THE 2017 TRINITY DRUG INDEX

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Executive Summary

This report marks the second installment of the Trinity Drug Index, a comprehensive evaluation of the performance of novel drugs approved by the FDA in 2014. In our inaugural Drug Index in 2016, we evaluated drugs approved by the FDA in 2013. Utilizing the same approach, each drug was assigned a score based on their commercial performance, therapeutic value, and R&D complexity. In addition to these drug rankings, we also provide commentary on the key trends observed:

Key findings of this report:

1 Immuno-oncology (I/O) agents represented two of the top three drugs of 2014: Keytruda led the way, followed by Harvoni and Opdivo. As observed in the inaugural Index, specialty agents rose to the top, confirming that targeting niche patient populations with high unmet need confers greater potential for commercial success compared to mass market products that are in therapeutic areas hampered by intense generic competition.

2 Anti-infective agents did not perform well commercially despite average to above average therapeutic scores. While these agents provide significant clinical value to society, their potential for commercial success is handicapped by the current pricing and reimbursement model for Qualified Infectious Disease (QIDP) products, especially in hospitals.

3 Orphan status does not guarantee a commercial home run. In fact, the commercial performance of orphan drugs approved in 2014 varied despite relatively high therapeutic values. Agents targeting hemophilia and idiopathic pulmonary fibrosis performed well while agents pursuing ultra-orphan indications did not perform as well, primarily because of prevalence-based limitations.

4 Achieving commercial success in mass markets continues to be challenging, as evidenced by the underperformance of several drugs in this category, some of which were even pulled from the market. However, a few drugs, including Trulicity and Farxiga, beat the odds by demonstrating a moderate degree of clinical differentiation that was bolstered by strong promotional firepower.

Introduction

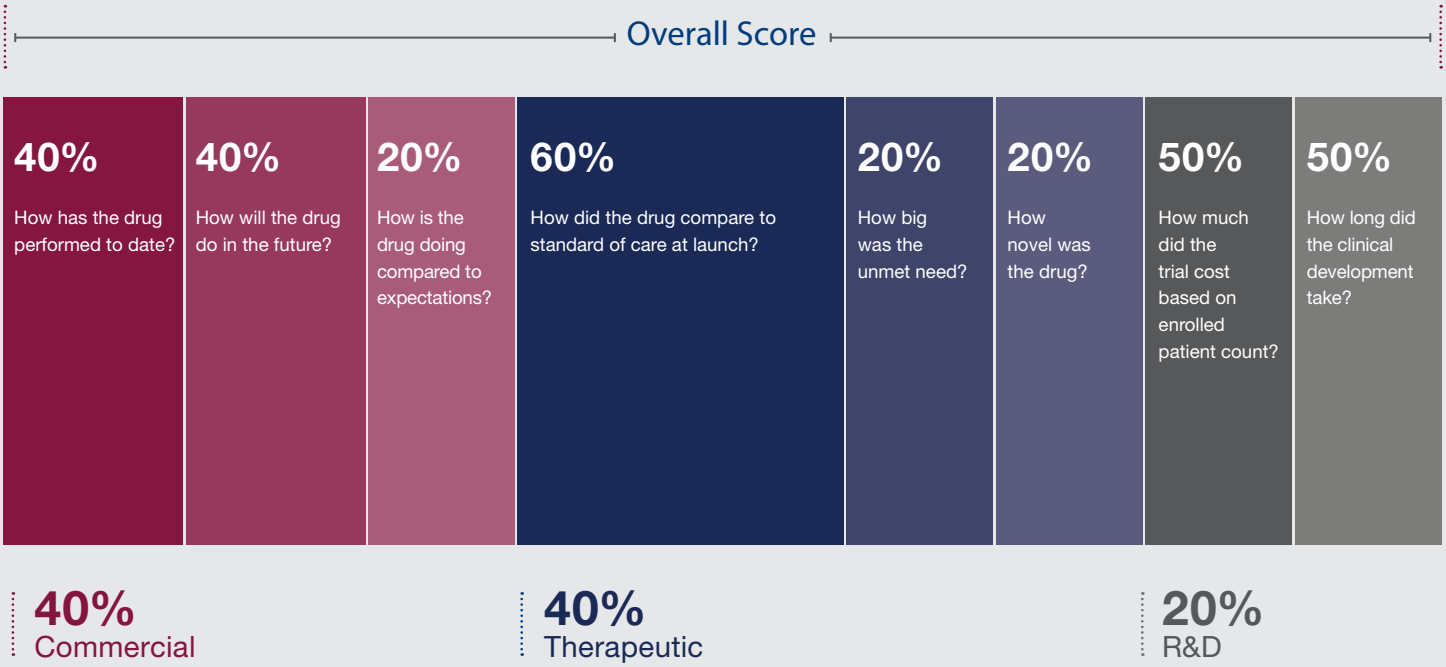
With increasing competition and tighter payer and regulatory controls, it has become more important for companies to prioritize certain investment opportunities to ensure an optimal return. One such way to inform strategic investment decisions is to leverage learnings from prior product launches. To this end, this report marks the second installment of the Trinity Drug Index, a comprehensive and reproducible framework to evaluate FDA-approved medications.

