SHP647 is an investigational biologic being evaluated for the treatment of moderate-to-severe inflammatory bowel disease.

In 2015, Shire acquired NPS Pharma, Meritage Pharma and Foresight.

The acquisition of NPS Pharma added global rights to an innovative product portfolio with multiple growth catalysts, including GATTEX/REVESTIVE and NATPARA. The acquisition of Meritage Pharma provided global rights to SHP621, a Phase 3 ready asset for the treatment of adolescents and adults with EoE, a rare, chronic inflammatory GI disease. This builds upon the Company's rare disease and GI commercial infrastructure and expertise. With the acquisition of Foresight Shire acquired the global rights to SHP640 (topical ophthalmic drops combining 0.6 percent povidone iodine (PVP-I) and 0.1 percent dexamethasone), a potential therapy in late-stage development for the treatment of infectious conjunctivitis, an ocular surface condition commonly referred to as pink eye. This acquisition has a clear strategic fit with XIIDRA, which is approved in the U.S. for the treatment of the signs and symptoms of dry eye disease, and further demonstrates Shire's commitment to building a leadership position in ophthalmics.

In 2016, Shire derived 32 percent (2015: 27 percent) of Product sales from outside of the U.S. Shire has ongoing commercialization and late-stage development activities, which are expected to further supplement the diversification of revenues in the future, including the following:

- > continued launch of INTUNIV, REVESTIVE and ONIVYDE across Europe;
- > review of MAAs for NATPAR and ADYNOVI in the EU;
- > review of NDA for SHP465 in U.S.;
- > submission of CALPEG NDA for ALL in U.S.;
- > submission of VONVENDI MAA in Europe;
- > headline data from registration studies for SHP643; and
- > geographic expansion of XIIDRA with submissions in other key markets.

## **R&D**

Shire's R&D efforts are focused on six therapeutic areas: Neuroscience, Ophthalmology, Hematology, Oncology, Immunology, GI/Metabolic/Endocrinology Diseases. Shire concentrates its resources on obtaining regulatory approval for later stage pipeline products within these therapeutic areas and focuses its early stage research activities in rare diseases.

Evidence of the successful progression of the late stage pipeline can be seen in the granting of approval and associated launches of the Company's products over the last three years. In this time, several products have received regulatory approval including: in the U.S., XIIDRA and CUVITRU in 2016, VONVENDI, DYNOVATE, NATPARA and VYVANSE for BED in 2015, HYQVIA and OBIZUR in 2014; in the EU, ONIVYDE and CUVITRU in 2016, ELVANSE/TYVENSE for adults, INTUNIV for children and adolescents and OBIZUR in 2015.

Shire's management reviews direct costs for all R&D projects by development phase.

Shire's R&D costs in 2016 and 2015 include expense on programs in all stages of development. The following table provides an analysis of the Company's direct R&D spend categorized by development stage, based upon the development stage of each program as of December 31, 2016 and 2015:

As of December 31	2016 \$'M	2015 \$'M
Early stage programs	325.7	177.2
Late stage programs	291.1	225.5
Currently marketed products	238.1	178.5
Total	854.9	581.2

Early stage programs include preclinical and research programs. In addition to the above, the Company recorded R&D employee costs of \$431.9 million in 2016 (2015: \$302.9 million) and other indirect R&D costs of \$153.0 million (2015: \$679.9 million), comprising mainly depreciation and milestone expense (2015 comprising mainly depreciation and impairment charges).

For a discussion of the Company's current development projects see pages 20 to 21.

### Patents and Market Exclusivity

The loss or expiration of patent protection or regulatory exclusivity with respect to any of the Company's major products could have a material adverse effect on the Company's revenues, financial condition and results of operations, as generic or biosimilar products may enter the market. Companies selling generic products often do not need to complete extensive clinical studies when they seek registration of a generic or biosimilar product and accordingly, are generally able to sell a generic version of the Company's products at a much lower price.

As expected, in 2009, Teva and Impax commenced commercial shipments of their authorized generic versions of ADDERALL XR, which led to lower sales of branded ADDERALL XR compared to the periods prior to the authorized generic launches.

In 2014 and 2015, generic versions of the Company's INTUNIV product was launched, which led to lower sales of INTUNIV product compared to the period before loss of exclusivity.

Shire is engaged in various legal proceedings with generic manufacturers with respect to its VYVANSE and LIALDA patents. For information regarding current patent litigation, see Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

### Corporate Development

Shire focuses its corporate development activity on the acquisition and in-licensing of businesses, products or compounds which offer a strategic fit and have the potential to deliver demonstrable value to all of the Company's stakeholders.

### Recent mergers and acquisitions

2016:

- > On January 22, 2016, Shire completed the acquisition of Dyax which expanded and extended Shire's industry-leading HAE portfolio by adding the currently approved product, KALBITOR for the treatment of sudden attacks of HAE in people 12 years of age and older and SHP643, a Phase 3 program for the treatment of HAE.
- > On June 3, 2016, Shire acquired all of the outstanding common stock of Baxalta. Baxalta was a global biopharmaceutical company, focused on developing, manufacturing and commercializing therapies for

orphan diseases and underserved conditions in hematology, oncology and immunology. Baxalta added a number of commercially approved products and enhanced Shire's existing pipeline with a number of drug candidates in different therapeutic areas under different phases of development. For further details, see pages 20 to 21.

2015:

- > On February 21, 2015, Shire acquired NPS Pharma, which added global rights to an innovative product portfolio with multiple growth catalysts, including GATTEX/REVESTIVE for the treatment of adults with SBS, a rare GI condition; and NATPARA/NATPAR, the only bioengineered parathyroid hormone therapy for use in the treatment of HPT, a rare endocrine disease.
- > On February 18, 2015, Shire acquired Meritage Pharma, which provided the Company with worldwide rights to SHP621 for the potential treatment of adolescents and adults with EoE, a rare, chronic inflammatory GI disease.
- > On July 30, 2015, Shire acquired Foresight, which added global rights to SHP640, a Phase 3 ready potential therapy for the treatment of infectious conjunctivitis, an ocular surface condition commonly referred to as pink eye.

### **Results of operations for the years ended December 31, 2016 and 2015**

Financial highlights for the year ended December 31, 2016 are as follows:

#### **Revenues**

- > Product sales increased by 78 percent to \$10,886 million (2015: \$6,100 million). This increase was primarily due to including \$3,887 million of Baxalta product sales following the acquisition, and double digit growth of existing franchises, with Genetic Diseases up 12 percent, Neuroscience up 13 percent and Internal Medicine up 17 percent. In addition, the Company launched XIIDRA in August 2016 and the Ophthalmology franchise contributed sales of \$54 million.
- > Royalties and other revenues increased by 61 percent to \$511 million, as the second half of 2016 benefited from additional revenue following the acquisition of Baxalta, primarily related to contract manufacturing activities.

#### **Operating results**

- > Operating income decreased 32 percent to \$963 million (2015: \$1,420 million), primarily due to the impact of the acquisition of Baxalta, including higher amortization of inventory fair value adjustments and acquired intangible assets, combined with higher integration and acquisition costs, partially offset by lower impairment charges related to R&D programs.

#### **Earnings per share ("EPS")**

- > Diluted earnings per ADS decreased 81 percent to \$1.27 (2015: \$6.59). The decrease was primarily due to lower operating income resulting from the impact of the acquisition of Baxalta and higher integration and acquisition costs, combined with the impact of additional shares issued as consideration for the Baxalta transaction.

#### **Cash flows**

- > Net cash provided by operating activities increased 14 percent to \$2,659 million (2015: \$2,337 million), primarily due to strong cash receipts from higher sales, partially offset by higher tax and interest payments, costs related to the Baxalta integration and a payment associated with the termination of a biosimilar collaboration acquired with Baxalta.

## Total revenues

The following table provides an analysis of the Company's total revenues by source:

	2016	2015	Change
As of December 31	\$'M	\$'M	%
Product sales	10,885.8	6,099.9	78
Royalties and other revenues	510.8	316.8	61
Total	11,396.6	6,416.7	78

## Product sales

As of December 31	2016	2015	Change
	\$'M	\$'M	%
<b>Product sales:</b>			
HEMOPHILIA	1,789.0	-	N/A
INHIBITOR THERAPIES	451.8	-	N/A
<b>Hematology total</b>	<b>2,240.8</b>	<b>-</b>	<b>N/A</b>
CINRYZE	680.2	617.7	10.1
ELAPRASE	589.0	552.6	6.6
FIRAZYR	578.5	445.0	30.0
REPLAGAL	452.4	441.2	2.5
VPRIV	345.7	342.4	1.0
KALBITOR	52.2	-	N/A
<b>Genetic Diseases total</b>	<b>2,698.0</b>	<b>2,398.9</b>	<b>12.5</b>
VYVANSE	2,013.9	1,722.2	16.9
ADDERALL XR	363.8	362.8	0.3
Other Neuroscience	112.8	115.4	(2.2)
<b>Neuroscience total</b>	<b>2,490.5</b>	<b>2,200.4</b>	<b>13.2</b>

IMMUNOGLOBULIN THERAPIES	1,143.9	-	N/A
BIO THERAPEUTICS	372.2	-	N/A
<b>Immunology total</b>	<b>1,516.1</b>	-	N/A
LIALDA/MEZAVANT	792.1	684.4	15.7
PENTASA	309.4	305.8	1.2
GATTEX/REVESTIVE	219.4	141.7	54.8
NATPARA	85.3	24.4	249.6
Other Internal Medicine	349.3	344.3	1.4
<b>Internal Medicine total</b>	<b>1,755.5</b>	1,500.6	N/A
<b>Oncology total</b>	<b>130.5</b>	-	N/A
<b>Ophthalmology total</b>	<b>54.4</b>	-	N/A
<b>Total Product sales</b>	<b>10,885.8</b>	6,099.9	78.5

### Hematology

Hematology, acquired with Baxalta June 2016, includes sales of recombinant and plasma-derived hemophilia products (primarily factor VIII and factor IX) and inhibitor therapies. Product sales of the franchise for the year ended December 31, 2016 were \$2,241 million.

### Genetic Diseases

Genetic Diseases product sales for the year ended December 31, 2016 increased to \$2,698 million or 12 percent from \$2,399 million in 2015, primarily driven by increased demand for HAE therapies.

FIRAZYR product sales for the year ended December 31, 2016 increased to \$579 million or 30 percent from \$445 million in 2015, primarily due to an increase in the number of patients on therapy in both the U.S. and international markets. CINRYZE sales for the year ended December 31, 2016 increased to \$680 million or 10 percent from \$618 million in 2015, as an increase in the number of patients on therapy was partially offset by reduced utilization as a result of a U.S. supply constraint during the second half of the year. Shire continues to execute on plans to increase CINRYZE production to meet both short-term and long-term patient demand.

### Neuroscience

Neuroscience product sales for the year ended December 31, 2016 increased to \$2,490 million or 13 percent from \$2,200 million in 2015, primarily driven by sales growth of VYVANSE.

VYVANSE sales for the year ended December 31, 2016 increased to \$2,014 million or 17 percent from \$1,722 million in 2015, due to prescription growth in the U.S. adult market, which includes ADHD and BED, and the benefit of price increases taken since 2015 and growth in the Company's international markets.

Information about litigations related to VYVANSE can be found in Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

### Immunology

Immunology, acquired with Baxalta in June 2016, reported product sales of \$1,516 million. Immunology includes antibody-replacement immunoglobulin and bio therapeutics therapies.

### Internal Medicine

Internal Medicine product sales for the year ended December 31, 2016 increased to \$1,756 million or 17 percent from \$1,501 million in 2015, primarily driven by sales growth from LIALDA/MEZAVANT, GATTEX/REVESTIVE and NATPARA.

LIALDA/MEZAVANT product sales increased to \$792 million or 16 percent for the year ended December 31, 2016 from \$684 million in 2015, primarily due to an increase in prescription demand, resulting in a U.S. market share of 40 percent at the end of 2016 (compared to 36 percent in 2015).

Information about litigations related to LIALDA can be found in Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

GATTEX/REVESTIVE and NATPARA product sales increased to \$219 million or 55 percent and \$85 million or 250 percent, respectively, for 2016, compared to product sales in 2015 primarily due to an increase in the numbers of patients on therapy.

### Oncology

Oncology, acquired with Baxalta in June 2016, reported product sales of \$131 million. Oncology includes sales of ONCASPAR and ONIVYDE. ONIVYDE was approved in the EU on October 18, 2016.

### Ophthalmology

Ophthalmology product sales relate to XIIDRA, which was made available to patients on August 29, 2016. XIIDRA product sales were \$54 million for the year ended December 31, 2016.

