The 2018 Trinity Drug Index

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Introduction

This third installment of the Trinity Drug Index provides a comprehensive evaluation of the performance of novel drugs approved by the FDA in 2015. Similar to prior versions of the Index, we scored each drug on its commercial performance, therapeutic value, and R&D investment.[1]

2015 saw 57 unique drug and biologic approvals[2], a record high in the past ~20 years. The majority of these therapies received one or more expedited review designations, continuing a trend from previous years. In this report, we describe the notable themes and trends within the industry and take a deeper look into a few products with outstanding performance.

2015 Drug Approval Highlights:

1. Oncology continued to reign as the therapeutic area with the greatest number of approvals (~30%, ~20%, and ~30% of approvals in 2015, 2014, and 2013, respectively, were for oncology), indicating continued innovation and growth in this space given high unmet need for novel therapies.
2. While oncology PD-1s and hepatitis C therapies made the headlines for their innovativeness in 2014, highly anticipated first-in-class products approved in 2015 spanned multiple indications, including several less prominent spaces:

> Reversal agent Bridion for neuromuscular blockade in adults undergoing surgery

> Almost 50% of the approvals were for orphan indications, including Strensiq (juvenile-onset hypophosphatasia), Orkambi (cystic fibrosis), and Kanuma (lysosomal acid lipase deficiency), to name a few

> Addyi for hypoactive sexual desire disorder, arguably one of the most controversial drugs approved in 2015

[1] For a more detailed description of the evaluation method, see prior Trinity Drug Index reports

[2] N=12 of these products (Anthrasil, Bexsero, Coagadex, Daklinza, Fluad, Kengreal, Lonsurf, Nuwiq, Odomzo, Praxbind, Raplixa, Xuriden) were excluded from the Index analysis due to a lack of commercial or therapeutic data. Additionally, N=2 of these products, Anthrasil and Quadracel, were excluded as they did not launch in the US until 2017 and 2018 (pending) respectively.

Drug Ranking

The overall and component scores for each drug are shown in Table 1 below.

TABLE 1: Drug scoring – Ratings on a 1-5 scale (Higher scores indicate better performance)

Brand Name (Company)	**Therapeutic Area 2015 Approval**	**Component Scores**			**Overall Score**
		Therapeutic	Commercial	R&D	
IBRANCE (Pfizer)	Breast Cancer	4.6	4.8	3.5	4.5
DARZALEX (Janssen)	Multiple Myeloma	4.8	4.6	3	4.4
GENVOYA (Gilead)	HIV	3.6	4.6	3.5	4.0
COSENTYX (Novartis)	Psoriasis	3.8	4.6	2.5	3.9
TAGRISSO (AstraZeneca)	Lung Cancer	3.8	3.6	4	3.8
STRENSIQ (Alexion)	Hypophosphatasia	5	2.4	4	3.8
ALECENSA (Roche)	Lung Cancer	4.6	2.6	4	3.7
ORKAMBI (Vertex)	Cystic Fibrosis	4.2	3.2	3.5	3.7
BRIDION (Merck)	Neuromuscular Block Reversal	4.8	2.8	3	3.6
NINLARO (Takeda)	Multiple Myeloma	3	3.6	4	3.4
TRESIBA (Novo Nordisk)	Diabetes	3.4	4	2	3.4
KANUMA (Alexion)	Lysosomal Acid Lipase Deficiency	4.4	1.2	5	3.2
REPATHA (Amgen)	High Cholesterol	3.8	2.8	2.5	3.1