Here we report findings from the novel drugs approved in 2014: a banner year for drug approvals with 41 new drugs approved by CDER and 10 approved by CBER. This list includes 17 first in-class agents, 17 agents indicated for orphan diseases, 25 agents that were granted priority review, and 9 agents that received breakthrough designations.

We assessed all novel drugs approved in 2014 using a framework consisting of three categories: commercial performance, therapeutic value, and R&D investment. We assigned each drug a score in these three categories as well as an overall composite score. In addition to the drug ranking, we provide a perspective on trends observed in the current set of approvals as well as revisit industry developments described in the inaugural Trinity Drug Index. Select case studies are also included to tell the "story behind the story" in cases of observed under/overperformance.

FIGURE 1

Drug scoring methodology



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

Commercial performance was determined by the cumulative sales to date (through December 2016), projected future sales (2017-21), and performance relative to analyst forecasts. EvaluatePharma was the primary source for sales data.

Therapeutic value was based on an evaluation of the incremental clinical value in comparison to the standard of care (SOC) at the time of launch, the fulfillment of unmet need, and level of innovation. This data was obtained via an internal survey of 60+ life sciences experts at Trinity.

The R&D investment was based on the cost of randomized clinical trials (RCTs) and duration of clinical development. Trial cost was estimated based on the total number of enrolled patients (from the drug's NDA or BLA filing with approximate patient numbers from Post Market Requirements drawn from clinicaltrials.gov) and then adjusted for per-patient trial costs from Parexel's biopharmaceutical statistical sourcebook. Clinical development duration was calculated based on time from the first clinical study on clinicaltrials.gov until FDA approval.

Drug Ranking

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

TABLE 1

Drug score – Ratings on a 1-5 scale

Brand Name	Component Scores			Overall Score
	Therapeutic	Commercial	R&D	
KEYTRUDA	5	4.2	3.5	**4.4**
HARVONI	4.6	4.4	3.5	**4.3**
OPDIVO	5	4.4	2	**4.2**
ELOCTATE	4	3.2	5	**3.9**
ENTYVIO	4	4.2	2.5	**3.8**
ALPROLIX	4	3	4.5	**3.7**
ESBRIET	4.8	3.6	1.5	**3.7**
OTEZLA	4	4	1.5	**3.5**
CYRAMZA	4.2	2.8	3	**3.4**
LYNPARZA	4.4	2.2	3.5	**3.3**
OFEV	4.2	3.4	1.5	**3.3**
VIMIZIM	4.2	1.4	4.5	**3.1**
ZYKADIA	3.8	1.6	4.5	**3.1**
TRULICITY	3	3.6	2	**3.0**
PLEGRIDY	3.2	2.6	3	**2.9**
BLINCYTO	4.4	1.6	2.5	**2.9**
HYQVIA	2.8	2.2	4.5	**2.9**
ZERBAXA	4	1.2	3.5	**2.8**
CERDELGA	3.4	1.6	3.5	**2.7**
FARXIGA	2.8	3.2	1.5	**2.7**
VIEKIRA PAK	2.8	2.2	3.5	**2.7**
JUBLIA	2.6	2.6	3	**2.7**
NORTHERA	3.8	1.8	2	**2.6**
TRUMENBA	3.6	1.8	2	**2.6**
ZYDELIG	3.2	1.4	3.5	**2.5**
OBIZUR	3.2	1.6	3	**2.5**
BELEODAQ	3.8	1.2	2.5	**2.5**
JARDIANCE	2.8	2.4	2	**2.5**
RUCONEST	3	1.6	3	**2.4**
SIVEXTRO	3.6	1.2	2.5	**2.4**
MOVANTIK	3	1.6	2.5	**2.3**
RAPIVAB	3.2	1	2.5	**2.2**
BELSOMRA	2.8	1	3	**2.1**
ORBACTIV	3	1	2.5	**2.1**
HETLIOZ	2.6	1.4	2	**2.0**
TANZEUM	2.8	1.4	1.5	**2.0**
MYALEPT	2.4	1.6	1.5	**1.9**
DALVANCE	3	1	1.5	**1.9**
ZONTIVITY	2.4	1	2	**1.8**