### Royalties and other revenues

As of	2016	2015	Change
December 31	\$'M	\$'M	%
SENSIPAR royalties	151.5	114.5	32
3TC and ZEFFIX royalties	58.9	49.1	20
FOSRENOL royalties	48.2	46.1	5
ADDERALL XR royalties	32.3	26.0	24
Other royalties and revenues	219.9	81.1	171
Total	510.8	316.8	61

Royalties and other revenues increased to \$511 million or 61 percent for the year ended December 31, 2016 from \$317 million in 2015, primarily due to \$99 million of contract manufacturing revenue from the acquisition of Baxalta.

### **Cost of product sales**

Cost of product sales increased by \$2,848 million to \$3,817 million for the year ended December 31, 2016 (35 percent of Product sales) from \$969 million in 2015 (16 percent of Product sales) primarily due to the impact of higher amortization of inventory fair value adjustments in 2016 following the acquisitions of Baxalta and Dyax and, to a lesser extent, the impact of lower margin product franchises acquired with Baxalta. Cost of product sales included \$1,118 million and \$31 million of amortization of inventory fair value adjustments in 2016 and 2015, respectively.

For the year ended December 31, 2016, Cost of product sales included additional depreciation totaling \$161 million (2015: \$46 million), primarily due to the acquisition of Baxalta.

### **R&D**

R&D expense decreased by \$124 million, or 8 percent, to \$1,440 million for the year ended December 31, 2016 (13 percent of Product sales) from \$1,564 million in 2015 (26 percent of Product sales), as lower IPR&D impairment charges in 2016 more than offset the increase in costs related to Baxalta and Dyax and costs related to licensing SHP647. R&D expense in 2015 included impairment charges of \$467 million related to the SHP625 IPR&D intangible asset, due to a lower probability of regulatory approval following trial results and revised commercial potential, and \$177 million related to the SHP608 IPR&D intangible asset, following preclinical toxicity findings. No significant impairment charges occurred in 2016.

R&D expense for the year ended December 31, 2016 included depreciation of \$34 million (2015: \$22 million).

### **SG&A**

SG&A expense increased by \$1,173 million, or 64 percent, to \$3,015 million for the year ended December 31, 2016 (28 percent of Product sales) from \$1,843 million in 2015 (30 percent of Product sales), primarily due to the inclusion of Baxalta related costs and XIIDRA launch and promotional costs.

For the year ended December 31, 2016, SG&A expense included depreciation of \$98 million (2015: \$71 million).

### **Amortization of acquired intangible assets**

For the year ended December 31, 2016, Shire recorded Amortization of acquired intangible assets of \$1,173 million compared to \$499 million in 2015. The increase of \$675 million was primarily related to amortization on the intangible assets acquired with the Baxalta and Dyax transactions.

### **Integration and acquisition costs**

For the year ended December 31, 2016, Shire recorded integration and acquisition costs of \$884 million, primarily related to the Baxalta and Dyax transactions, which included severance and employee termination benefits and office closure related expenses.

In 2015, Shire recorded net integration and acquisition costs of \$40 million, representing acquisition and integration costs of \$190 million, primarily related to NPS, ViroPharma, Baxalta and Dyax. These costs were offset by a net credit of \$150 million from the change in fair value of contingent consideration, primarily relating to SHP625 and SHP608.

### **Reorganization costs**

For the year ended December 31, 2016, Shire recorded reorganization costs of \$121 million primarily related to the planned closure of a facility at the Los Angeles manufacturing site acquired with Baxalta in June 2016.

Reorganization costs of \$98 million for the year ended December 31, 2015, primarily related to the relocation of roles from Pennsylvania to Massachusetts.

### **Interest Expense**

Other expense, net increased by \$443 million to \$477 million for the year ended December 31, 2016 from \$34 million in 2015, primarily due to higher interest expense and amortization of one-time borrowing costs, including the write off of certain financing costs related to the bridge facility for the Baxalta transaction.

During the third quarter of 2016, the bridge facility was fully repaid with the proceeds from the \$12.1 billion public debt offering.

### **Taxation**

The effective tax rate on income from continuing operations for the year ended December 31, 2016 was a benefit of 26 percent (2015: charge of 3 percent). The effective tax rate on income from continuing operations in 2016 was lower primarily due to the combined impact of the relative quantum of the profit before tax for the period by jurisdiction and the reversal of deferred tax liabilities (including in higher tax territories) from the Baxalta acquisition, inventory and intangible asset amortization, as well as acquisition and integration costs.

### **Discontinued operations**

The loss from discontinued operations for the year ended December 31, 2016 was \$276 million, net of tax benefit of \$99 million, primarily related to legal contingencies for the divested DERMAGRAFT business. The loss from discontinued operations for the year ended December 31, 2015 was \$34 million, net of tax, primarily related to a change in estimate for abandoned facilities charges.

### **Liquidity and Capital Resources**

#### **General**

The Company's funding requirements depend on a number of factors, including the timing and extent of its development programs; corporate, business and product acquisitions; the level of resources required for the expansion of certain manufacturing and marketing capabilities as the product base expands; increases in accounts receivable and inventory which may arise with any increase in Product sales; competitive and technological developments; the timing and cost of obtaining required regulatory approvals for new products; the timing and quantum of milestone payments on business combinations, in-licenses and collaborative projects; the timing and quantum of tax and dividend payments; the timing and quantum of purchases by the Employee Benefit Trust ("EBT") of Shire shares in the market to satisfy awards granted under Shire's employee share plans; and the amount of cash generated from sales of Shire's products and royalty receipts.

An important part of Shire's business strategy is to protect its products and technologies through the use of patents, proprietary technologies and trademarks, to the extent available. The Company intends to defend its intellectual property and as a result may need cash for funding the cost of litigation.

The Company finances its activities through cash generated from operating activities; credit facilities; private and public offerings of equity and debt securities; and the proceeds of asset or investment disposals.

Shire's Consolidated Balance Sheets included \$529 million of Cash and cash equivalents as of December 31, 2016.

Shire has a revolving credit facility (“RCF”) of \$2,100 million which matures in 2021, \$450 million of which was utilized as of December 31, 2016. The RCF incorporates a \$250 million U.S. Dollar and Euro swingline facility operating as a sub-limit thereof.

On September 23, 2016, Shire Acquisitions Investments Ireland Designated Activity Company (“SAIIDAC”), a wholly owned subsidiary of the Company, issued senior notes guaranteed by Shire plc with a total aggregate principal amount of \$12.1 billion. On December 1, 2016, Baxalta guaranteed the outstanding notes issued by SAIIDAC.

In addition, in connection with the acquisition of Baxalta, on June 3, 2016, Shire plc guaranteed senior notes issued by Baxalta with a total aggregate principal amount of \$5 billion and assumed \$336 million of capital lease obligations. The details of these senior notes are presented in Note 18, Borrowings and Capital Lease Obligations, to the Consolidated Financial Statements.

Further in connection with the acquisitions of Dyax and Baxalta, respectively, Shire entered into a \$5.6 billion amortizing term loan facility in November 2015 and an \$18 billion bridge loan in January 2016. The November 2015 term loan facility was fully utilized as of December 31, 2016 in the amount of \$5 billion. The bridge loan was fully repaid and canceled subsequent to the issuance of \$12.1 billion in senior notes on September 23, 2016. The details of these facility agreements are presented in Note 18, Borrowings and Capital Lease Obligations, to the Consolidated Financial Statements.

In addition, Shire also has access to certain short-term uncommitted lines of credit which are available to utilize from time to time to provide short-term cash management flexibility. As of December 31, 2016, these lines of credit were not utilized.

The Company may also engage in financing activities from time to time, including accessing the debt or equity capital markets.

### Senior Notes Issuance

On September 23, 2016, SAIIDAC, issued senior notes with a total aggregate principal value of \$12.1 billion (“SAIIDAC Notes”), guaranteed by Shire plc and, as of December 1, 2016, by Baxalta. SAIIDAC used the net proceeds to fully repay amounts outstanding under the January 2016 Facilities Agreement (discussed below), which was used to finance the cash consideration payable related to the Company’s acquisition of Baxalta. Below is a summary of the SAIIDAC Notes as of December 31, 2016:

	Aggregate amount \$'M	Coupon rate %	Effective interest rate %	Carrying amount \$'M
Fixed-rate notes due 2019	3,300.0	1.900	2.05	3,287.5
Fixed-rate notes due 2021	3,300.0	2.400	2.53	3,283.0
Fixed-rate notes due 2023	2,500.0	2.875	2.97	2,487.9
Fixed-rate notes due 2026	3,000.0	3.200	3.30	2,980.8
	12,100.0			12,039.2

The SAIIDAC Notes are senior unsecured obligations and may be redeemed at SAIIDAC's option at the greater of (1) 100 percent of the principal amount plus accrued and unpaid interest or (2) the sum of the present values of the remaining scheduled payments of interest and principal discounted to the date of redemption on a semi-annual basis at the applicable treasury rate (as defined) plus an incremental margin, plus, in either case, accrued and unpaid interest. The SAIIDAC Notes also contain a change of control provision that may require that SAIIDAC to offer to purchase the SAIIDAC Notes at a price equal to 101 percent of the principal amount plus accrued and unpaid interest to the date of purchase under certain circumstances.

The costs and discount associated with this offering of \$61 million have been recorded as a reduction to the carrying amount of the debt on the Consolidated Balance Sheets. These costs will be amortized as additional interest expense using the effective interest rate method over the period from issuance through maturity. Interest on the SAIIDAC Notes is payable March 23 and September 23 of each year, beginning on March 23, 2017.

### Baxalta Notes

Shire plc guaranteed senior notes issued by Baxalta with a total aggregate principal amount of \$5 billion in connection with the Baxalta acquisition ("Baxalta Notes"). Below is a summary of the Baxalta Notes as of December 31, 2016:

	Aggregate principal \$'M	Coupon rate %	Effective rate %	interest	Carrying \$'M	amount
Variable-rate notes due 2018	375.0	LIBOR plus 0.780	2.20		371.6	
Fixed-rate notes due 2018	375.0	2.000	2.00		374.8	
Fixed-rate notes due 2020	1,000.0	2.875	2.80		1,004.3	
Fixed-rate notes due 2022	500.0	3.600	3.30		508.4	
Fixed-rate notes due 2025	1,750.0	4.000	3.90		1,772.8	
Fixed-rate notes due 2045	1,000.0	5.250	5.10		1,031.7	
<b>Total Baxalta Notes</b>	<b>5,000.0</b>				<b>5,063.6</b>	

The effective interest rates above exclude the effect of any related interest rate swaps. The book values above include any premiums and adjustments related to hedging instruments. For further details related to the interest rate derivative contracts, please see Note 16, Financial Instruments, to the Consolidated Financial Statements.

## Revolving Credit Facilities Agreement

On December 12, 2014, Shire entered into a \$2,100 million revolving credit facilities agreement (the "RCF") with a number of financial institutions. Shire is an original borrower and original guarantor under the RCF. On January 15, 2016, SAIDAC became additional guarantor to the RCF and on December 1, 2016, Baxalta became additional guarantor to the RCF. Shire has agreed to act as guarantor for any of its subsidiaries that become additional borrowers under the RCF. As of December 31, 2016 the Company utilized \$450 million of the RCF.

The RCF, which terminates on December 12, 2021, may be applied towards financing the general corporate purposes of Shire. The RCF incorporates a \$250 million U.S. Dollar and Euro swingline facility operating as a sub-limit thereof.

Interest on any loans made under the RCF is payable on the last day of each interest period, which may be one week or one, two, three or six months at the election of Shire, or as otherwise agreed with the lenders. The interest rate for the RCF is: LIBOR (or, in relation to any revolving loan in Euro, EURIBOR); plus 0.30 percent per annum subject to change depending upon (i) the prevailing ratio of Net Debt to EBITDA (each as defined in the RCF) in respect of the most recently completed financial year or financial half year and (ii) the occurrence and continuation of an event of default in respect of the financial covenants or the failure to provide a compliance certificate.

Shire shall also pay (i) a commitment fee equal to 35 percent of the applicable margin on available commitments under the RCF for the availability period applicable thereto and (ii) a utilization fee equal to (a) 0.10 percent per year of the aggregate of all outstanding loans up to an aggregate base currency amount equal to \$700 million, (b) 0.15 percent per year of the amount by which the aggregate base currency amount of all outstanding loans exceeds \$700 million but is equal to or less than \$1,400 million and (c) 0.30 percent per year of the amount by which the aggregate base currency amount of all outstanding loans exceeds \$1,400 million.

The RCF includes customary representations and warranties, covenants and events of default, including requirements that Shire's (i) ratio of Net Debt to EBITDA in respect of the most recently-ended 12-month relevant period (each as defined in the RCF) must not, at any time, exceed 3.5:1 except that, following an acquisition fulfilling certain criteria, Shire may elect to increase this ratio to (a) 5.5:1 for the relevant period in which the acquisition was completed (b) 5.0:1 in respect of the first relevant period following the relevant period in which the acquisition was completed and (c) 4.5:1 in respect of the second relevant period following the relevant period in which the acquisition was completed and (ii) ratio of EBITDA to Net Interest for the most recently-ended 12-month relevant period (each as defined in the RCF) must not be less than 4.0:1. Shire elected to increase the Net Debt to EBITDA ratio in connection with the period ending June 30, 2016, following the completion of the acquisition of Baxalta during the period. Consequently, the applicable ratio for the period ending December 31, 2016 is 5.0:1.