Brand Name (Company)	**Therapeutic Area 2015 Approval**	**Component Scores**			**Overall Score**
		Therapeutic	Commercial	R&D	
REXULTI (Otsuka)	Schizophrenia, Major Depressive Disorder	3.4	3.2	2.5	3.1
LENVIMA (Eisai)	Thyroid Cancer	3.8	2.8	2.5	3.1
ADYNOVATE (Shire)	Hemophilia	3	2.4	4.5	3.1
ENTRESTO (Novartis)	Heart Failure	4	2.6	2	3.0
VONVENDI (Shire)	Von Willebrand Disease	4	1.6	4	3.0
NATPARA (Shire)	Hypocalcemia in Hypoparathyroidism	4	2	3	3.0
PRALUENT (Sanofi)	High Cholesterol	4	2	3	3.0
VELTASSA (Vifor Pharma)	Hyperkalemia	3.8	1.6	4	3.0
UPTRAVI (J&J)	Pulmonary Arterial Hypertension	3	3	2.5	2.9
NUCALA (GlaxoSmithKline)	Asthma	3.8	2.6	1.5	2.9
ARISTADA (Alkermes)	Schizophrenia	2.6	2.5	4	2.8
UNITUXIN (United Therapeutics)	Neuroblastoma	4.2	1.8	2	2.8
VIBERZI (Allergan/Ironwood)	Irritable Bowel Syndrome with Diarrhea	3	2.4	3	2.8
KYBELLA (Allergan)	Submental Fat	4	1.2	3	2.7
AVYCAZ (Allergan)	Complicated Urinary Tract Infections	4.2	1.2	2.5	2.7

Brand Name (Company)	**Therapeutic Area 2015 Approval**	**Component Scores**			**Overall Score**
		Therapeutic	Commercial	R&D	
VRAYLAR (Allergan)	Schizophrenia, Bipolar Disorders	2.6	2.8	2.5	2.7
EMPLICITI (Bristol-Myers Squibb)	Multiple Myeloma	3	1.8	3.5	2.6
IXINITY (Aptevo Therapeutics)	Hemophilia	2.8	1.4	4.5	2.6
FARYDAK (Novartis)	Multiple Myeloma	3.2	1.2	3.5	2.5
COTELLIC (Roche)	Melanoma	3.2	1	3.5	2.4
YONDELIS (Janssen)	Liposarcoma, Leiomyosarcoma	3.2	1.8	1.5	2.3
CHOLBAM (Retrophin)	Peroxisomal Disorders, Bile Acid Synthesis Disorders	2	1.4	4.5	2.3
PORTRAZZA (Eli Lilly)	Lung Cancer	3.2	1	2.5	2.2
ZURAMPIC (Astra Zeneca)	High Uric Acid in Gout	2.8	1	2.5	2.0
CRESEMBA (Astellas Pharma)	Aspergillosis, Mucormycosis	2.4	1.6	2	2.0
CORLANOR (Amgen)	Heart Failure	3.2	1.2	1	2.0
VARUBI (Tesaro)	Chemotherapy-Induced Nausea and Vomiting	2.6	1	2	1.8
ADDYI (Bausch Health)	Hypoactive Sexual Desire Disorder	2.2	1	1.5	1.6
IMLYGIC (Amgen)	Melanoma	1.6	1.2	2	1.5

Key Findings

Ibrance, Darzalex, and Genvoya were the highest performing 2015 approvals on the Index

> Ibrance (palbociclib), a kinase inhibitor indicated for breast cancer, was granted accelerated approval based on strong efficacy reported in Phase II and has demonstrated strong commercial performance given its first-mover advantage.

> Darzalex (daratumumab) was the first antibody to be approved in multiple myeloma and has maximized its commercial potential by moving up the treatment paradigm through combination use.

> While Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), an anti-retroviral combination therapy, had a slightly lower therapeutic rating than Ibrance and Darzalex, it lowered treatment burden for HIV patients with its once-daily dosing thus filling unmet need.