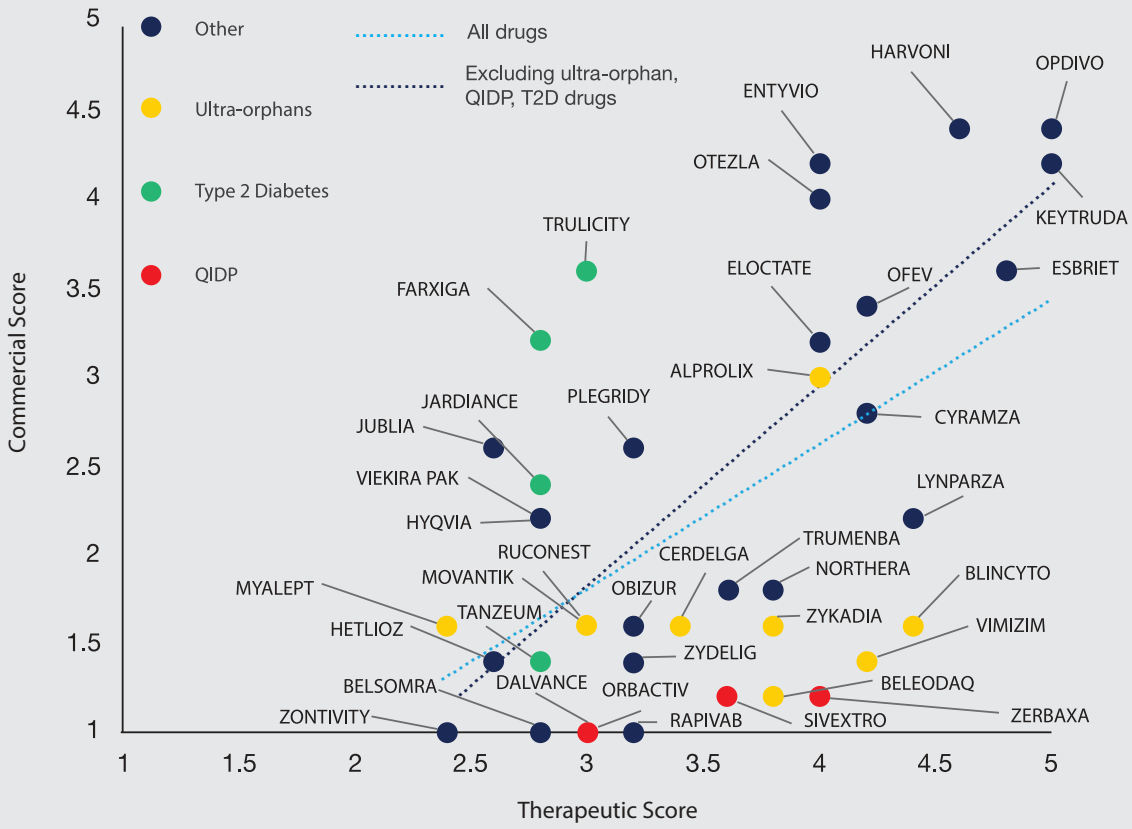
* The following compounds were excluded from the analysis because commercial performance data were not available or because they were not considered novel products: Akynzeo, Impavido, Gardasil 9, Kerydin, Striverdi Respimat, Sylvant, Xtoro, Ragwitek, Grastek and Oralair

Commercial Performance Versus Therapeutic Value

We assess the association between therapeutic value and commercial success by comparing the commercial and therapeutic scores from agents approved in 2014. Additionally, we look back at the comparison of commercial and therapeutic scores from the inaugural Index in 2016 to provide additional context around this association.

