The 2016 Trinity Drug Index

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TRINITY

Executive Summary

Every year, the FDA approves 20-40 novel drugs through the BLA or NDA pathway. A novel therapeutic must demonstrate that it is safe and effective in order to receive approval, which in turn allows the new drug to be marketed in the United States. The FDA, however, unlike the EMA and many other regulatory agencies, generally does not judge how much additional value the new drug brings to patients, instead letting the market dictate comparative value. Likewise, the approval alone does not imply commercial success, and does not even guarantee that the R&D costs borne by the manufacturer will be recouped.

So what does it take to succeed? An ideal scenario is that a new drug achieves therapeutic and commercial excellence with minimal costs (especially in terms of R&D expenditures). But is this scenario realistic, and what actually takes place in the real world? One approach to answer these questions is to examine the performance of recently approved drugs to understand what distinguishes top performers from laggards.

In this report, we rate drug performance as measured by a retrospective look at commercial success relative to therapeutic value and R&D effort. We find that success can be elusive in the world of pharmaceuticals and biologics–some drugs shine, but many struggle. And while therapeutic excellence often translates to commercial success, there are some notable exceptions.

This report inaugurates the Trinity Drug Index, a comprehensive and reproducible approach to assess novel drugs. Our first Drug Index focuses on novel drugs approved in 2013.

Key findings of this report:

- Sovaldi topped the 2013 Trinity Drug Index, followed by Imbruvica and Tecfidera
- Most of the top performers are specialty drugs
- Drugs for primary care markets such as COPD and diabetes tend to show weaker differentiation and limited commercial performance, exacerbated by significant R&D expense
    - Invokana represents a notable exception, being an example of a discontinuous innovation (new mechanism with novel attributes) in a crowded market
- Commercial underperformance given significant therapeutic value is rare, and could be due to a rapidly changing competitive environment (e.g., Kynamro)
- Well-executed business strategy may boost commercial performance of drugs that are not vastly superior therapeutically (e.g., Pomalyst)
- Drugs can vary greatly in terms of market durability, making lifecycle management a key strategic component–in some cases, success may be built over time (e.g., Imbruvica), while other cases are opportunistic and make the most of a short window (e.g., Olysio)

Introduction

Every year a few dozen novel drugs are approved by the FDA–their number has fluctuated in recent years from a low of 21 in 2010 to a high of 45 in 2015[1]. FDA approval signals the successful end of a long and arduous journey of drug development: on average, it takes over 10 years for a drug to proceed from discovery to launch and only 10% of drug candidates that enter human trials are ultimately approved[2]. In addition, the average R&D costs of development from Phase I to approval are estimated at ~$250M; taking failed candidates and the cost of capital into account brings the average overall R&D costs to about $2.6 billion[3].

[1] CDER-approved new molecular entities (NMEs)
[2] Clinical Development Success Rates, BIO Industry Analysis white paper (2016)
[3] DiMasi et al., Innovation in the pharmaceutical industry: New estimates of R&D costs, J Health Econ (2016) May; 47; 20-33

As the life sciences world is abuzz with innovative ideas, it is imperative for companies to prioritize their investment in order to achieve an optimal return. One of the ways to inform such decisions is to look at what history tells us – what was the performance of recently approved drugs, and what distinguishes top performers from laggards? In many cases, the story of a drug's performance may be as straightforward as its superior efficacy and market differentiation. In other cases, however, product success and failure are more strongly tied to strategic decisions.