The RCF restricts, subject to certain exceptions, Shire's ability to incur additional financial indebtedness, grant security over its assets or provide loans/grant credit. Further, any lender may require mandatory prepayment of its participation if there is a change of control of Shire, subject to certain exceptions for schemes of arrangement and analogous schemes.

Events of default under the RCF include, subject to customary grace periods and materiality thresholds: (i) non-payment of any amounts due under the finance documents (as defined in the RCF), (ii) failure to satisfy any financial covenants, (iii) material misrepresentation in any of the finance documents, (iv) failure to pay, or certain other defaults, under other financial indebtedness, (v) certain insolvency events or proceedings, (vi) material adverse changes in the business, operations, assets or financial condition of Shire as a whole, (vii) if it becomes unlawful for Shire (or any successor parent company) or any of their respective subsidiaries

that are parties to the RCF to perform their obligations thereunder or (viii) if Shire (or any successor parent company) or any subsidiary thereof which is a party to the RCF repudiates such agreement or other finance document, among others.

## **Term Loan Facilities Agreement**

### **January 2016 Facilities Agreement**

On January 11, 2016, Shire (as original guarantor and original borrower), entered into an \$18 billion bridge facilities agreement with various financial institutions (the "January 2016 Facilities Agreement"). The January 2016 Facilities Agreement comprised two credit facilities: (i) a \$13 billion term loan facility originally maturing on January 11, 2017 ("January 2016 Facility A") and (ii) a \$5 billion revolving loan facility originally maturing on January 11, 2017 ("January 2016 Facility B"). On April 1, 2016 SAIDAC became additional borrower and additional guarantor to the January 2016 Facilities Agreement.

The January 2016 Facility A was utilized to finance the cash consideration payable in respect of the acquisition of Baxalta on June 3, 2016 in the amount of \$12,390 million. The net proceeds from the issuance of the SAIDAC Notes were used to fully repay the amounts outstanding under the January 2016 Facility A in September 2016. The January 2016 Facility B was canceled effective July 11, 2016, in accordance with its terms.

### **November 2015 Facilities Agreement**

On November 2, 2015, Shire (as original guarantor and original borrower) entered into a \$5.6 billion facilities agreement with various financial institutions (the "November 2015 Facilities Agreement"). The November 2015 Facilities Agreement comprises three credit facilities: (i) a \$1.0 billion term loan facility of which, following the exercise of the one year extension option in the amount of \$400.0 million, \$600.0 million matured and was repaid on November 2, 2016 and \$400.0 million matures on November 2, 2017 ("November 2015 Facility A"), (ii) a \$2.2 billion amortizing term loan facility which matures on November 2, 2017 ("November 2015 Facility B") and (iii) a \$2.4 billion amortizing term loan facility which matures on November 2, 2018 ("November 2015 Facility C").

On January 15, 2016, SAIDAC became additional borrower and additional guarantor to the November 2015 Facilities Agreement and on December 1, 2016, Baxalta became an additional guarantor to the November 2015 Facilities Agreement. As of December 31, 2016, the November 2015 Facilities Agreement was fully utilized by SAIDAC as borrower in the amount of \$5.0 billion to finance the cash consideration payable and certain costs related to the acquisition of Dyax. On January 30, 2017, SAIDAC made its first repayment installment of \$400.0 million of the November 2015 Facility B in accordance with the terms of the agreement.

Interest on any loans made under the November 2015 Facilities Agreement is payable on the last day of each interest period, which may be one week or one, two, three or six months, or as otherwise agreed with the lenders. The interest rate applicable is LIBOR plus, in the case of the November 2015 Facility A, 0.55 percent per annum, in the case of the November 2015 Facility B, 0.65 percent per annum and, in the case of the November 2015 Facility C, 0.75 percent per annum, in each case subject to change depending on (i) the prevailing ratio of Net Debt to EBITDA (each as defined in the November 2015 Facilities Agreement) in respect of the most recently completed financial year or financial half year and (ii) the occurrence and continuation of an event of default in respect of the financial covenants or failure to provide a compliance certificate.

The November 2015 Facilities Agreement includes customary representations and warranties, covenants and events of default, including requirements that Shire's (i) ratio of Net Debt to EBITDA in respect of the most recently ended 12-month relevant period, (each as defined in the November 2015 Facilities Agreement), must not, at any time, exceed 3.5:1, except that following an acquisition fulfilling certain criteria, Shire may elect to increase this ratio to (a) 5.5:1 for the relevant period in which the acquisition was

completed, (b) 5.0:1 in respect of the first relevant period following the relevant period in which the acquisition was completed, Shire has elected to increase this ratio in connection with the period ended June 30, 2016, following the completion of the acquisition of Baxalta during the period and (c) 4.5:1 in respect of the second relevant period following the relevant period in which the acquisition was completed, Shire has elected to increase this ratio in connection with the period ending June 30, 2016, following the completion of the acquisition of Baxalta during the period and (ii) ratio of EBITDA to Net Interest in respect of the most recently ended 12-month relevant period, (each as defined in the November 2015 Facilities Agreement), must not be less than 4.0:1.

The November 2015 Facilities Agreement restricts, subject to certain exceptions, Shire's ability to incur additional financial indebtedness, grant security over its assets or provide loans/grant credit. Further, any lender may require mandatory prepayment of its participation if there is a change of control of Shire, subject to certain exceptions for schemes of arrangement and analogous schemes.

Events of default under the November 2015 Facilities Agreement include, subject to customary grace periods and materiality thresholds: (i) non-payment of any amounts due under the finance documents (as defined in the November 2015 Facilities Agreement), (ii) failure to satisfy any financial covenants, (iii) material misrepresentation in any of the finance documents, (iv) failure to pay, or certain other defaults, under other financial indebtedness, (v) certain insolvency events or proceedings, (vi) material adverse changes in the business, operations, assets or financial condition of Shire as a whole, (vii) if it becomes unlawful for Shire (or any successor parent company) or any of their respective subsidiaries that are parties to the November 2015 Facilities Agreement to perform their obligations thereunder or (viii) if Shire (or any successor parent company) or any subsidiary thereof which is a party to the November 2015 Facilities Agreement repudiates the November 2015 Facilities Agreement or any other finance document, among others.

#### **January 2015 Facility Agreement**

On January 11, 2015, Shire entered into an \$850.0 million term facility agreement with various financial institutions (the "January 2015 Facility Agreement") with an original maturity date of January 10, 2016. The maturity date was subsequently extended to July 11, 2016 in line with the provisions within the January 2015 Facility Agreement allowing the maturity date to be extended twice, at Shire's option, by six months on each occasion.

The January 2015 Facility Agreement was used to finance Shire's acquisition of NPS Pharma (including certain related costs). On September 28, 2015, the Company reduced the January 2015 Facility Agreement by \$100.0 million. In January 2016 and at various points thereafter, the Company canceled parts of the January 2015 Facility Agreement. On February 22, 2016, the Company repaid the remaining balance of \$100.0 million of the January 2015 Facilities Agreement in full.

#### **Short-term uncommitted lines of credit ("Credit lines")**

Shire has access to various Credit lines from a number of banks which are available to be utilized from time to time to provide short-term cash management flexibility. These Credit lines can be withdrawn by the banks at any time. The Credit lines are not relied upon for core liquidity. As of December 31, 2016, these Credit lines were not utilized.

#### **Financing**

Shire anticipates that its operating cash flow together with available cash, cash equivalents, and the RCF will be sufficient to meet its anticipated future operating expenses, capital expenditures, tax and interest payments, lease obligations, repayment of the term loans and milestone payments as they become due over the next 12 months.

If the Company decides to acquire other businesses, it expects to fund these acquisitions from cash resources, the RCF and through new borrowings (including issuances of debt securities) or the issuance of new equity, if necessary.

### Sources and uses of cash

The following table provides an analysis of the Company's gross and net cash (excluding restricted cash), as of December 31, 2016 and 2015:

As of December 31	2016	2015
	\$'M	\$'M
Cash and cash equivalents	528.8	135.5
Long-term borrowings	(19,552.6)	(69.9)
Short-term borrowings	(3,061.6)	(1,511.5)
Other debt	(353.6)	(13.4)
Total debt	(22,967.8)	(1,594.8)
Net debt	(22,439.0)	(1,459.3)

- > Substantially all of the Company's cash and cash equivalents are held by foreign subsidiaries (i.e. those subsidiaries incorporated outside of Jersey, Channel Islands, the jurisdiction of Shire plc's incorporation). The amount of cash and cash equivalents held by foreign subsidiaries has not had, and is not expected to have, a material impact on the Company's liquidity and capital resources.
- > Net (debt)/cash is a Non GAAP measure. The Company believes that Net (debt)/ cash is a useful measure as it indicates the level of net cash/borrowings after taking account of the Cash and cash equivalents that could be utilized to pay down the outstanding borrowings. See above for reconciliation to cash and cash equivalents.

### Cash flow activity

Net cash provided by operating activities for the year ended December 31, 2016 increased 14 percent to \$2,658.9 million (2015: \$2,337.0 million), primarily due to increased cash receipts from higher sales, partially offset by higher tax and interest payments, costs related to the Baxalta integration and a payment associated with the termination of a biosimilar collaboration acquired with Baxalta.

Net cash provided by operating activities for the year ended December 31, 2015 decreased by 45 percent to \$2,337.0 million (2014: \$4,228.4 million). Net cash provided by operating activities in 2014 included the receipt of the \$1,635 million break fee related to AbbVie's terminated offer for Shire, and the benefit of the \$417 million repayment received from the Canadian revenue authorities. The net cash flows from operating activities was also impacted by an increase of \$160.6 million as a result of higher cash receipts from gross product sales and royalties, which were partially offset by higher operating expense payments.

Net cash used in investing activities was \$18,092.2 million for the year ended December 31, 2016, primarily related to the cash paid for the acquisitions of Baxalta (\$12,367 million, less cash acquired of \$583 million)

and Dyax (\$5,934 million, less cash acquired of \$241 million). The Company's investing activities also included the purchase of \$649 million of PP&E due to the continued investment in manufacturing operations.

Net cash used in investing activities was \$5,619.9 million for the year ended December 31, 2015, primarily related to the cash paid for the acquisition of NPS Pharma of \$5,220 million (excluding cash acquired with NPS Pharma of \$42 million) and for the acquisitions of Foresight (\$299 million) and Meritage Pharma (\$75 million).

Net cash provided by financing activities was \$15,825.8 million for the year ended December 31, 2016, principally due to the issuance of the SAIDAC Notes in addition to the drawings, net of subsequent repayments, made under various other borrowing facilities to partially fund the acquisitions of Baxalta and Dyax. In addition, the Company made dividend payments of \$171.3 million.

Net cash provided by financing activities was \$439.0 million for the year ended December 31, 2015, principally due to the drawings, net of subsequent repayments, made under Shire's various borrowing facilities to partially fund the NPS Pharma, Meritage Pharma and Foresight acquisitions. In addition, the Company made dividend payments of \$134.4 million.

### Outstanding Letters of credit

As of December 31, 2016, the Company had irrevocable standby letters of credit and guarantees with various banks totaling \$139.7 million, providing security for the Company's performance of various obligations. These obligations are primarily in respect of the recoverability of insurance claims, lease obligations and supply commitments.

### Cash Requirements

As of December 31, 2016, the Company's cash requirements for current and non-current liabilities reflected on the Consolidated Balance Sheets and other contractual obligations were as follows:

	<b>Total</b>	Less than 1	1-3 years	3-5 years	More than 5
	<b>\$'M</b>	year	\$'M	\$'M	years
		\$'M			\$'M
Borrowings and capital lease obligations	<b>27,452.0</b>	3,072.6	6,569.5	4,456.8	13,353.1
Operating leases obligations	<b>985.2</b>	155.5	215.9	171.9	441.9
Purchase obligations	<b>3,488.6</b>	1,092.7	1,398.4	799.0	198.5
Other non-current liabilities	<b>587.9</b>	-	452.7	42.0	93.2
<b>Total</b>	<b>32,513.7</b>	4,320.8	8,636.5	5,469.7	14,086.7

- > Borrowings and capital lease obligations include interest payments related to the fixed-rate borrowings.
- > The Company leases certain land, facilities, motor vehicles and certain equipment under operating leases expiring through 2021.
- > Purchase obligations include agreements to purchase goods, investments or services (including clinical trials, contract manufacturing and capital equipment), and open purchase orders, that are

enforceable and legally binding and that specify all significant terms. Shire expects to fund these commitments with cash flows from operating activities.