FIGURE 2

Comparison of therapeutic and commercial scores for drugs FDA-approved in 2014



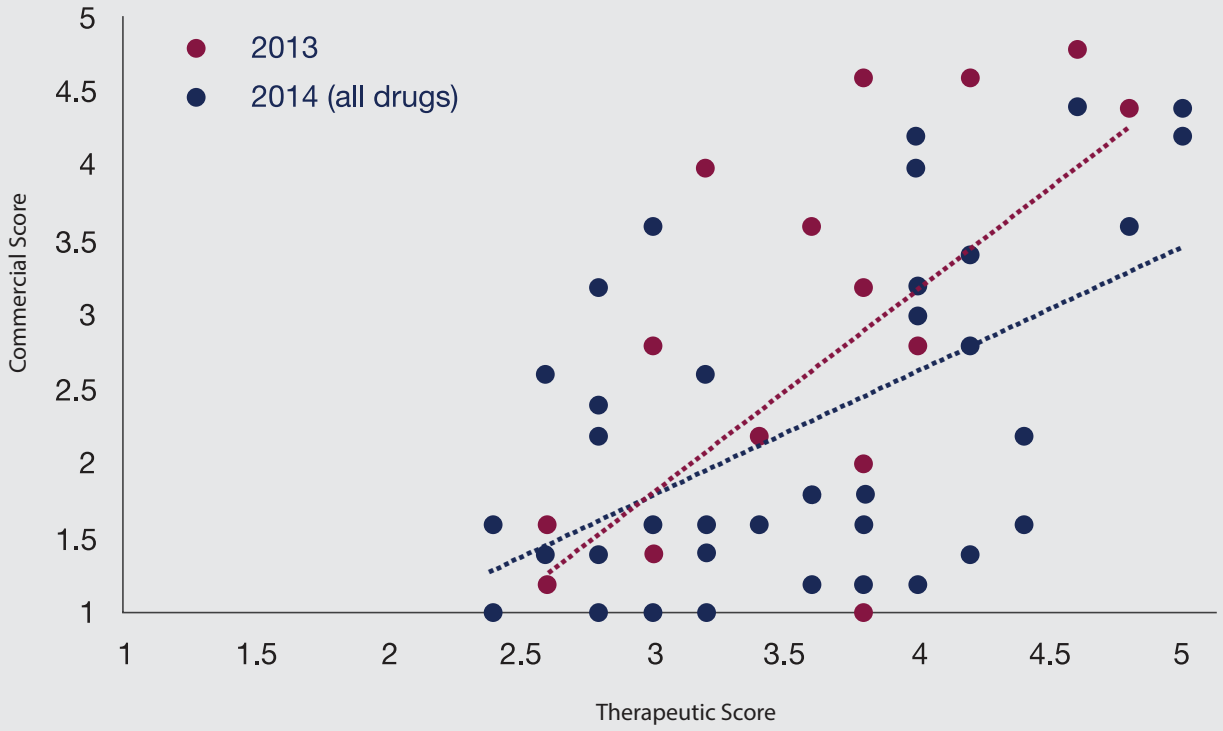
Similar to last year's Drug Index that scored drugs approved in 2013, this year we found that most drugs approved in 2014 fell along a linear trendline indicating that therapeutic value was closely associated with commercial performance.

Importantly, products that scored above the trendline achieved greater commercial success than their therapeutic value suggested while those below the trendline underperformed commercially.