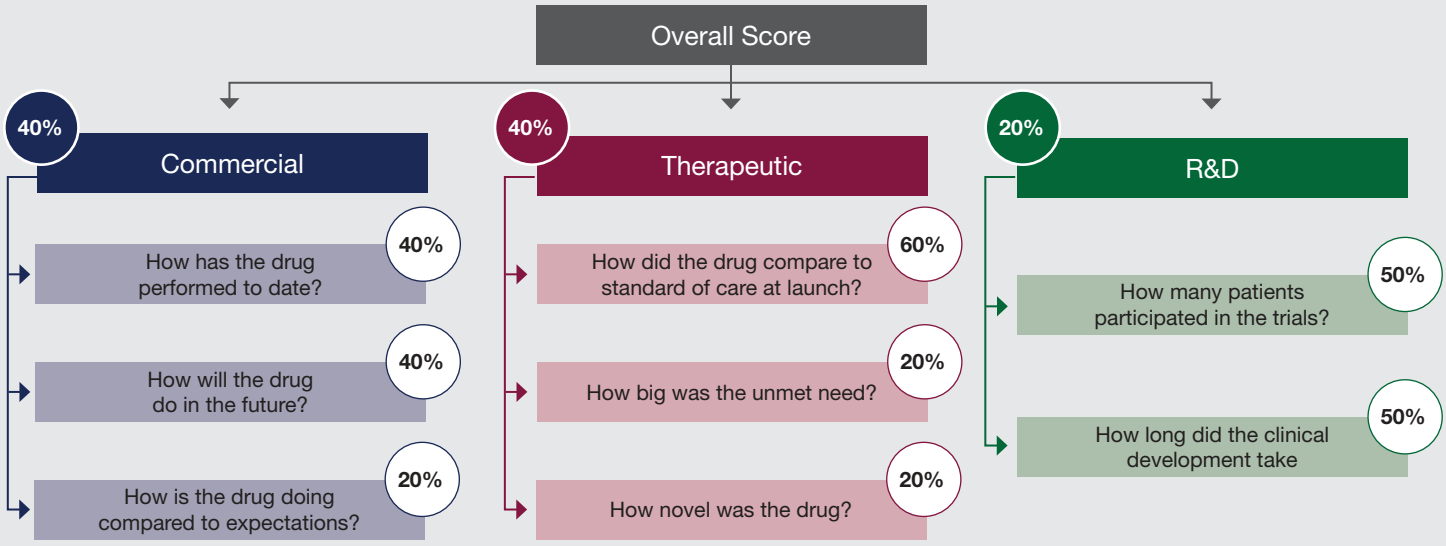
This report inaugurates the Trinity Drug Index, a comprehensive and reproducible approach to evaluate FDA-approved medications. We assessed all of the novel drugs approved in 2013 using a framework of 3 key categories: commercial performance, therapeutic value, and R&D complexity. Each drug received a score in each of the categories as well as an overall composite score. Select case studies are also included to provide additional context in cases of observed under/overperformance.

Methodology Overview

Each drug received a score in the three pillar categories (commercial, therapeutic and R&D) and those scores were combined into the overall score by upweighting commercial and therapeutic components.

FIGURE 1

Drug scoring methodology



Commercial performance was determined by the cumulative sales to date (through December 2015) and projected future sales (2016-20), as well as taking into account under/overperformance relative to analyst forecasts. EvaluatePharma was the primary source for the cumulative sales.

Therapeutic assessment was largely based on the evaluation of the additional value the drug in question brought in comparison to the standard of care (SOC) at the time of launch. This was previously identified as one of the key drivers of differentiation, as opposed to unmet needs and innovativeness[4]. This data was obtained via an internal survey of 50+ life sciences experts at Trinity. In addition, Trinity partnered with Toluna, a leading survey provider, to supplement those findings with a survey of 101 practicing physicians.

The R&D assessment was a composite score incorporating the cost of randomized clinical trials (RCTs) and duration of clinical development. Trial cost was estimated based on the total number of enrolled patients (per ClinicalTrials.gov) and per patient trial costs from Parexel's biopharmaceutical statistical sourcebook. Clinical development duration was calculated based on Thompson Reuters' Cortellis database.

[4] Gudiksen M, et al. What drives success for specialty pharmaceuticals? Nat Rev Drug Discov. 2008 Jul;7(7):563-7

Drug Ranking

The overall and component scores for each drug are shown in Table 1 below. Higher scores indicate better performance.