- > Unrecognized tax benefits and associated interest and penalties of \$201.1 million are included within payments due in one to three years.

The following items have been excluded from the table above:

- > Cash outflows related to the assumed pension and other post-employment benefit plans, in which timing of funding is uncertain and dependent on future movements in interest rates and investment returns, changes in laws and regulations and other variables.
- > In connection with the Company's acquisitions, the Company recorded contingent consideration liabilities related to development, regulatory and commercial milestones and royalty payments. These liabilities were recorded at fair value on the respective acquisition dates and revalued each reporting period. The Company may pay up to approximately \$2.0 billion, which excludes royalty related payments, upon achieving clinical, regulatory and commercialization milestones. For additional information, see Note 15, Fair Value Measurement.
- > Milestone payments to third-parties upon the achievement of development, regulatory and commercial milestones, as well as potential royalty payments, associated with in-licensing and collaboration agreements. Potential future milestone payments associated with collaborations was approximately \$1.7 billion, which excludes potential royalty payments.
- > Milestone payments related with collaboration agreements that become payable only if the Company chooses to exercise one or more of its options and potential contingent payments associated with R&D costs that may be funded by collaboration partners in the future.
- > An unfunded commitment of \$76.4 million as a limited partner in multiple investment companies, in which the timing of future payments is uncertain.

#### **Off-balance sheet arrangements**

There are no off-balance sheet arrangements, aside from those outlined above, that have, or are reasonably likely to have, a current or future material effect on the Company's financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources.

#### **Foreign currency fluctuations**

A number of the Company's subsidiaries have a functional currency other than the U.S. Dollar. As such, the consolidated financial results are subject to fluctuations in exchange rates, particularly in the Euro, Swiss Franc, Japanese Yen and Pound Sterling against the U.S. Dollar.

Accumulated foreign currency translation differences of \$1,505.4 million are reported within Accumulated other comprehensive income as of December 31, 2016. Foreign gains for the year ended December 31, 2016 of \$17.7 million are reported in the Consolidated Statements of Operations.

As of December 31, 2016, the Company had outstanding foreign exchange swap and forward contracts that manage the currency risk associated with intercompany transactions. As of December 31, 2016 the fair value of these contracts was a net asset of \$10.9 million.

**Inflation**

Although at reduced levels in recent years, inflation continues to apply upward pressure on the cost of goods and services which are used in the business. However, the Company believes that the net effect of inflation on its revenues and operations has been minimal during the past three years.

**Treasury policies and organization**

The Company's principal treasury operations are coordinated by its corporate treasury function. All treasury operations are conducted within a framework of policies and procedures approved annually by the Board of Directors. As a matter of policy, the Company does not undertake speculative transactions that would increase its credit, currency or interest rate exposure.

**Interest rate risk**

The Company is exposed to the risk that its earnings and cash flows could be adversely impacted by fluctuations in benchmark interest rates relating to its debt obligations on which interest is set at floating rates. The Company's policy is to manage this risk to an acceptable level. The Company is principally exposed to interest rate risk on any borrowings under the Company's various debt facilities and on part of the senior notes assumed in connection with the acquisition of Baxalta. Interest on each of these debt obligations is set at floating rates, to the extent utilized. Shire's exposure under these facilities is to changes in U.S. Dollar interest rates. For details see Note 16, Financial Instruments, to the Consolidated Financial Statements.

The Company is also exposed to interest rate risk on its restricted cash, cash and cash equivalents and on foreign exchange contracts on which interest is set at floating rates. As the Company maintains all of its cash, liquid investments and foreign exchange contracts on a short-term basis for liquidity purposes, this risk is not actively managed. For the year ended December 31, 2016, the average interest rate received on cash and liquid investments was less than 1 percent per annum. These cash and liquid investments were primarily invested in U.S. Dollar term deposits with banks and money market and liquidity funds or held as cash on account.

As of December 31, 2016, Shire estimates that a hypothetical increase and decrease of 100 basis points in interest rates would increase and decrease net interest costs by approximately \$60.0 million and \$50.0 million respectively during 2017, and decrease and increase the fair value of long-term interest rate sensitive instruments by approximately \$970.0 million and \$1,061.0 million, respectively, during the same period.

**Foreign exchange risk**

The Company operates in numerous countries and as a consequence has foreign exchange exposure. The main operating currencies of the Company are the U.S. Dollar, Pounds Sterling, Swiss Franc, Canadian Dollar, Japanese Yen and the Euro. It is the Company's policy that these exposures are minimized to the extent practicable by denominating transactions in the subsidiary's functional currency.

Where significant exposures remain, the Company uses foreign exchange contracts (spot, forward and swap contracts) to manage the exposure for balance sheet assets and liabilities that are denominated in currencies different to the functional currency of the relevant subsidiary. These assets and liabilities relate predominantly to inter-company financing. The Company has not elected hedge accounting for these transactions. Cash flows from derivative instruments are presented within net cash provided by operating activities in the Consolidated Statements of Cash Flows, unless the derivative instruments are economically hedging specific investing or financing activities.

Translational foreign exchange exposure arises on the translation into U.S. Dollars of the financial statements of non-U.S. Dollar functional subsidiaries. For details see Note 16, Financial Instruments, to the Consolidated Financial Statements.

### Foreign exchange risk sensitivity

The following exchange rate sensitivity analysis summarizes the sensitivity of the Company's reported revenues and net income to hypothetical changes in the average annual exchange rates of the Euro, Pound Sterling and Swiss Franc against the U.S. Dollar, (assuming a hypothetical 10 percent strengthening of the U.S. Dollar against each of the aforementioned currencies in the year ended December 31, 2016):

	Reduction in revenues	Reduction in net income
	\$'M	\$'M
Euro	(153.2)	(64.6)
Pound Sterling	(25.3)	(11.6)
Swiss Franc	(5.8)	(1.4)

A 10 percent weakening of the U.S. Dollar against the aforementioned currencies would have an equal and opposite effect.

As of December 31, 2016 the Company had designated and undesignated foreign exchange forward contracts. For more detail of foreign exchange forward contracts, see Note 16, Financial Instruments, to the Consolidated Financial Statements.

### Concentration of credit risk

Financial instruments that potentially expose Shire to concentrations of credit risk consist primarily of short-term cash investments, derivative contracts and trade accounts receivable from Product sales and from third-parties from which the Company receives royalties. Cash is invested in short-term money market instruments, including money market and liquidity funds and bank term deposits or held on account. The money market and liquidity funds where Shire invests are all triple A rated by both Standard and Poor's and by Moody's credit rating agencies.

The Company is exposed to the credit risk of the counterparties with which it enters into bank term deposit arrangements and derivative instruments. The Company limits this exposure through a system of internal credit limits which vary according to ratings assigned to the counterparties by the major rating agencies. The internal credit limits are approved by Shire's Board of Directors and exposure against these limits is monitored by the Company's corporate treasury function. The counterparties to these derivatives contracts are major international financial institutions.

The Company's revenues from Product sales in the U.S. are mainly governed by agreements with major pharmaceutical wholesalers and relationships with other pharmaceutical distributors and retail pharmacy chains. For the year ended December 31, 2016, there were three customers in the U.S. that accounted for 38 percent of the Company's Product sales.

Such customers typically have significant cash resources and as such the risk from concentration of credit is considered acceptable. The Company has taken positive steps to manage any credit risk associated with these transactions and operates clearly defined credit evaluation procedures. However, an inability of one or more of these wholesalers to honor their debts to the Company could have an adverse effect on the Company's financial condition and results of operations.

A substantial portion of the Company's accounts receivable in countries outside of the U.S. is derived from Product sales to government-owned or government-supported healthcare providers. The Company's

recovery of these accounts receivable is therefore dependent upon the financial stability and creditworthiness of the relevant governments. In recent years global and national economic conditions have negatively affected the growth, creditworthiness and general economic condition of certain markets in which the Company operates. As a result, in some countries outside of the U.S., specifically, Argentina, Brazil, Greece, Italy, Portugal and Spain, the Company is experiencing delays in the remittance of receivables due from government-owned or government-supported healthcare providers. Of those, the only significant accounts receivable as of December 31, 2016 is \$140.2 million from Brazil.

The Company will continue to evaluate all its accounts receivable for potential collection risks and has made provision for amounts where collection is considered to be doubtful. Any such loss could have an adverse effect on the Company's financial condition and results of operations. The Company does not consider it is currently exposed to significant credit risk outside of the countries listed above.

## **4. Principal risks and uncertainties**

### **Risk management framework**

As a highly regulated biotechnology company focused on serving people with rare diseases, Shire has implemented policies, procedures and processes intended to reduce risk and ensure appropriate and lawful conduct within the increasing number of countries in which the Company operates. Success in these areas is of benefit to shareholders and other stakeholders alike. Shire's risk management strategy is to identify, assess and mitigate any significant risks that it faces. Despite this, it should be noted that no risk management strategy can provide absolute assurance against loss.

### **Board of Directors**

The Board is responsible ensuring the maintenance of sound systems of risk management and internal control and determining the Company's risk appetite. In fulfilling this responsibility, the Board sets Shire's risk culture and ensures it is embedded throughout the organization. The Board interacts with key executive risk and internal controls stakeholders on a periodic and ad-hoc basis, enabling it to monitor and review the Company's principal risks and the effectiveness of its risk management and internal control programs. During the year the Board undertook a robust assessment of the principal risks facing the Company, including those that would threaten its business model, future performance, solvency or liquidity. Stakeholders to the risk management framework, which is overseen by the Board and designed to enable the identification, assessment and mitigation of the Group's risks, are detailed below.

### **Audit, Compliance & Risk Committee**

The Audit, Compliance & Risk Committee supports the Board by monitoring and reviewing risk management and internal control programs, maintaining oversight through its interaction with key stakeholders and its evaluation of periodic updates from management. On a biannual basis the Committee reviews the principal risks faced by the Company, with each risk assessed on likelihood of materialization and potential financial and non-financial impact.

### **Executive Committee**

The Executive Committee ensures the implementation of the Company's risk management and internal control programs, overseeing their effective operation. On a biannual basis the Committee reviews and validates principal risks identified during the Enterprise Risk Assessment before they are presented to the Audit, Compliance & Risk Committee for consideration. Executive Committee members also receive regular updates from functional and business unit stakeholders and, along with the Chief Compliance and Risk Officer and the Head of Internal Audit, are responsible for escalating matters of risk, risk management and internal control to the Audit, Compliance & Risk Committee and/or the Board, as required.

### **ERM Core Team**

The ERM Core Team is led by the Chief Compliance and Risk Officer, includes the Head of Monitoring and Risk Management and the Head of Risk Management and Business Continuity Management and is advised by external consultants as required. The ERM Core Team is charged with implementing and operating the Enterprise Risk Management program. This consists of maintaining the enterprise risk universe and risk assessment methodology, facilitating the biannual Enterprise Risk Assessment, providing risk training and awareness to stakeholders across the Group and providing support to the Executive Committee and Audit, Compliance & Risk Committee. The ERM Core Team also identifies executive and functional risk owners for each key risk and, as part of the biannual Enterprise Risk Assessment process, facilitates the assessment of Shire's enterprise risk universe, conducted in conjunction with individual business units and corporate functions. Following completion of the Enterprise Risk Assessment, a principal risk reporting package is prepared for review and validation by the Executive Committee prior to the Chief Compliance and Risk Officer's presentation to the Audit, Compliance & Risk Committee.

### **Global Compliance and Risk Management Department**

The Department, led by the Chief Compliance and Risk Officer, is made up of compliance, privacy and risk management capability. It is responsible for supporting the development, implementation and maintenance of effective risk management and compliance programs and systems. This is achieved through governance, policy, capability and process development, the implementation of awareness and training programs as well as communications, audits and investigations. Such activity provides for the timely undertaking of mitigation and remediation actions, as well for the escalation of matters to the Executive Committee and Audit, Compliance & Risk Committee as appropriate.

### **Chief Compliance and Risk Officer**

The Chief Compliance and Risk Officer is responsible for the global compliance and risk management programs, providing the Executive Committee and the Audit, Compliance & Risk Committee with biannual updates on risk and risk mitigation, as well as more regular updates on compliance monitoring and investigation.

### **Internal Audit**

The Internal Audit function provides independent assurance to the Audit, Compliance & Risk Committee on the effectiveness and operation of internal controls, risk mitigation and risk management programs.

### **Business units and corporate functions**

The business units and corporate functions participate in the biannual Enterprise Risk Assessment and broader Enterprise Risk Management program and are responsible for implementing relevant risk management processes, including identification, monitoring, escalation and reporting controls, within their respective organizations.

### **Principal risks and uncertainties**

The Company's business and assets are subject to varying degrees of risk and uncertainty. Set out below are the principal risks and uncertainties associated with the business that have been identified through the Company's risk management and internal control programs. The Company believes that these risks and uncertainties apply equally and therefore all should be carefully considered before any investment is made in Shire.