Importantly, products that scored above the trendline achieved greater commercial performance than their therapeutic value suggested while those below the trendline underperformed commercially. In line with this, we observed that the I/O drugs, Opdivo and Keytruda, were associated with the greatest therapeutic and commercial scores, falling above the linear trendline. It is also worth noting a few under- and over-performing groups – in particular, the ultra-orphan drugs (with the exception of Alprolix whose commercial score outperformed all in this class) and the Qualified Infectious Disease Products (QIDP) showed limited commercial success almost independent of therapeutic value, while three type 2 diabetes drugs (Trulicity, Farxiga, Jardiance) that demonstrated mild/moderate therapeutic improvement over SOC resulted in significantly greater commercial success over their undifferentiated counterparts.

FIGURE 3

Comparison of therapeutic and commercial scores for drugs FDA-approved in 2013 or 2014



When we compared the relationship between therapeutic and commercial scores for all novel drugs approved in 2014 and those approved in 2013, we observed a stronger correlation between the therapeutic and commercial scores for 2013 drugs compared to the 2014 drugs. This was primarily due to the presence of several outlier drug classes in the 2014 drug rankings, including QIDP and ultra-orphan agents (commercial underperformers) and T2D drugs (commercial overperformers).

Key Observations

Top Performers: Keytruda rose to the top of the Trinity Drug Index with Harvoni and Opdivo trailing closely behind in 2nd and 3rd place, respectively

As observed in the previous turn of the Drug Index, innovative specialty products for high unmet need indications dominate the top of the charts.

Harvoni was an even bigger blockbuster than its predecessor Sovaldi, which ranked #1 on the 2016 installment of the Drug Index.

Opdivo received a lower overall score compared to Keytruda due to lower R&D score, despite demonstrating comparable therapeutic benefit.[2]

[1] R&D Score was calculated based on the cost-adjusted number of patients dosed in clinical trials and the time required for clinical development (defined as the time between the first phase I study and FDA Approval). According to clinicaltrials.gov, the first reported clinical study for Opdivo began in 2006 whereas the first reported clinical study for Keytruda began in 2011. This difference contributed to the difference in R&D score, resulting in Keytruda taking the higher spot in our rankings.

Drugs that are approved in multiple indications are intrinsically more likely to be commercially durable

Drugs targeting more than one indication tend to rise to the top, in terms of commercial success, given access to a larger patient pool and the ability of follow-on indications to benefit from the existing indication (and vice versa).

Developing products for multiple indications is a popular brand growth strategy as it allows manufacturers to de-risk the follow-on indications. However, if the initial price is set in relation to a condition with lower therapeutic need, higher-value follow-on indications may not be as profitable due to limited differential pricing power. Sequencing indications is therefore a critical strategic decision for brands that have multiple indication options.

Timing of M&A activity may impact the commercial success of a drug and should be taken into consideration in an industry that is increasingly reliant on external innovation

As several mid-large firms look outside their own walls for innovation, M&A activity has spiked over the past few years. Unsurprisingly, of the drugs approved in 2014, ~65% were either in-licensed or acquired.

5 of these products were acquired during the regulatory review process or after FDA approval – Esbriet, Northera, Dalvance, Sivextro, and Zerbaxa – and all but Esbriet underperformed.

While it is common to acquire or in-license during the later stages of development, this observation may be a signal that the likelihood of a successful product decreases as the acquisition nears the time of market entry, a period that should be focused on meeting strategic launch objectives in a disruption-free environment.

Furthermore, regulatory success does not guarantee commercial success and may not be the most appropriate value inflection point for triggering an acquisition.

An orphan indication with a hefty price tag does not necessarily translate into a slam dunk in terms of commercial success

Expedited clinical and regulatory pathways as well as the need for relatively small commercial infrastructure have motivated the life sciences industry to shift its focus towards developing products for niche patient populations. In 2014, ~41% of new drugs were approved to treat orphan diseases.

While several orphan drugs achieved high commercial scores (Eloctate, Alprolix, Esbriet, Ofev), others were not able to achieve the commercial success expected based on their therapeutic value (Vimizim, Beleodaq, Cerdelga). More often than not, these unsuccessful products fell into the “ultra-orphan” category (prevalence of <1:30K).

While the commercial success of “ultra-orphans” may be intrinsically limited by the size of the market itself, their underperformance may also be an indicator of limited clinical differentiation.