TABLE 1

Drug scoring[5]–overall and by component–ratings on 1-5 scale

Brand Name	Component Scores			Overall Score
	Therapeutic	Commercial	R&D	
SOVALDI	4.8	4.4	3.5	**4.4**
IMBRUVICA	4.2	4.6	3.5	**4.2**
TECFIDERA	4.6	4.8	1.5	**4.1**
INVOKANA	3.8	4.6	2.5	**3.9**
OPSUMIT	3.8	3.2	4.5	**3.7**
TIVICAY	3.6	3.6	3.5	**3.6**
TAFINLAR/MEKINIST	4	2.8	3.5	**3.4**
OLYSIO	4	3	2.5	**3.3**
POMALYST	3.2	4	2	**3.3**
KADCYLA	4	2.8	2.5	**3.2**
GAZYVA	3.8	2	4	**3.1**
ADEMPAS	3.4	2.2	4	**3.0**
XOFIGO	3.4	2.2	2	**2.6**
BRINTELLIX	3	2.8	1.5	**2.6**
KYNAMRO	3.8	1	3.5	**2.6**
OSPHENA	4	1.2	2.5	**2.6**
RIXUBIS	2.8	1	5	**2.5**
ANORO	3	1.4	3	**2.4**
BREO	2.6	1.6	2.5	**2.2**
APTIOM	2.8	1.4	2	**2.1**
DUAVEE	2.6	1.2	2	**1.9**
NESINA	2.8	1	1.5	**1.8**

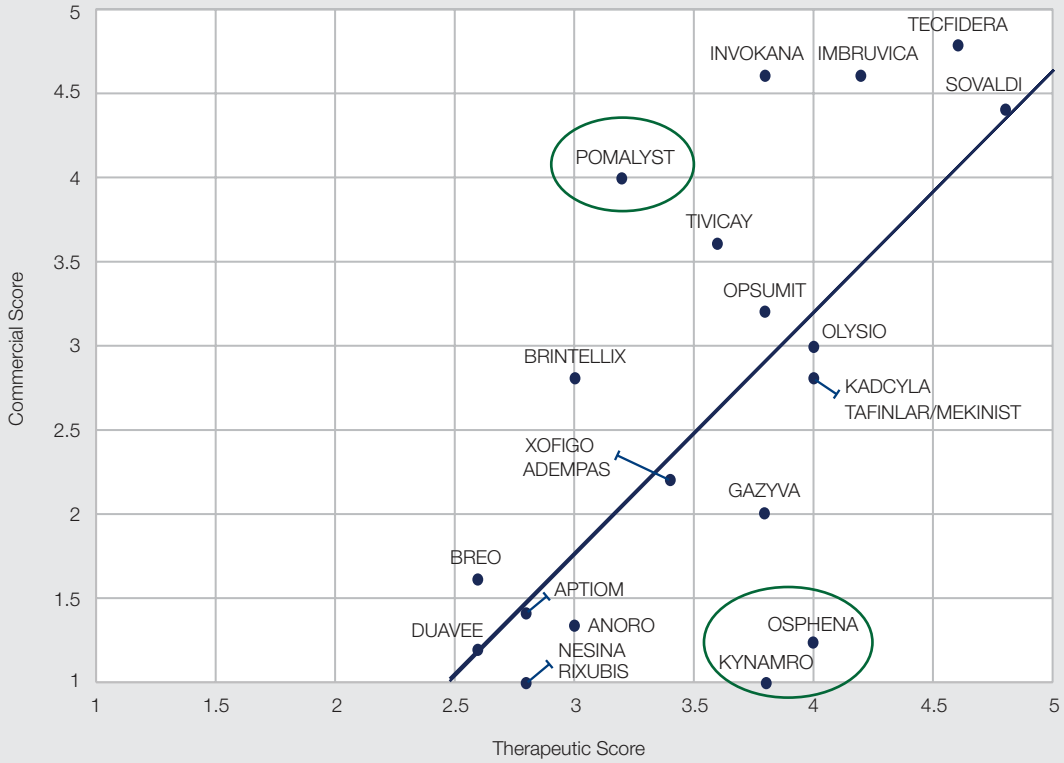
[5] The following drugs were excluded from the analysis: Gilotrif (commercial performance data not available), Novoeight (only launched in the US in 2015), Luzu, Tretten, and Bat (<$100M in 2014-15 cumulative sales, limited data on therapeutic value)

Commercial Success Versus Therapeutic Value

It is often assumed that therapeutic value begets commercial success, but we assessed the extent of this association by comparing our Commercial and Therapeutic scores.