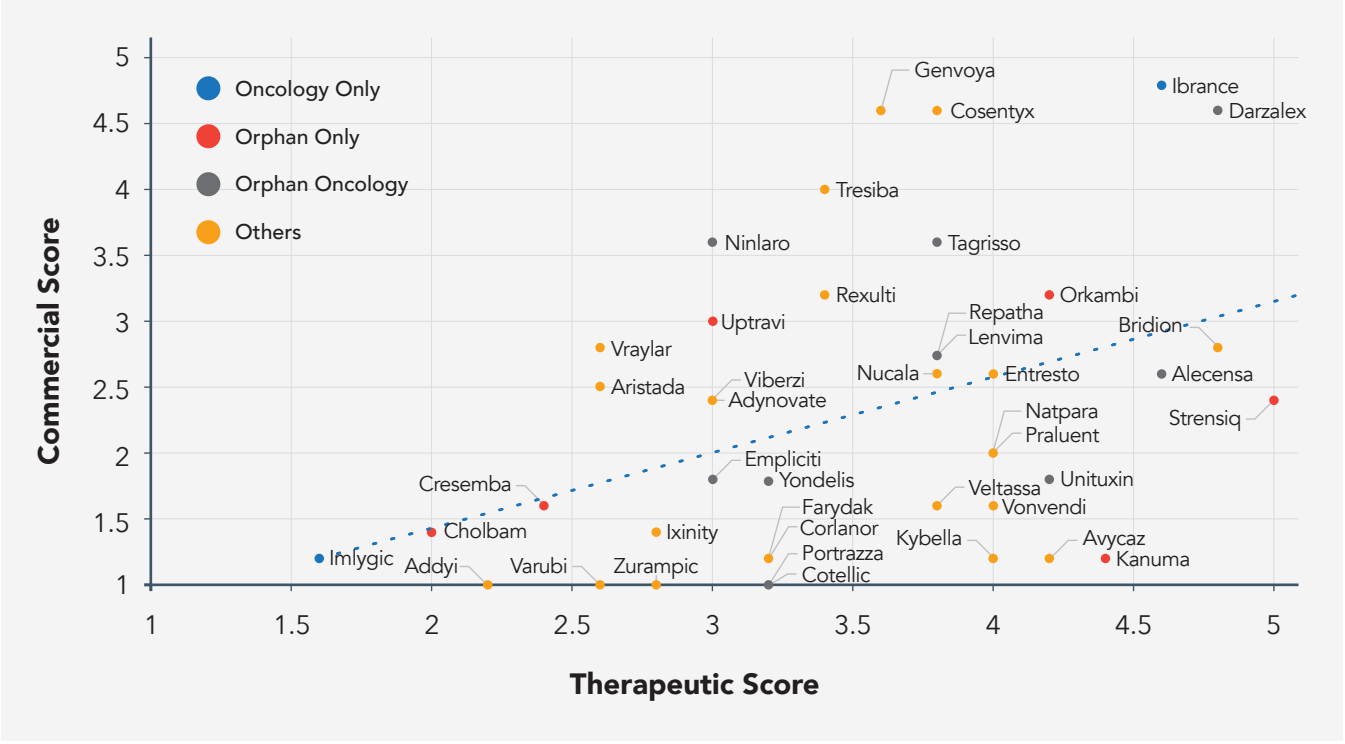

Figure 1: Comparison of therapeutic and commercial scores for drugs FDA-approved in 2015

In Figure 1, as expected, we observed that **most drugs fell along a positively-sloped line, indicating that increased therapeutic value was typically associated with increased commercial success.** Drugs that fall above the line are considered to be "over-performing" while drugs that fall under the line are thought to be "under-performing."

Once again, oncology dominated FDA approvals with 15 unique products

> High performers among these products were Ibrance, Darzalex, Alecensa, and Tagrisso.

> Other oncology products, such as Cotellic, Portrazza, and Imlygic, struggled to perform well commercially. Cotellic was only approved for a rare form of melanoma, Portrazza's label contains a black box warning, and Imlygic's cumbersome administration and treatment regimen hindered its success.

Multiple products with the same compelling mechanism of action tend to be approved in rapid succession of each other, resulting in a higher bar for differentiation between products

> For example, in 2015, multiple PCSK9 inhibitors were approved (Praluent and Repatha) while in 2014, multiple PD-1 inhibitors were approved (Keytruda and Opdivo).