The primary care market continues to be a tough nut to crack. To be successful, mass market products must demonstrate at least moderate therapeutic innovation coupled with substantial marketing power

In crowded and highly genericized PCP-driven markets, launching a “me too” product is rarely a commercially viable strategy. Furthermore, leveraging marketing power to bolster “me too” products is generally ineffective as evidenced by the underperformance of products such as Belsomra (insomnia), Zontivity (reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral arterial disease), and Tanzeum (improve glycemic control in T2D) that were developed by big players in the industry.

Exceptions to the above trend include diabetes drugs Trulicity and Farxiga that achieved strong commercial success because they demonstrated moderate clinical differentiation (in the form of dosing convenience) and were heavily promoted by industry giants Eli Lilly and AstraZeneca, respectively. Specifically, intensive DTC marketing allowed Trulicity, a product that provided a weekly dosing option in a market with daily regimens, to acquire significant commercial success.

Case Studies

To shed light on why products over- or under-performed commercially relative to their therapeutic value, Trinity has selected three cases studies: I/O agents (overperformers), QIDPs (underperformers), and Ultra-Orphan agents (underperformers)

I/O Agents

The first PD-1 targeting I/O therapeutic, Keytruda, was approved in September 2014 for the treatment of advanced or unresectable melanoma patients who are no longer responding to other drugs. Opdivo, another PD-1 targeting I/O therapeutic was approved in December 2014 for the same indication. Both Keytruda and Opdivo have been strong commercial performers since their launch.

The approval of PD-1 inhibiting I/O agents, including Keytruda and Opdivo, was thought to be the beginning of a revolution in the way that cancers were treated — 'unlocking' the immune system to attack previously hard to treat disease. Compared to TAFINLAR/MEKINIST and chemotherapy, the standard of care for BRAF positive and negative melanoma, respectively, the I/O agents were a marked improvement in safety and efficacy. We awarded Keytruda and Opdivo the highest therapeutic values in this report based on the efficacy they demonstrated in advanced melanoma and were expected to demonstrate in other cancers, including various forms of lung cancer. In our commercial versus therapeutic score analysis, we see that both I/O agents achieved higher commercial scores than might be expected. This success was driven by the follow-on indications in major tumor types. To that end, unlocking additional value by having a "product as a pipeline" continues to be an excellent strategy to achieve greater commercial performance.

In our commercial versus therapeutic score analysis, we see that both I/O agents achieved higher commercial scores than might be expected.

Qualified Infectious Disease Products

Several Qualified Infectious Disease Products were approved in 2014, marking a significant year in the development of novel agents for the multi-drug resistant (MDR) pathogens that represent an enormous health risk to society and require effective treatments. Per the GAIN act, a 2013 bill focused on incentivizing the development of antibiotics for certain high priority MDR pathogens, manufacturers developing treatment agents are given market exclusivity and fast track and priority review status for QIDPs. Additionally, the proposed READI act includes tax credits for 50% of the cost of clinical testing for qualifying agents. Despite the need for these life-saving therapeutics, the current reimbursement structure, specifically DRG reimbursement for inpatients (the primary patient targets for these products), is not set up to value QIDPs appropriately given limited utilization latitude. As such, these agents did not score well on our commercial scale.

Zerbaxa, approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), has not generated revenue in line with what was expected given its relatively high therapeutic value. Zerbaxa is a combination of a 5th generation cephalosporin agent and a β-lactamase inhibitor with notable efficacy against gram-negative agents such as Pseudomonas Aeruginosa, a pathogen for which there are few effective treatments. It was viewed as a clinical breakthrough due to its demonstrated in-vitro and in-vivo efficacy against these gram-negative bacteria. In addition to facing headwinds caused by an unfavorable reimbursement structure, Zerbaxa was part of a portfolio of products that was launched immediately following an acquisition by Merck. Zerbaxa launched into a market that did not fully appreciate the benefits of the product over a similar antibiotic, AvyCaz, and may have benefited from additional messaging support. Despite the hurdles facing QIDPs, we believe that there is still an opportunity for these products to be successful if they are approved for large indications and their value is messaged appropriately.