FIGURE 2

Comparison of commercial and therapeutic value scores



In Figure 2, as expected, we observed that most drugs fell along a positively-sloped line, indicating that increased therapeutic value was associated with increased commercial success. We noted, however, instances were drugs under- or overperformed commercially relative to their therapeutic value. Pomalyst, for example, appeared to have had a higher level of commercial success given its therapeutic value. On the other end of the spectrum, both Kynamro and Osphena performed below their commercial expectations, given their perceived therapeutic value. We investigated each of these three cases to understand the cause of their unexpected commercial performance–these are provided as case studies in the next section.

Key Observations

Top performers: Sovaldi topped the Trinity Drug Index, followed by Imbruvica and Tecfidera

- Sovaldi and Imbruvica had high marks across all three component scores, validating their designation as FDA Breakthrough therapies[6]
- Tecfidera required a relatively larger R&D investment, so its overall score was slightly lower compared to Sovaldi

[6] Gazyva was also designated as a Breakthrough Therapy in 2013, but was ranked lower on the Trinity Index list, due in part to its commercial score

Most of the top performers are specialty drugs that treat rare or complex diseases and typically have large price tags

- Specialty drugs have accounted for the majority of FDA approvals over the past few years as companies are focusing on the development of treatments for higher unmet need conditions, where commercialization costs and reimbursement barriers are perceived to be lower
- The high cost of specialty drugs has not dampened their commercial success (yet), but we can mark 2013 as the year where a lot of things changed in this regard. Going forward, we see far tighter payer controls for products that have the potential to disrupt payer budgeted spend, with PCSK9s as a prime example. What looked like a compelling clinical value proposition when viewed retrospectively transformed into "wait for the outcomes study results" and a 10 page prior authorization form designed to confuse even the sharpest administrator.

Drugs for primary care-based markets such as COPD and diabetes tend to show weaker differentiation and limited commercial performance, exacerbated by significant R&D expense due to larger and longer clinical trials

- "Me too" drugs aim to take advantage of widely-diagnosed conditions (i.e., a small share of a large market can be profitable), but with a lack of differentiation and the threat of generic alternatives, they struggle to establish any significant presence
- Primary care markets can be difficult to crack and expectations for drugs in this area should be tempered unless they represent a discontinuous innovation, as first-in-class Invokana was in a crowded diabetes market
- While PCP-driven markets are typically crowded and genericized, with limited opportunity for branded agent success, specialty markets are (for now) largely brand-heavy, highly differentiated, have no cheap alternatives and are often predominantly biologics-based
- There have, however, been recent changes in some specialty markets; as biosimilars emerge, these largely branded markets are starting to become more crowded, and payers are becoming more cost-conscious, especially in areas such as Rheumatoid Arthritis and Inflammatory Bowel Disorders. In these scenarios, manufacturers can take lessons from PCP-driven markets in the importance of true product differentiation and innovation.

Drugs vary greatly in terms of market durability, making lifecycle management a key strategic component

- In the case of an oncology drug like Imbruvica, success may be built over time as additional indications are added. In oncology, neurology, immunology, and many other therapeutic areas, it is essential to build a strategy that optimizes opportunities with different patient populations and expand the brand over time.
- Other cases were more opportunistic in nature and made the most of a short window. Olysio, for example, took advantage of its common pairing with fast-rising Sovaldi and achieved its peak sales a year after launch. While increased competition in hepatitis C over the past few years leaves Olysio with only niche opportunity, its peak commercial success far exceeded expectations.