Even in crowded and seemingly saturated markets, true clinical differentiation relative to the standard of care translates to commercial success

> The most commercially successful products in 2015 were those that demonstrated a marked improvement in clinical efficacy over the standard of care, particularly Cosentyx and Tresiba, which both achieved success despite being late-to-market in crowded indications.

> Genvoya also witnessed success in the highly competitive HIV market (that was bolstered by Gilead's established commercial presence in the space) by fulfilling an unmet need for a more convenient therapy.

Drugs that are approved in multiple indications, or even for multiple lines of therapy within an indication, are more likely to be commercially durable

> Within the neurology space, next-generation atypical anti-psychotic drugs (Rexulti and Vraylar) saw strong commercial performances because of launches in multiple indications and approval for combination use.

> For oncology products, moving up in line of therapy leads to higher commercial success, as seen with Darzalex, which received a fourth-line indication at launch, but has since added four additional indications within multiple myeloma.

> This is similar to the "product as a pipeline" approach that we reported on in last year's report around the immuno-oncology agents for oncology (Keytruda and Opdivo). Those products expanded their commercial reach by expanding to new indications; whereas here, the products are expanding their reach within their respective indications.

Similar to last year's report, we continue to find that ultra-orphan products (such as Kanuma and Unituxin) tend to have a lower commercial performance given their therapeutic value. However, some orphan drugs did perform well commercially; for example, Orkambi for cystic fibrosis and Strensiq, the first ever treatment for hypophosphatasia.

MULTIPLE MYELOMA

Four 2015 approvals with radically varied commercial success

Multiple myeloma experienced a major inflection in 2015 with four novel product approvals: Farydak (Novartis) was approved in February 2015 and Darzalex (Janssen), Ninlaro (Takeda), and Empliciti (BMS) were approved in November 2015. With three novel mechanisms of action represented amongst the four products, all of which were marketed by major players in oncology, experts struggled to predict how the cards would fall. This analysis has highlighted a wide range in commercial performance across these four products with Darzalex earning the highest score, followed by Ninlaro, Empliciti, and ending with Farydak. Below are a few key points that help tell the story.

DARZALEX

> A driver of Darzalex's success has been their continued expansion into four additional indications. Despite initially receiving a restrictive fourth-line monotherapy label, Darzalex's launch created a new niche in the market and provided a treatment choice where none existed. Proving efficacy in that initial population drove spontaneous use and fueled subsequent combination indications as first, second, and third-line therapies within multiple myeloma. Janssen's strategic annual staggering of these indication expansions in addition to physicians' post-launch experience of strong clinical efficacy has kept Darzalex top of mind for physicians and driven high utilization.

NINLARO

> Ninlaro proved that commercial success can be found independent of an expanded indication. As the first oral therapy in its class, the convenience of once-weekly oral administration amongst the other novel injectable and intravenous therapies was a value driver. However, Ninlaro was often reserved for patients unable to tolerate the intravenous administration of standard of care Velcade, which limited its value proposition to a pure convenience play.

EMPLICITI, FARYDAK

> Physicians have been largely unimpressed with the efficacy demonstrated by both Empliciti and Farydak, which is evidenced by their slow and limited uptake. Juxtaposition with high-efficacy Darzalex further highlights the lack of efficacy-based differentiation for both Empliciti and Farydak. When combined with both products' labels limiting their respective eligible patient populations, it is unsurprising to observe their commercial under-performance relative to Darzalex and Ninlaro.

ADDYI

One of the lowest scoring products approved in 2015

As the first approved treatment for Hypoactive Sexual Desire Disorder (HSDD) in 2015, Addyi was positioned as a victory for female patients suffering from a disease with no available prescription treatments. Addyi, however, did not demonstrate enough clinical value to capitalize on its first-to-market advantage, underscoring the importance of validating a commercial profile in parallel with (or in advance of) pivotal trials. Three years, two launches, and hundreds of millions of dollars later, Addyi has been a commercial failure.