Additional risks and uncertainties not presently known to the Company or that it currently deems immaterial may also adversely affect its business. If any of these events or circumstances occur, the business, financial condition, results of operations, or prospects of the Company could be materially harmed. In such circumstances, the value of the Company's securities could decline and an investor could lose part or all of his or her investment. In addition, forward-looking statements that are contained in this Annual Report or in the Company's other reports, filings or statements may be subject to the principal risks and uncertainties described below as well as other risks and uncertainties.

### **Risks Related to the Business**

#### **The Company's products may not be a commercial success**

The commercial success of the Company's marketed products and other new products that the Company may launch in the future, will depend on their approval and acceptance by physicians, patients and other key decision-makers, as well as the receipt of marketing approvals in different countries, the time taken to obtain such approvals, the scope of marketing approvals as reflected in the product labels, approval of reimbursement at commercially sustainable prices in those countries where price and reimbursement is negotiated, and safety, efficacy, convenience and cost-effectiveness of the product as compared to competitive products.

The Company's revenues, financial condition or results of operations may be adversely affected if any or all of the following occur:

- > if the Company's products, or competitive products, are genericized;
- > if the prices of the Company's products suffer forced reductions or if prices of competitor products are reduced significantly;
- > if launches of new products or launch of the Company's products in new markets are not successful;
- > if there are unanticipated adverse events experienced with the Company's products or those of a competitor not seen in clinical trials that impact physicians' willingness to prescribe the Company's products;
- > if issues arise from clinical trials being conducted for post-marketing purposes or for registration in another country which raise questions or concerns about a product;
- > if the regulatory agencies in one country act in a way that raises concerns for regulatory agencies or for prescribers or patients in another country;
- > if there is a reduction in the use of the Company's products by patients, payers or physicians due to the development of or preferences for alternative technologies or treatments;
- > if the Company's products are subject to more stringent government regulation than competitor products;
- > if patent protection or other forms of exclusivity are lost or curtailed, or if competitors are able to successfully challenge or circumvent the Company's patents or other forms of exclusivity (see Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements for details of current litigation);
- > if the sizes of the patient populations for the Company's products are less than expected; or
- > if there are lawsuits filed or government investigations initiated against Shire, including but not limited to, product liability claims, consumer law claims, payer or reimbursement litigation and prior sales or marketing practices; or
- > if there are adverse developments in investigations or government proceedings.

If the Company is unable to commercialize its products successfully, there may be a material adverse effect on the Company's revenues, financial condition or results of operations.

**Increased pricing pressures and limits on patient access as a result of governmental regulations and market developments may affect the Company's future revenues, financial condition and results of operations**

The Company's product revenues are subject to increasing pressures from governmental initiatives to regulate or influence prices and access to customers. Regulations in the U.S., the European Union and other jurisdictions mandating price controls or imposing constraints on patients' ability to purchase Shire's products significantly impact its business. In the U.S., the new administration has made public and social media statements regarding proposed changes to existing government initiatives, like the Patient Protection and Affordable Care Act ("ACA"), which has created significant uncertainty for the future of federal government policies that regulate or influence prices and access to customers. Any future changes in such laws,

regulations, practices or policies may adversely affect the Company's financial condition and results of operations.

Regulatory measures that could have a material adverse effect on the Company include the imposition of government-approved drug pricing schedules, the use of drug formularies, prohibitions on direct-to-consumer advertising or drug marketing practices, new regulations or new interpretations of existing or historical regulations relating to governmental drug discount or rebate programs that increase the Company's drug discount or rebate liability, and caps or limits on the level of reimbursement provided to the Company by governmental reimbursement schemes for its products.

These pressures have also resulted in market developments, such as the consolidation of managed healthcare organizations and private health insurers that have increased the relative bargaining power of institutional drug purchasers and enhanced their ability to negotiate discounts and extract other concessions in exchange for purchasing Shire's products.

Such regulatory and market developments create downward pressures on the prices at which the Company can offer its products and on the level of reimbursement its treatments receive from healthcare providers, private health insurers and other organizations, such as health maintenance organizations and managed care organizations.

Additional factors affecting the Company's ability to obtain and maintain adequate prices and levels of reimbursement for its products include:

- > higher levels of controls on the use of the Company's products and/or requirements for further price concessions mandated or negotiated by managed healthcare organizations or government authorities;
- > legislative proposals to reform health care and government insurance programs in many of the Company's markets; and
- > price controls, unsuccessful government tenders, or non-reimbursement of new medicines or new indications.

Moreover, the cost of treatment for some of the Company's products is high, particularly those which are used for the treatment of rare diseases. The Company may encounter difficulty in obtaining or maintaining satisfactory pricing and reimbursement for such products. The failure to obtain and maintain pricing and reimbursement at satisfactory levels for its products may adversely affect the Company's revenues, financial condition or results of operations.

**The Company depends on third-parties to supply certain inputs and services critical to its operations including certain inputs, services and ingredients critical to its manufacturing processes.**

The Company relies on third-party suppliers, vendors and outsourcing partners to, among other things, research, develop, manufacture and commercialize its products, to provide certain key ingredients and manufacturing inputs and to manage certain sales, distribution, marketing, information technology, accounting, transaction-processing and other business services. While the Company depends on these third-parties for multiple aspects of its product development, manufacturing, commercialization and business activities, it does not control these third-parties directly.

As a result, there is a possibility these third-parties may not complete activities on schedule or in accordance with the Company's expectations, and their failure to meet certain contractual, regulatory or other obligations to Shire, or any disruption of Shire's relationship with these third-parties could delay or prevent the development, approval, manufacture or commercialization of the Company's products, result in non-

compliance with applicable laws and regulations, disrupt Shire's operations, or result in reputational or other harm to the Company.

This outsourcing risk is of particular concern with respect to third-party suppliers of key manufacturing inputs of certain of Shire's drug products, including, but not limited to, ADVATE, ADYNOVATE, HYQVIA, ELAPRASE, FIRAZYR, REPLAGAL and GATTEX/REVESTIVE where the Company currently relies on a single active ingredient source for each. Shire also relies on limited third-party sources to provide the donated plasma necessary for the manufacture of CINRYZE. In addition, although the Company dual-sources certain key products and/or active ingredients, the Company currently relies on a single source for production of the final drug product for certain of its products, including, but not limited to, ADDERALL XR, CINRYZE, CUVITRU, FIRAZYR, LIALDA and PENTASA.

For many of those components and materials for which a sole supplier is used, the Company seeks to address potential supply disruption by, among other things, regularly evaluating such risk and, if appropriate, holding strategic inventory in the case of such potential supply disruptions. If such efforts prove unsuccessful, it could have a material adverse effect on the Company's revenues, financial condition or results of operations.

Any failure by a single-source supplier to provide the Company with the required volumes on time or at all, or to provide products that do not meet regulatory requirements, could lead to significant delays in the production of Shire's products, increases in operating costs, lost product sales, an interruption of research activities, or the delay of new product launches, all of which could have a material adverse effect on the Company's revenues, financial condition or results of operations.

**Any disruption to the supply chain for any of the Company's products, or any difficulties or delays in the manufacturing, distribution and sale of its products may result in the Company being unable to continue marketing or developing a product, or may result in the Company being unable to do so on a commercially viable basis for some period of time**

A disruption, delay or other difficulties in the manufacturing, distribution and sale of Shire's products, or in the supply chain of any of its products, may have a material adverse effect on the Company and its revenues, financial condition and results of operations. Examples of such manufacturing and supply chain difficulties include, but are not limited to:

- > regulatory or enforcement actions that result in shut-downs, delays in or withdrawal of regulatory approvals necessary to carry on manufacturing activities, product recalls and penalties or fines resulting in unanticipated costs in production, whether imposed directly on the Company or imposed indirectly through one or more of its third-party suppliers;
- > the inability of the Company to increase its production capacity for certain drugs commensurate with market demand;
- > the possibility that the supply of incoming materials may be delayed or become unavailable and that the quality of incoming materials may be substandard and not detected;
- > the possibility that the Company may fail to maintain appropriate quality standards throughout its internal and third-party supply network, or to comply with current manufacturing best practices, rules or other applicable regulations;
- > disruptions to supply chain continuity as a result of natural or man-made disasters at the Company's facilities or at one or more of its third-party suppliers' facilities; and
- > failure to maintain the integrity of the Company's supply chains against fraudulent and criminal acts, such as intentional product adulteration, diversion, theft, or counterfeiting activities.

Also, as noted above, the Company has also entered into many agreements with third-parties for the provision of goods and services to enable it to manufacture its products. If these third-parties are unable to manufacture products, or provide these goods and services, in each case in accordance with its respective contractual obligations, the Company's ability to manage its manufacturing processes or to operate its business, including to continue the development or commercialization of its products as planned or on a commercial basis, may be adversely impacted.

**The manufacture of the Company's products is subject to extensive oversight by various regulatory agencies. Regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches** Pharmaceutical and device manufacturing sites must be inspected and approved by regulatory agencies such as the FDA and similar agencies in other countries. Active ingredients, excipients and packaging materials used in the manufacturing process must be obtained from sources approved by regulatory agencies.

The development, approval and manufacturing of the Company's products depend on the ability to procure ingredients and packaging materials from approved sources and for the manufacturing process to be conducted at approved sites. Changes of manufacturer or changes of source of ingredients or packaging materials must generally be approved by the regulatory agencies, which will involve testing and additional inspections to ensure compliance with the applicable regulatory agency's regulations and standards. The need to qualify a new manufacturer or source of ingredients or packaging materials can take a significant amount of time. Should it become necessary to change a manufacturer or supplier of ingredients or packaging materials, or to qualify an additional supplier, the Company may not be able to do so quickly, or at all, which could delay or disrupt the manufacturing process.

U.S.-based manufacturers must be registered with the DEA and similar regulatory authorities in other countries if they handle controlled substances. Certain of the Company's products, including ADDERALL XR and VYVANSE, contain ingredients which are controlled substances subject to quotas managed by the DEA. As a result, the Company's procurement and production quotas may not be sufficient to meet commercial demand.

Certain of the Company's products, including but not limited to CINRYZE, ELAPRASE, REPLAGAL, FEIBA, HYQVIA and GAMMAGARD LIQUID and VPRIV are manufactured using highly complex biological processes. The complexity of the manufacturing results in a number of risks, including the risk of microbial contamination. Additionally, some of the Company's therapies, including CINRYZE, FEIBA, HYQVIA and GAMMAGARD LIQUID are derived from human plasma, and are therefore subject to the risk of biological contamination inherent in plasma-derived products.

The failure to obtain regulatory approvals promptly or at all and/or regulatory interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, an increase in operating costs, lost product sales, an interruption of research activities, the delay of new product launches or constraints on manufacturing output, all of which could have a material adverse effect on the Company's revenues, financial condition and results of operations.

**The nature of producing plasma-based therapies may prevent Shire from timely responding to market forces and effectively managing its production capacity**

The production of plasma-based therapies is a lengthy and complex process, and Shire sources its plasma both internally and externally through suppliers. Efforts to increase the collection of plasma or the production of plasma-based therapies may include the construction and regulatory approval of additional plasma collection facilities and plasma fractionation facilities. In connection with the combination with Baxalta, the

Company acquired a yet to be completed state-of-the-art manufacturing facility near Covington, Georgia to support growth of its plasma-based treatments. The Company has completed construction of all buildings associated with the Covington facility and is going through a rigorous commissioning and testing process to receive licensing from the FDA and international regulatory agencies. Commercial production at the facility remains scheduled to begin in 2018. The development of such facilities involves a lengthy regulatory process and is highly capital intensive. In addition, access to and transport and use of plasma may be subject to restrictions by governmental agencies both inside and outside the United States. As a result, the Company's ability to match its collection and production of plasma-based therapies to market demand is imprecise and may result in a failure to meet market demand for its plasma-based therapies or, alternatively, an oversupply of inventory. Failure to meet market demand for Shire's plasma-based therapies may result in customers transitioning to available competitive products resulting in a loss of market share or customer confidence. In the event of an oversupply, Shire may be forced to lower the prices it charges for some of its plasma-based therapies, close collection and processing facilities, record asset impairment charges or take other action which could have a material adverse effect on the Company's revenues, financial condition and results of operations.

**The Company has a portfolio of products in various stages of research and development. The successful development of these products is highly uncertain and requires significant expenditures and time, and there is no guarantee that these products will receive regulatory approval**

Products that initially appear promising in research or development may be delayed or fail to reach later stages of development as:

- > preclinical or clinical tests may show the product to lack safety or efficacy;
- > delays may be caused by: slow enrollment in clinical studies; regulatory requirements for clinical trial drug supplies; extended length of time to achieve study endpoints; additional time requirements for data analysis or dossier preparation; time required for discussions with regulatory agencies, including regulatory agency requests for additional preclinical or clinical data; regulatory agencies due to staffing or resource limitations; analysis of or changes to study design; unexpected safety, efficacy, or manufacturing issues; shared control with collaborative partners in the planning and execution of the product development, scaling of the manufacturing process, or obtaining approval for manufacturing;
- > manufacturing issues, pricing or reimbursement issues, or other factors may render the product economically unviable;
- > the proprietary rights of others and their competing products and technologies may prevent the product from being developed or commercialized; or
- > submission of an application for regulatory approval of any of the Company's product candidates may be subjected to lengthy review and ultimately rejected.