Case Studies

In order to demonstrate how products overachieve or underperform commercially relative to their therapeutic value, Trinity has selected three cases studies: Pomalyst (overperformer), Kynamro (underperformer), and Osphena (underperformer).

Pomalyst

Pomalyst was approved in February of 2013 for the treatment of multiple myeloma (MM), and, since its launch, has seen strong commercial performance relative to its perceived therapeutic value.

When Pomalyst launched as a later-line MM product, Kyprolis and dexamethasone were considered to be the standard of care, though Kyprolis and Pomalyst were both viewed by the market as follow-ons to Velcade and Revlimid, respectively. On both efficacy and safety, Pomalyst was not considered overall to be a marked improvement over previously established products, though it did prove effective in patients already treated with Revlimid, which was a surprising and valuable clinical benefit considering they are in the same drug class. However, while Pomalyst falls towards the middle of the pack on therapeutic value in comparison to other 2013 launches, its commercial performance exceeded expectations.

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This “over-achievement” was likely attributable to the market situation–patients were very sick and had few options in a therapeutic area where high prices were the norm. Even absent a truly game-changing product profile, there was opportunity in the MM market for a home run, or, at the very least, a base hit. Celgene, Pomalyst’s manufacturer, was thus able to leverage the unmet need and pricing power to boost commercial performance. The experience and reputation of Celgene also likely played a role in the commercial success, aas Pomalyst became the third product in Celgene’s multiple myeloma portfolio, joining Thalomid and Revlimid. Celgene’s broader portfolio at the time also included three other hematology and oncology products, establishing the company’s reputation as a trusted hematology and oncology manufacturer, enabling it to leverage its strong and well-established sales and marketing capabilities in this therapeutic area.

Kynamro

Kynamro was approved in January 2013 for the treatment of homozygous familial hypercholesterolemia (HoFH), and, in spite of a promising therapeutic value at launch, has underperformed commercially.

Facing a stronger competitor in a market with very few patients, Kynamro was never able to gain traction, despite reasonable clinical data as well as a significantly lower price.

Homozygous familial hypercholesterolemia is a rare genetic disorder causing very high levels of LDL and early cardiovascular disease that, through late 2012, was treated with Crestor and other cholesterol-lowering products. In late December 2012, just a month before Kynamro, a rival product, Juxtapid, received FDA approval for the treatment of HoFH. Although the two drugs were never studied head-to-head, Juxtapid became the preferred treatment for most physicians due to its comparable efficacy profile and ease of administration relative to Kynamro.

Facing a stronger competitor in a market with very few patients, Kynamro was never able to gain traction, despite reasonable clinical data as well as a significantly lower price ($176K for Kynamro versus $235-$295K for Juxtapid). While anticipating Juxtapid’s impact and devising a mitigating marketing strategy may have helped to increase sales, the high risk associated with entering a competitive, small-population market remained, and likely contributed to Kynamro’s poor commercial performance.

Osphena

Osphena was approved in February 2013 for the treatment of postmenopausal dyspareunia, and, despite a promising therapeutic value at launch, has underperformed commercially. Osphena’s value proposition to women was that it offered a non-hormonal oral alternative in a market primarily managed with vaginally administered hormone replacement therapy. Unfortunately, these value propositions did not pan out as expected.

For more than a decade, women have been avoiding hormone replacement therapy, an otherwise effective option, because of the associated increased risk of breast cancer and cardiovascular events such as clotting and stroke. While Osphena offers an alternative to direct hormone replacement, it carries a boxed warning similar to the estrogen replacement therapies warning of cardiovascular events and endometrial cancer risks. It is also associated with increased hot flashes, a side effect that postmenopausal women are trying to avoid.

Osphena’s oral formulation was also underwhelming to women, who seemed to prefer to use topical, locally-applied gels and creams as needed. The on-demand nature of some vaginally administered alternatives, in addition to the stigma associated with taking a daily pill for painful intercourse, severely dampened the potential value of an oral formulation.