Ultra-Orphan Agents

Agents indicated for diseases with prevalence less than 1/30,000 are considered to be "ultra-orphan" drugs. In 2014, we saw the approval of eight of these agents for a variety of indications. These ultra-orphan agents (and the relatively more common orphan diseases, with prevalence up to 200,000 in the US) typically receive regulatory incentives, in the form of a 7-year exclusivity period after regulatory approval, waiving of the FDA user fee, a priority review voucher for other products (if the rare disease indication is pediatric), and a 50% tax credit on clinical expenses. However, the limited number of treatable patients and pricing pressure from private and national payers typically limits the revenue potential of

this class of agents. Accordingly, we see that nearly all ultra-orphan drugs have low commercial scores relative to their therapeutic scores, placing them near the bottom of our commercial performance versus therapeutic value plot. The small to midsize revenue opportunity for these agents makes them disproportionately valuable to smaller companies which can develop these products with leaner infrastructures. The potential to leverage regulatory incentives makes development of these orphan and ultra-orphan products that much more affordable and attractive to smaller companies that have different revenue expectations than large multi-national pharmaceutical and biotech companies which are financially obligated to develop drugs that achieve revenues above a certain threshold.

We noticed that some of these agents (Vimizim and Zykadia) received relatively high R&D scores which was a function of the low patient numbers and years required to put forth an acceptable clinical package for FDA approval. On the other hand, the R&D scores for other ultra-orphan agents fell in the middle of the pack of drugs that we analyzed in our study. This is evidence of the stringent regulatory burden that FDA upholds, even in ultra-rare diseases where clinical development is incentivized by the government. One notable caveat is that some of these agents also received breakthrough designation which can reduce the regulatory burden to approval, although sponsors must eventually submit all required clinical data to satisfy FDA's regulatory requirements.

While commercial success may be elusive, we believe that orphan and ultra-orphan agents are important therapeutics that provide treatment options for patients that desperately need them and provide ancillary benefits (e.g., review vouchers and tax credits) to the manufacturer beyond revenue.

Looking Ahead to 2015 Approvals

We are excited to look forward to the next edition of the Trinity Index: 2015 was a record-setting year, with 45 NME approvals by CDER as well as a number of CBER approvals. The wealth of new data will help to further refine our observations of the complex relationship between therapeutic value and commercial success: does the linear relationship hold well in most cases, or are there a significant number of distinct "outlier" drug classes? Additionally, we expect to discuss a variety of other themes associated with the new approvals and also build upon prior reports:

Several highly effective first-in-class drugs for mass market conditions have been approved in 2015 (Entresto for heart failure, Repatha and Praluent for elevated cholesterol). Will they be able to convert these therapeutic advantages into commercial success in light of increased payer scrutiny? What will be the initial track record of outcomes-based pricing?

14 out of the 45 CDER approvals (31%) in 2015 were in oncology, including four in multiple myeloma alone. What are the key determinants of success in this high unmet need space?

FDA has been leveraging various tools in its regulatory arsenal to speed up drug approvals: Fast Track, Accelerated Approval, Breakthrough designation, Priority Review, and Orphan Drug designation. It has been reported that drugs receiving expedited review status are indeed significantly differentiated; for example, drugs that underwent Priority Review provide larger health gains (measured in quality-adjusted life years)[2].

Challenges in achieving commercial success in ultra-orphan conditions will remain of interest in 2015, with approvals of drugs such as Xuriden for hereditary orotic aciduria (reported in approximately 20 patients worldwide[3]) and Unituxin for high-risk neuroblastoma (about 700 cases per year[4]). The impact of the FDA Priority Review Voucher program will be considered.

As life sciences companies continue to navigate an ever-changing marketplace, one thing is certain – clearly and effectively demonstrating the value of novel agents is essential to garnering commercial success. While therapeutic value often leads to commercial success, we continue to observe individual drugs and therapeutic classes that appear to buck the trend. We also recognize that success can be achieved in all therapeutic areas, even with the unique challenges presented by certain markets. The key to executing a winning clinical and commercial strategy is to establish a strong understanding of emerging risks and challenges tailored to the situation and to pull the right levers to unlock the product's potential.

[2] Drugs Cleared Through the FDA's Expedited Review Offer Greater Gains Than Drugs Approved By Conventional Process, Chambers JD, Health Aff, 36 (2017)
[3] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm457867.htm
[4] https://www.cancer.org/cancer/neuroblastoma/about/key-statistics.html