Success in preclinical and early clinical trials does not ensure that late-stage clinical trials will be successful. Clinical results are frequently susceptible to varying interpretations that may delay, limit, or prevent regulatory approvals. The length of time necessary to complete clinical trials and to submit an application for marketing approval for a final decision by a regulatory authority varies significantly and may be difficult to predict. Moreover, once an application is submitted, additional data may be sought by regulators or an application may be rejected. The Company has a range of programs in its product pipeline that are in registration or entering late-stage clinical development, including, but not limited to SHP643 for the treatment of HAE, which is in Phase 3 clinical trials, SHP465 for the treatment of ADHD, which is currently in registration, SHP621 for the treatment of EOE, which is in Phase 3 clinical trials, and SHP647 for the

treatment of IBD, which is in Phase 2. If the Company's large-scale or late-stage clinical trials for a product are not successful, the Company will not recover its substantial investments in that product.

In addition, even if the products receive regulatory approval, they remain subject to ongoing regulatory requirements, including, for example, obligations to conduct additional clinical trials or other non-clinical testing, changes to the product label (which could impact its marketability and prospects for commercial success), new or revised requirements for manufacturing, written notifications to physicians, or product recalls or withdrawals.

**The actions of certain customers could affect the Company's ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely affect the Company's revenues, financial conditions or results of operations**

A considerable portion of the Company's product sales are made to major pharmaceutical wholesale distributors, as well as to large pharmacies, in both the U.S. and Europe. For the year ended December 31, 2016, 38 percent of the Company's product sales were attributable to three customers in the United States: AmerisourceBergen Drug Corp, McKesson Corp. and Cardinal Health, Inc. In the event of financial failure of any of these customers there could be a material adverse effect on the Company's revenues, financial condition or results of operations. The Company's revenues, financial condition or results of operations may also be affected by fluctuations in customer buying or distribution patterns. These fluctuations may result from seasonality, pricing, wholesaler inventory objectives, or other factors. A significant portion of the Company's revenues for certain products for treatment of rare diseases are also concentrated within a small number of customers. Changes in the buying patterns of those customers may have an adverse effect on the Company's revenues, financial condition or results of operations.

**Failure to comply with laws and regulations governing the sales and marketing of its products could materially impact Shire's revenues and profitability**

The Company engages in various marketing, promotional and educational activities pertaining to, as well as the sale of, pharmaceutical products and medical devices in a number of jurisdictions around the world. The promotion, marketing and sale of pharmaceutical products and medical devices is highly regulated and the sales and marketing practices of market participants, such as the Company, have been subject to increasing supervision by governmental authorities, and Shire believes that this trend will continue.

In the United States, the Company's sales and marketing activities are monitored by a number of regulatory authorities and law enforcement agencies, including the U.S. Department of HHS, the FDA, the U.S. Department of Justice, the SEC and the DEA. These authorities and agencies and their equivalents in countries outside the United States have broad authority to investigate market participants for potential violations of laws relating to the sale, marketing and promotion of pharmaceutical products and medical devices, including the False Claims Act, the Anti-Kickback Statute, the UK Bribery Act of 2010 and the Foreign Corrupt Practices Act, among others, for alleged improper conduct, including corrupt payments to government officials, improper payments to medical professionals, off-label marketing of pharmaceutical products and medical devices, and the submission of false claims for reimbursement by the federal government. Healthcare companies may also be subject to enforcement actions or prosecution for such improper conduct. Any inquiries or investigations into the operations of, or enforcement or other regulatory action against, the Company by such authorities could result in significant defense costs, fines, penalties and injunctive or administrative remedies, distract management to the detriment of the business, result in the exclusion of certain products, or the Company, from government reimbursement programs or subject the Company to regulatory controls or government monitoring of its activities in the future. The Company is also subject to certain ongoing investigations by governmental agencies. For further information, see Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

**The Company's products and product candidates face substantial competition in the product markets in which it operates**

Shire faces substantial competition throughout its business from international and domestic biopharmaceutical companies of all sizes. Competition is primarily focused on cost-effectiveness, price, service, product effectiveness and quality, patient convenience and technological innovation.

Competition may increase further as existing competitors enhance their offerings or additional companies enter Shire's markets or modify their existing products to compete directly with Shire's products. If Shire's competitors respond more quickly to new or emerging technologies and changes in customer requirements, the Company's products may be rendered obsolete or non-competitive. If Shire's competitors develop more effective or affordable products, or achieve earlier patent protection or product commercialization than the Company does, its operations will likely be negatively affected. If Shire is forced to reduce its prices due to increased competition, Shire's business could become less profitable. The Company's sales could be adversely affected if any of its contracts with customers (including with hospitals, treatment centers and other healthcare providers, distributors, group purchasing organizations and integrated delivery networks) are terminated due to increased competition or otherwise.

**The Company's patented products are subject to significant competition from generics**

In addition to the competition referred to above, Shire faces significant competition from the manufacturers of generic drug products in all of its major markets and in the future may face competition with respect to its biologic and biosimilar products. The introduction of lower-priced generics by the Company's competitors or their successful efforts in aggressively commercializing and marketing their alternative drug products pose significant challenges to maintaining Shire's market share, revenues and sales growth.

For example, since 2009, generic versions of ADDERALL XR have been marketed and, since 2014, generic versions of INTUNIV have been marketed in the United States. As a result, product sales of ADDERALL XR and INTUNIV declined.

Factors which could cause further or more rapid declines in Shire's product sales include:

- > the loss or earlier than expected expiration of intellectual property rights or regulatory exclusivity periods with respect to the Company's branded products;
- > generic or authorized generic versions of these products capturing more of Shire's branded market share than expected;
- > lower prices and the actual or perceived greater effectiveness or safety of generic drug products relative to Shire's branded products;
- > the FDA approving additional ANDAs for these products or additional ANDAs for generic versions of these products which, if launched, would further reduce branded market share or impact the amount of Shire's authorized generic product sales;
- > changes in reimbursement policies of third-party payers; or
- > changes to the level of sales deductions for branded Shire products for private or public payers.

Should any of the above developments occur, the resulting generic competition could reduce sales and market share of Shire's branded products and have a material adverse effect on the Company's revenues, financial condition or results of operations.

**Adverse outcomes in legal matters and other disputes, including the Company's ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on the Company's revenues, financial condition or results of operations**

During the ordinary course of its business the Company may be involved in claims, disputes and litigation with third-parties, employees, regulatory agencies, governmental authorities and other parties. The range of matters of a legal nature that might arise is extremely broad but could include, without limitation, intellectual property claims and disputes, product liability claims and disputes, regulatory litigation, contract claims and disputes, employment claims and disputes, and tax or other governmental agency audits and disputes.

Any unfavorable outcome in such matters could adversely impact the Company's ability to develop or commercialize its products, adversely affect the product sales and profitability of existing products, subject the Company to significant defense costs, fines, penalties, audit findings and injunctive or administrative remedies, distract management to the detriment of the business, result in the exclusion of certain products, or the Company, from government reimbursement programs or subject the Company to regulatory controls or government monitoring of its activities in the future. Any such outcomes could have a material adverse effect on the Company's revenue, financial condition or results of operations. For further information, see Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

**The Company may fail to obtain, maintain, enforce or defend the intellectual property rights required to conduct its business**

The Company's success depends upon its ability and the ability of its partners and licensors to protect their intellectual property rights. Where possible, the Company's strategy is to register intellectual property rights, such as patents and trademarks. The Company also relies on various trade secrets, unpatented knowhow and technological innovations and contractual arrangements with third-parties to maintain its competitive position. The failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third-parties to make competing products or impact the Company's ability to develop, manufacture and market its own products on a commercially viable basis, or at all, which could have a material adverse effect on the Company's revenues, financial condition or results of operations.

The Company intends to enforce its patent rights vigorously and believes that its commercial partners, licensors and third-party manufacturers intend to enforce vigorously those patent rights they have licensed to the Company. However, the Company's patent rights, and patent rights that the Company has licensed, may not provide valid patent protection sufficiently broad to prevent any third-party from developing, using or commercializing products that are similar or functionally equivalent to the Company's products or technologies. These patent rights may be challenged, revoked, invalidated, infringed or circumvented by third-parties. Laws relating to such rights may in the future also be changed or withdrawn.

Additionally, the Company's products, or the technologies or processes used to formulate or manufacture those products may now, or in the future, infringe the patent rights of third-parties. It is also possible that third-parties will obtain patent or other proprietary rights that might be necessary or useful for the development, manufacture or sale of the Company's products. The Company may need to obtain licenses for intellectual property rights from others and may not be able to obtain these licenses on commercially reasonable terms, if at all.

The Company also relies on trade secrets and other unpatented proprietary information, which it generally seeks to protect by confidentiality and nondisclosure agreements with its employees, consultants, advisors and partners. These agreements may not effectively prevent disclosure of confidential information and may not provide the Company with an adequate remedy in the event of unauthorized disclosure. In addition, if the Company's employees, scientific consultants or partners develop inventions or processes that may be applicable to the Company's products under development, such inventions and processes will not necessarily become the Company's property, but may remain the property of those persons or their employers.

The Company has filed applications to register various trademarks for use in connection with its products in various countries and also, with respect to certain products, relies on the trademarks of third-parties. These

trademarks may not afford adequate protection or the Company or the third-parties may not have the financial resources to enforce their rights under these trademarks which may enable others to use the trademarks and dilute their value.

In the regular course of business, the Company is party to litigation or other proceedings relating to intellectual property rights. For details of current intellectual property litigation, see Note 26, Legal and Other Proceedings, to the Consolidated Financial Statements.

**The Company faces intense competition for highly qualified personnel from other companies and organizations**

The Company relies on recruiting and retaining highly skilled employees to meet its strategic objectives. The Company faces intense competition for highly qualified personnel and the supply of people with the requisite skills may be limited, generally or geographically. The range of skills required and the geographies in which they are required by the Company may also change over time as Shire's business evolves. If the Company is unable to retain key personnel or attract new personnel with the requisite skills and experience, it could adversely affect the implementation of the Company's strategic objectives and ultimately adversely impact the Company's revenues, financial condition or results of operations. Recent acquisitions by the Company, including without limitation, the Dyax and Baxalta acquisitions, and the terminated acquisition by AbbVie, Inc. ("AbbVie") as well as internal reorganizations and transitions of our offices in Pennsylvania, the United Kingdom and other locations, may increase the Company's difficulty in recruiting and retaining employees.

**Failure to successfully execute or attain strategic objectives from the Company's acquisitions and growth strategy may adversely affect the Company's financial condition and results of operations**

The Company's business depends to a significant extent on its ability to improve and expand its product pipeline through strategic acquisitions. Such improvements and expansions, however, are subject to the ability of the Company's management to effectively identify appropriate strategic targets and effectuate the contemplated transactions, the availability and relative cost of acquisition opportunities as well as competition from other pharmaceutical companies seeking similar opportunities.

Moreover, even when such transactions are successfully executed, the Company may face subsequent difficulties in integrating the operations, infrastructure and personnel of acquired businesses and may experience unanticipated risks or liabilities that were not discovered, accurately disclosed or sufficiently assessed during the transactions' due diligence process. Finally, even successfully acquired and integrated businesses may ultimately fail or fall short of achieving the Company's strategic objectives for the transaction over the long term.

Any failures in the execution of a transaction, in the integration of an acquired business or in achieving the Company's strategic objectives, including expected synergies, with respect to such transactions could result in slower growth, higher than expected costs, the recording of asset impairment charges and other actions which could adversely affect the Company's business, financial condition and results of operations.