While Osphena’s value proposition seemed favorable when considered in a vacuum, it did not translate to success in the dyspareunia market. Osphena only superficially addressed the market’s unmet needs, and its therapeutic value was ultimately insufficient to generate commercial success.

Looking Ahead

Our observation that therapeutic value and commercial excellence are correlated engenders confidence that healthcare markets overall are rewarding what is truly valuable for patients, despite occasional inefficiencies displayed by the system (e.g., pricing controversies around Turing, Valeant and Mylan). However, as an indirect result of the record-breaking success of Sovaldi and its corresponding impact to payer pharmacy budgets and profits, newer agents will face increased scrutiny in terms of the cost-benefit of their innovations. More than ever, it will be critical to demonstrate a product’s value vis-à-vis existing competition.

We look forward to the next installment of the Trinity Drug Index because 2014 was a banner year for drug approvals, with 41 novel new drugs approved. This included 17 first-in-class agents, 17 approvals for orphan diseases, 25 agents that were granted priority review, and 9 with breakthrough designations. Themes we will be analyzing in the future include:

- The impact of Keytruda and Opdivo on future oncology drug development across the board. With over 40 phase 3 trials ongoing for immune checkpoint inhibitors, every company investing in oncology needs to consider the impact of the PD-1 / PDL-1 class on the future landscape. Understanding patient sub-segmentation, combination potential, and payer implications will be critical to success in many tumor types.
- The uptake of novel agents in high unmet need areas. Ofev and Esbriet were both approved for IPF on the same day, and their push to penetrate this previously untapped market will provide commercialization lessons for years to come.
- The PCP market, and reports of its demise. With 3 new approvals in type 2 diabetes, as well as new agents for sleep disorders, onychomycosis and COPD, there are several agents to help fine tune our assessment of new agents in competitive, mass market therapeutic areas.
- An assessment of the Qualified Infectious Disease Program, and the (lack of) success of the 4 antibiotics that used this incentive program on the way to FDA approval.
- The performance of specialty drugs, and especially those for orphan conditions. While 1/3 of CDER-approved drugs in 2013 had an orphan designation, only three (Kynamro, Adempas, Opsumit) were approved outside of oncology. In 2014 and 2015 between 41 and 47% of new approvals were for orphan conditions, with many outside of oncology (e.g., Vimizim for Morquio A syndrome, Orkambi for cystic fibrosis, Esbriet and Ofev for idiopathic pulmonary fibrosis)[7]. Clearly, the focus on orphan diseases has been a strategic choice for many companies – but how well is it being translated into products that are successful both therapeutically and commercially?
- In 2016, we are on pace for under 25 innovative new drug approvals. Is it just one down year in the continuing era of therapeutic progress, or a line demarking the return to lower novel R&D throughput and more focus on incremental innovations or cost savings? At Trinity, we are wagering on the former.
- Another topic of significant interest to the biotech and pharma community is the impact of M&A and in-house development versus in-licensing on R&D and commercial outcomes. Over the past several decades the pharmaceutical industry has shifted from a fully integrated model to one that incorporates a significant proportion of external innovation; this trend has been underscored by a continuous increase in the number of M&As[8]. The evidence on the benefits of this approach, however, has been ambiguous.

It is the golden age of drug development and innovation, and seeds that were planted a decade ago are now bearing fruit. Scientific understanding of the genetic underpinnings, and the inter- and intra-cellular pathways of disease, allow for an ever-evolving improvement in the standard of care. It is clear, though, that we are at a crossroads where the biopharma industry must demonstrate with precision and clarity the value of their medicines in order to be adopted broadly. Developing drugs is risky business; making them a commercial success doubles that risk. Comprehensive understanding of these risks from all the perspectives of all stakeholders, and investing in the right trials for the right products, is essential to success in the high stakes game of innovative new drug development.

[7] CDER Novel New Drugs Summary for 2014 and 2015

[8] The business of healthcare innovation, 2nd edition, edited by L.R. Burns (2012)