BACKGROUND

> Addyi, dubbed the 'female Viagra,' had been lauded by numerous women's-focused advocacy groups as a monumental victory for women, but the wave of public opinion was not enough to overcome what seem like obvious roadblocks in hindsight. Addyi was indicated for a condition that the medical community has not fully embraced, had questionable efficacy and unquestioned side effects (which were exacerbated by alcohol), and had failed two prior attempts at FDA approval.

RESULTS

> Valeant, who had spent nearly one billion dollars in cash to acquire the sponsor of Addyi's NDA, Sprout Pharmaceuticals, in the months following FDA approval, returned Addyi's rights to shareholders in exchange for a low single-digit royalty nearly two years after they initially acquired them for $500M upfront and nearly $1B in total deal value.

COMMERICAL LEARNINGS

> While no amount of commercial muscle can overcome a clinically lackluster product, commercial headwinds could have been identified in advance of launch with thoughtful target product profile testing, and we encourage all companies to fully understand how a given product will be perceived in the market prior to launch.

PRALUENT & REPATHA

An example of how challenges navigating the payer landscape can limit the commercial performance of even highly promising drugs

Lipid-lowering PCSK9 inhibitors Praluent and Repatha were considered the biggest advancement in treating cholesterol since the development of the statins. Upon approval, both drugs generated significant excitement and were forecasted to achieve blockbuster status; however, sales have fallen far below expectations.

BACKGROUND

> The development of the PCSK9s was considered a vital breakthrough as they provide incremental reduction in cholesterol and are also better tolerated compared to statins. Commensurate with their compelling therapeutic value, both Praluent and Repatha launched with a list price of approximately $14K per year.

RESULTS

> Insurance companies balked at the sticker price of the PCSK9s, especially because statins are available in generic form and only cost a few hundred dollars per year. Despite promising clinical efficacy and later trials that demonstrated the PCSK9 inhibitors significantly cut the risk of heart attacks and stroke, payers implemented barriers to accessing Repatha and Praluent. Insurance companies argued that unrestricted use of Repatha and Praluent would effectively "break the bank." High denial rates for dispensing the PCSK9s slowed adoption, leaving both products in a lurch.

LEARNINGS

> Upon realizing the influence payers exert in this market, manufacturers of Praluent and Repatha significantly reduced the price of their drugs. Additionally, to boost payer coverage and differentiate themselves from the cheaper statins, both drugs entered into value-based contracts with US payers that link financial incentives to improved patient health. These types of innovative contracts are likely to increase over the next few years as payers tighten their purse strings and novel, high-priced therapies emerge. We will be watching these developments over the next few years, with particular interest in whether the benefits are realized by all parties involved (patients, payers, manufacturers).

Looking Ahead To 2016 Approvals

FDA approvals took a nosedive in 2016, leaving many wondering whether the drop was due to a decrease in R&D productivity or a lull in regulatory activity. At Trinity, we are wagering that this apparent slump was likely part of a natural phasing process and signals a return to a more sustainable level of activity. Taking a closer look at the 23 novel drugs approved in 2016, we are excited to analyze a variety of themes:

> Innovation in oncology continued an upward trend, with several novel breakthrough therapies. As the oncology space becomes increasingly crowded, it will be important to understand how the value of innovation evolves, especially in the eyes of payers.

> Nearly half of new drugs approved in 2016 were indicated for orphan diseases highlighting that investing in this space remains a strategic choice for many companies. Notable orphan drugs include the controversial Exondys 51 (Duchenne muscular dystrophy), Spinraza (spinal muscular atrophy), and Ocaliva (primary biliary cirrhosis). Analysis of these therapies will help to fine tune our assessment of the commercial potential of orphan drugs relative to their therapeutic value.

Heightened pricing pressure, the looming threat of biosimilars, an increasingly competitive environment, and a rising bar for innovation are all pushing manufacturers to be even more strategic in bringing novel therapies to market. Although the industry faces immense challenges, substantial room for growth remains as demonstrated by this report; therapies that provide compelling clinical benefit relative to the standard of care can achieve commercial success even in crowded markets.

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