The Company has recently completed a number of strategic acquisitions, including Dyax in January 2016 and Baxalta in June 2016. Furthermore, the Company is currently exploring, and expects to continue to explore, opportunities for additional strategic acquisitions or combinations in the future. Proposed and completed acquisitions, as well as any future acquisitions, each entail various risks, which include but are not limited to:

- > a proposed acquisition may not be consummated due to the occurrence of an event, change or other circumstances that gives rise to the termination of the applicable agreement;
- > a governmental, regulatory, board, shareholder or other approval required for a proposed acquisition may not be obtained, or may be obtained subject to conditions that are not anticipated, or another

condition to the closing of a proposed acquisition may not be satisfied, resulting in delays or ultimate failure of consummating a proposed acquisition;

- > shareholders may initiate legal action to prevent or delay consummation of a proposed acquisition or to seek judicial reevaluation of a proposed acquisition's consideration;
- > a lengthy, uncertain process when pursuing a potential combination could disrupt relationships between Shire and a target company's customers, suppliers and employees, distract Shire's or a target company's management from operating its business, and could lead to additional and unanticipated costs;
- > a target company may be unable to retain and hire key personnel and/or maintain its relationships with customers, suppliers and other business partners pending the consummation of the proposed acquisition by Shire;
- > after the consummation of an acquisition, the Company may be unable to retain the acquired company's key personnel, existing customers, suppliers and other business partners or attract new customers;
- > the businesses of an acquired company may be otherwise disrupted by the acquisition, including increased costs and diversion of its management's time and resources;
- > failure to achieve the targeted growth and expected benefits of the acquisition if sales of an acquired company's products are lower than anticipated, or these products cannot be successfully commercialized or cannot obtain necessary regulatory approvals;
- > any integration of an acquired company into Shire could be complex and time-consuming, and difficulties in effectuating these integrations may lead to the combined companies not being able to realize the expected operating efficiencies, cost savings, revenue enhancements, synergies or other benefits in the timeframe anticipated, or at all;
- > failure to successfully obtain regulatory approval of an acquired company's late-stage pipeline assets in a timely manner or at all, or to successfully commercialize such products after regulatory approval has been obtained;
- > undiscovered or unanticipated risks and liabilities, including legal and compliance related liabilities, may emerge in connection with an acquisition, or may be higher than anticipated; and
- > even after successfully completing an acquisition and integrating the acquired company's businesses into Shire, the anticipated benefits of the combinations, including expected synergies, may ultimately prove less than anticipated.

**Shire's growth strategy depends in part upon its ability to expand its product portfolio through external collaborations, which, if unsuccessful, may adversely affect the development and sale of its products**

Shire intends to continue to explore opportunities to enter into collaboration agreements and external alliances with other parties. These third-party collaborators may include other biopharmaceutical companies, academic and research institutions, governments and government agencies and other public and private research organizations.

These third-party collaborators are often directly responsible for clinical development under these types of arrangements, and the Company does not have the same level of decision-making capabilities for the

prioritization and management of development-related activities as it does for its internal research and development activities. Failures by these partners to meet their contractual, regulatory, or other obligations to the Company, or any disruption in the relationships between the Company and these partners, could have a material adverse effect on the Company's pipeline and business. In addition, the Company's collaborative relationships for research and development extend for many years and may give rise to disputes regarding the relative rights, obligations and revenues of Shire and its partners, including the ownership of intellectual property and associated rights and obligations. These could result in the loss of intellectual property rights or other intellectual property protections, delay the development and sale of potential pharmaceutical products, and lead to lengthy and expensive litigation or arbitration.

Long-term public-private partnerships with governments and government agencies, including in certain emerging markets, may include technology transfers to support local manufacturing capacity and technical expertise. Shire cannot predict whether these types of transfers and arrangements will become more common in the future.

These types of technology transfers and similar arrangements could have a material adverse effect on the Company's results of operations as a result of lost exclusivity with respect to certain manufacturing and technical capabilities, particularly if this model becomes widely used. Public-private partnerships are also subject to risks of doing business with governments and government agencies, including risks related to sovereign immunity, shifts in the political environment, changing economic and legal conditions and social dynamics.

**A slowdown of global economic growth, or economic instability of countries in which the Company does business, could have negative consequences for the Company's business and increase the risk of non-payment by the Company's customers**

Growth of the global pharmaceutical market has become increasingly tied to global economic growth. Accordingly, a substantial and lasting slowdown of the global economy, or major national economies, could negatively affect growth in the markets in which the Company operates. Such a slowdown, or any resultant austerity measures adopted by governments in response to a slowdown, could result in national governments making significant cuts to their public spending, including national healthcare budgets, or reducing the level of reimbursement they are willing and able to provide to the Company for its products and, as a result, adversely affect the Company's revenues, financial condition or results of operations.

A slowdown of a nation's economy could also lead to financial difficulties for some of the Company's significant customers, including national governments, and result in a greater risk of delayed orders or payments, defaults or non-payments of outstanding payment obligations by the Company's customers in that country, which could adversely affect the Company's revenues, financial condition or results of operations.

**Changes in foreign currency exchange rates and interest rates could have a material adverse effect on Shire's operating results and liquidity**

Shire reports its financial results in U.S. Dollars, but generates a substantial portion of its revenue (approximately 33 percent of its total revenue in 2016) outside the United States. As a result, Shire's financial results may be adversely affected by fluctuations in foreign currency exchange rates. Shire cannot predict with any certainty changes in foreign currency exchange rates or the ability of the Company to mitigate these risks. Shire may experience additional volatility as a result of inflationary pressures and other macroeconomic factors in certain emerging market countries. Shire is also exposed to changes in interest rates, and Shire's ability to access the money markets and capital markets could be impeded if adverse liquidity market conditions occur.

For discussion of the financial impact of foreign exchange rate and interest rate fluctuations, and the ways and extent to which Shire attempts to mitigate such impact. For details see note 16, Financial Instruments, to the Consolidated Financial Statements.

**The Company is subject to evolving and complex tax laws, which may result in additional liabilities that may adversely affect the Company's financial condition or results of operations**

The Company is subject to evolving and complex tax laws in the jurisdictions in which it operates, and routinely obtains advice on matters, including the tax treatment of the break fee received in connection with the terminated offer for Shire by AbbVie in 2014. Significant judgment is required in determining the Company's tax liabilities and the Company's tax returns are periodically examined by various tax authorities. The Company regularly assesses the likelihood of outcomes resulting from these examinations to determine the adequacy of its accrual for tax contingencies; however, due to the complexity of tax matters, the ultimate resolution of any tax matters may result in payments greater or less than amounts accrued. In addition, the Company may be affected by changes in tax laws, including tax rate changes, new tax laws, and revised tax law interpretations in domestic and foreign jurisdictions and between jurisdictions, including by the EU.

**If a marketed product fails to work effectively or causes adverse side effects, this could result in damage to the Company's reputation, the withdrawal of the product and legal action against the Company**

Unanticipated side effects or unfavorable publicity from complaints concerning any of the Company's products, or those of its competitors, could have an adverse effect on the Company's ability to obtain or maintain regulatory approvals or successfully market its products. The testing, manufacturing, marketing and sales of pharmaceutical products and medical devices entail a risk of product liability claims, product recalls, litigation and associated adverse publicity. The cost of defending against such claims is expensive even when the claims are not merited. A successful product liability claim against the Company could require the Company to pay a substantial monetary award. The Company does not carry product liability insurance for its products due to the Company's analysis of the risk, frequency and severity of a loss and the cost of insurance for the risk. Accordingly, if the Company does not have sufficient financial resources to satisfy a liability resulting from such a claim or to fund the legal defense of such a claim, it could become insolvent. Moreover, an adverse judgment in a product liability suit could generate substantial negative publicity about the Company's products and business and inhibit or prevent commercialization of other products.

**The Company is dependent on information technology and its systems and infrastructure face certain risks, including from service disruptions, the loss of sensitive or confidential information, cyber-attacks and other security breaches or data leakages that could have a material adverse effect on the Company's revenues, financial condition or results of operations**

The Company relies to a large extent upon sophisticated information technology systems to operate its businesses. In the ordinary course of business, the Company collects, stores and transmits large amounts of confidential information (including, but not limited to, personal information and intellectual property), and it is critical that the Company does so in a secure manner to maintain the confidentiality and integrity of such confidential information. The size and complexity of the Company's information technology and information security systems, and those of third-party vendors with whom the Company contracts (and the large amounts of confidential information that is stored on them), make such systems potentially vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by the Company's employees or vendors, or from attacks by malicious third-parties.

The Company and its vendors' sophisticated information technology operations are spread across multiple, sometimes inconsistent platforms, which pose difficulties in maintaining data integrity across systems. The ever-increasing use and evolution of technology, including cloud-based computing, creates opportunities for the unintentional dissemination or intentional destruction of confidential information stored in the Company's systems. The Company and its vendors could also be susceptible to third-party attacks on their information security systems, which attacks are of ever-increasing levels of sophistication and are made by groups and individuals with a wide range of motives and expertise, including criminal groups, "hackers" and others. While

the Company has taken steps to protect such information and invested heavily in information technology, there can be no assurance that these efforts will prevent service interruptions or security breaches in its systems, the loss of data or other confidential information due to a lack of redundant backup systems, or the unauthorized or inadvertent wrongful use or disclosure of confidential information that could adversely affect the Company's business operations or result in the loss, dissemination, or misuse of critical or sensitive information. A breach of the Company's security measures or the accidental loss, inadvertent disclosure, unapproved dissemination, misappropriation or misuse of trade secrets, proprietary information, or other confidential information, whether as a result of theft, hacking, fraud, trickery or other forms of deception, or for any other cause, could enable others to produce competing products, use the Company's proprietary technology or information, and/or adversely affect the Company's business position. Further, any such interruption, security breach, loss or disclosure of confidential information, could result in financial, legal, business, and reputational harm to the Company and could have a material adverse effect on the Company's revenues, financial condition or results of operations.

In addition, legislators and/or regulators in countries in which the Company operates are increasingly adopting or revising privacy, information security and data protection laws, as well as focusing on increased privacy-related enforcement activity, that potentially could have a significant impact on the Company's current and planned privacy, data protection and information security-related practices, its collection, use, sharing, retention and safeguarding of consumer and/or employee information, and some of its current or planned business activities.

#### **Shire faces risks relating to the expected exit of the United Kingdom from the European Union.**

On June 23, 2016, the United Kingdom held a remain-or-leave referendum on the United Kingdom's membership within the European Union, the result of which favored the exit of the United Kingdom from the European Union ("Brexit"). A process of negotiation will likely determine the future terms of the United Kingdom's relationship with the European Union, as well as whether the United Kingdom will be able to continue to benefit from the European Union's free trade and similar agreements. The timing of the Brexit and potential impact of Brexit on Shire's market share, sales, profitability and results of operations is unclear. Depending on the terms of Brexit, economic conditions in the United Kingdom, the European Union and global markets may be adversely affected by reduced growth and volatility. The uncertainty before, during and after the period of negotiation is also expected to have a negative economic impact and increase volatility in the markets, particularly in the eurozone. Such volatility and negative economic impact could, in turn, adversely affect the Company's revenues, financial condition or results of operations.

#### **Risks Related to the Combination with Baxalta Incorporated**

##### **The Company may not successfully integrate the businesses of Shire and Baxalta**

Achieving the anticipated benefits of the combination of Shire and Baxalta will depend in part upon whether the two companies integrate their businesses in an effective and efficient manner. The Company may not be able to accomplish this integration process successfully or realize the expected synergies as planned. The integration of businesses is complex and time-consuming. The difficulties that could be encountered include the following:

- > integrating personnel, operations and systems, while maintaining focus on selling and promoting existing and newly acquired or produced products;
- > coordinating geographically dispersed organizations;
- > distraction of management and employees from operations;
- > changes or conflicts in corporate culture;
- > management's inability to manage a substantial increase in the number of employees;

- > management's inability to train and integrate personnel, who may have limited experience with the respective companies' business lines and products, and to deliver a consistent message regarding diseases treated by the Company;
- > retaining existing customers and attracting new customers;
- > retaining existing employees and attracting new employees;
- > maintaining business relationships; and
- > inefficiencies associated with the integration and management of the operations of the two companies.

In addition, there have been, and will continue to be, integration costs and non-recurring transaction costs (such as fees paid to legal, financial, accounting and other advisors and other fees paid in connection with the combination) associated with the combination, including costs associated with combining operations and achieving the expected synergies as planned, and such costs may be significant.

An inability to realize the full extent of the anticipated benefits of the combination of Shire and Baxalta, including estimated cost synergies, as well as any delays encountered in the integration process and realizing such benefits, could have an adverse effect upon the revenues, level of expenses and operating results of the Company, which may materially adversely affect the value of the Company's Ordinary Shares and American Depository Shares ("ADSs").

**Shire has incurred significant additional indebtedness in connection with the acquisition, which has decreased the Company's business flexibility and increased its interest expense. All of the Company's debt obligations have priority over the Company's Ordinary Shares and ADSs with respect to payment in the event of a liquidation, dissolution or winding up**

As of December 31, 2016, Shire had gross debt of approximately \$23 billion comprising \$12.1 billion of Senior Notes issued in September 2016, \$5 billion of Baxalta notes acquired with the acquisition of Baxalta, \$5 billion outstanding borrowing under the term loan facility, \$450 million outstanding borrowing under the \$2.1 billion Revolving Credit Facility and certain capital lease and other debt obligations.

The Company's aggregate indebtedness could have the effect, among other things, of reducing the Company's flexibility to respond to changing business and economic conditions. The Company is required to abide by certain covenants within the various financing arrangements, which if not adhered to, would require immediate repayment of the indebtedness.

Moreover, the Company may be required to raise additional financing. The Company's ability to arrange additional financing and the costs of that financing will depend on, among other factors, the Company's financial position and performance, as well as prevailing market conditions and other factors beyond Shire's control.

In any liquidation, dissolution or winding up of Shire, the Company's Ordinary Shares and ADSs would rank below all debt claims against Shire or any of its subsidiaries. As a result, holders of the Company's Ordinary Shares and ADSs will not be entitled to receive any payment or other distribution of assets upon any liquidation or dissolution until after Shire's obligations to its debt holders, which rank senior to the Company's Ordinary Shares and ADSs, have been satisfied.

**Uncertainties associated with the combination may cause a loss of employees and may otherwise affect the future business and operations of Shire and the combined company**

Uncertainty about the effect of the combination on employees and customers may have an adverse effect on the Company following the combination. These consequent uncertainties may impair the Company's ability to retain and motivate key personnel and could also cause customers, suppliers, licensees, partners and other business partners to defer entering into contracts with, making other decisions concerning, or seeking to change existing business relationships with the Company. Because the Company depends on the experience and industry knowledge of their executives and other key personnel to execute their business plans, the Company may be unable to meet its strategic objectives.

**Baxalta only operated as an independent company from July 1, 2015 until the consummation of its merger with Shire. on June 3, 2016, and Baxalta's historical financial information is not necessarily representative of the results that Baxalta would have achieved as a separate, publicly traded company, and may not be a reliable indicator of future results of Baxalta. Moreover, any pro forma financial information published by the Company is not necessarily representative of the results that the Company would have achieved, and may not be a reliable indicator of future results.**

Any historical financial information about Baxalta prior to July 1, 2015 refers to Baxalta's business as operated by and integrated with Baxter. Baxalta's historical and pro forma financial information for such periods was derived from the Consolidated Financial Statements and accounting records of Baxter. In addition, certain pro forma financial information for the Company has incorporated Baxalta's historical financial information for such periods. Accordingly, such historical and pro forma financial information of Baxalta or the Company does not necessarily reflect the financial condition, results of operations or cash flows that Baxalta would have achieved as a separate, publicly traded company during the periods presented, or those that Shire would have achieved had the combination occurred as assumed for the preparation of the pro forma financial information. As a result, the Company's pro forma financial information is not necessarily representative of the results that the Company will achieve after the merger with Baxalta, and may not be a reliable indicator of future results.

**Baxter may not satisfy its obligations under various transaction agreements that have been executed as part of the separation or Shire may fail to have necessary systems and services in place when certain of the transaction agreements expire**

In connection with Baxalta's separation from Baxter, the parties entered into various agreements, including a separation and distribution agreement, a transition services agreement, a tax matters agreement, a manufacturing and supply agreement, an employee matters agreement, license agreements and commercial agreements. The separation and distribution agreement, the tax matters agreement and employee matters agreement determined the allocation of assets and liabilities between the companies following the separation for those respective areas and provide for indemnifications related to liabilities and obligations. The transition services agreement sets forth certain services to be performed by each company for the benefit of the other for a period of time after the separation. Baxalta and now Shire will rely on Baxter to satisfy its performance and payment obligations under these agreements. If Baxter does not satisfy its obligations under these agreements, including its indemnification obligations, Shire may not be able to meet its financial reporting requirements and/or could incur operational difficulties or losses as they relate to Baxalta's businesses. If Shire is unable to successfully integrate the Baxalta businesses into Shire's systems and services, or if Shire does not have agreements with other providers of these services once certain transaction agreements expire, Shire may not be able to operate the Baxalta businesses effectively and Shire's profitability may decline.

**The acquisition of Baxalta could result in significant liability to the Company if the combination causes the spin-off of Baxalta from Baxter or a Later Distribution, as defined below, to be taxable**

In connection with the signing of the merger agreement, Baxter, Shire and Baxalta entered into the Letter Agreement, which, among other things, supplement certain aspects of the tax matters agreement referenced above. Under the Letter Agreement, from and after the closing of the merger, Baxalta agreed to indemnify, and the Company agreed to guarantee such indemnity to, Baxter and each of its affiliates and each of their respective officers, directors and employees against certain tax-related losses attributable to, or resulting

from, in whole or in part, the merger. If the contribution of property by Baxter in one or more transfers to Baxalta in exchange for shares of Baxalta common stock, cash, and the assumption of certain liabilities, together with the distribution by Baxter on July 1, 2015 of approximately 80.5 percent of the shares of Baxalta common stock to shareholders of Baxter (the “spin-off”), Baxter’s distribution of cash received from Baxalta to its creditors and/or a Later Distribution, collectively, the “Baxter Transactions”, are determined to be taxable as a result, in whole or in part, of the merger (for example, if the merger is deemed to be part of a plan, or series of related transactions, that includes the Baxter Transactions), Baxter and its shareholders could incur significant tax liabilities. Under the tax matters agreement, and the Letter Agreement, Baxalta and the Company may be required to indemnify Baxter for any such tax liabilities. Baxter’s waiver of the provisions under the tax matters agreement restricting Baxalta’s ability to enter into and consummate the merger will not relieve Baxalta or the Company of its obligation to indemnify Baxter if the merger causes any of the Baxter Transactions to be taxable.

In connection with the signing and closing of the merger agreement, the Company received an opinion from Cravath, Swaine & Moore LLP (“Cravath”), tax counsel to the Company, to the effect that the merger will not cause the Baxter Transactions to fail to qualify as tax-free to Baxter and its shareholders under Sections 355, 361 and 368(a)(1)(D) of the Internal Revenue Code of 1986, as amended.

The tax opinions referred to in the immediately preceding paragraph are based upon various factual representations and assumptions, as well as certain undertakings made by the Shire, Baxter and Baxalta. If any of the factual representations or the assumptions in the tax opinions are untrue or incomplete in any material respect, an undertaking is not complied with or the facts upon which the tax opinions are based are materially different from the facts at the time of the merger, the opinions may not be valid. Moreover, opinions of counsel are not binding on the Internal Revenue Service (the “IRS”). As a result, the conclusions expressed in the tax opinions could be challenged by the IRS. None of Shire, Baxalta or Baxter has requested a ruling from the IRS regarding the impact of the merger on the tax treatment of the Baxter Transactions, since such rulings are not made by the IRS. Further, the tax opinions do not address all tax aspects of the spin-off, a Later Distribution and other related transactions and it is possible the Company may be obligated to indemnify Baxter despite the continuing validity of the tax opinions.

The Company’s indemnification obligations to Baxter and its affiliates, officers, directors and employees under the tax matters agreement and Letter Agreement are not limited in amount or subject to any cap. If Baxalta or the Company is required to indemnify Baxter and its affiliates and their respective officers, directors and employees under the circumstances set forth in the tax matters agreement, as supplemented by the Letter Agreement, it could have a material adverse effect on the Company.

References to the “Later Distributions” includes the following transactions that were undertaken by Baxter prior to the closing of the merger: (i) two debt-forequity exchanges (and related underwritten offerings) with respect to Baxalta shares, (ii) an offer to exchange Baxter shares for Baxalta shares, and (iii) a contribution of Baxalta shares to Baxter’s U.S. pension fund, which, in each case, were undertaken prior to the earlier of any Baxalta or Company stockholder vote with respect to the merger and that were intended to be part of a plan that includes the spin-off.

**In connection with the merger with Baxalta, the separation and the Later Distributions could result in significant liability to the Company due to Baxalta’s spin-off from Baxter**

The Baxter Transactions are intended to qualify for tax-free treatment to Baxter and its stockholders under Sections 355, 361, and 368(a)(1)(D) of the Code. Completion of the separation was conditioned upon, among other things, the receipt of a private letter ruling from the IRS regarding certain issues relating to the tax-free treatment of the Baxter Transactions. Although the IRS private letter ruling is generally binding on the IRS, the continuing validity of such ruling is subject to the accuracy of factual representations and assumptions made in the ruling. Completion of the initial distribution of Baxalta shares on July 1, 2015 was also conditioned upon Baxter’s receipt of a tax opinion from KPMG LLP, or KPMG regarding certain aspects

of the separation not covered by the IRS private letter ruling. The opinion was based upon various factual representations and assumptions, as well as certain undertakings made by Baxter and Baxalta. If any of the factual representations or assumptions in the IRS private letter ruling or tax opinion are untrue or incomplete in any material respect, an undertaking is not complied with, or the facts upon which the IRS private letter ruling or tax opinion are based are materially different from the actual facts relating to the Baxter Transactions, the opinion or IRS private letter ruling may not be valid. Moreover, opinions of a tax advisor are not binding on the IRS. As a result, the conclusions expressed in the opinion of a tax advisor could be successfully challenged by the IRS. If any of the factual representations or assumptions in the IRS private letter ruling or tax opinion are untrue or incomplete in any material respect, an undertaking is not complied with, or the facts upon which the IRS private letter ruling or tax opinion are based are materially different from the actual facts relating to the Baxter Transactions, the opinion or IRS private letter ruling may not be valid. Moreover, opinions of a tax advisor are not binding on the IRS. As a result, the conclusions expressed in the opinion of a tax advisor could be successfully challenged by the IRS.

If the Baxter Transactions are determined to be taxable, Baxter and its stockholders could incur significant tax liabilities, and under the tax matters agreement and the letter agreement which were assumed by Shire following the merger, the Company may be required to indemnify Baxter for any liabilities incurred by Baxter if the liabilities are caused by any action or inaction undertaken by Baxalta following the separation (including as a result of the merger).

**Certain Baxalta agreements may contain change of control provisions that may have been triggered by the merger that, if acted upon or not waived, could cause the Company to lose the benefit of such agreement and incur liabilities or replacement costs, which could have a material adverse effect on the Company**

Prior to and following the merger, Baxalta and its affiliates are each party to various agreements with third-parties, including certain license agreements, business development-related agreements, production and distribution related agreements, bonding/financing facilities, contracts for the performance of services material to the operations of Baxalta and/or its affiliates, IT contracts, technology licenses and employment agreements that may contain change of control provisions that may have been triggered upon the closing of the merger. Agreements with change of control provisions typically provide for or permit the termination of the agreement upon the occurrence of a change of control of one of the parties which can be waived by the relevant counterparties. In the event that there is such a contract or arrangement requiring a consent or waiver in relation to the merger for which such consent or waiver was not obtained, the Company could lose the benefit of the underlying agreement and incur liabilities or replacement costs, which could have an adverse effect on the Company.

**New regulations issued by the U.S. Department of Treasury may impact the Company following the merger with Baxalta.**

On April 4, 2016, the U.S. Department of Treasury issued new regulations applicable to acquisitions of U.S. companies by non-U.S. companies. These regulations, among other things, change the manner in which thresholds contained within the so-called “anti-inversion” rules that govern how the combined company will be taxed are calculated. These calculations are affected by the merger and could impact any future acquisitions of U.S. companies funded in whole or in part by Shire securities. These calculations are complicated and depend on several factors. Moreover, the U.S. Department of Treasury also introduced proposed “earnings stripping” regulations as revised on October 13, 2016 that may, among other things, cause certain related-party debt instruments issued by a U.S. corporation to be treated as equity, resulting in the loss of deductible interest payments for U.S. federal income tax purposes.

These regulations are newly issued and complex, and as such their application to any particular set of facts is uncertain. Shire believes that the regulations are not likely to affect the expected tax position of the Company following the acquisition of Baxalta, which belief is based on, among other things, facts that may

change or judgments that may prove to be incorrect and, if incorrect, could have an adverse impact on the expected tax position of the Company.

Furthermore, the U.S. tax authorities could issue additional guidance as to the application of these regulations or issue new regulations that could have an adverse effect on the expected tax position of the Company.

## **5. Directors responsibilities statement**

The following responsibility statement is repeated here solely for the purpose of complying with DTR 6.3.5. This statement relates to and is extracted from page 194 of the 2016 Annual Report.

These responsibilities are for the full 2016 Annual Report and not the extracted information presented in this announcement or otherwise.

We confirm that to the best of our knowledge:

- > the financial statements, prepared in accordance with United Kingdom Generally Accepted Accounting Practice, give a true and fair view of the assets, liabilities, financial position and profit or loss of the company and the undertakings included in the consolidation taken as a whole;
- > the strategic report includes a fair review of the development and performance of the business and the position of the company and the undertakings included in the consolidation taken as a whole, together with a description of the principal risks and uncertainties that they face; and
- > the annual report and financial statements, taken as a whole, are fair, balanced and understandable and provide the information necessary for shareholders to assess the company's performance, business model and strategy.

This responsibility statement was approved by the Board of Directors on February 22, 2017 and is signed on its behalf by:

**Flemming Ornskov, MD, MPH**

**Chief Executive Officer**

February 22, 2017

**Jeffrey Poulton**

**Chief Financial Officer**

February 22, 2017