WHITE PAPER

LEVERAGING FDA'S ACCELERATED PATHWAYS FOR MARKET ADVANTAGE

Over the past 15 years, the FDA and Congress developed several accelerated pathways to provide incentives for manufacturers to develop innovative new drugs to treat conditions with substantial unmet need. The objective of this white paper is to describe recent trends in the use of the FDA's accelerated pathways and to examine the market advantage associated with these pathways, particularly in oncology.

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OVERVIEW OF ACCELERATED PATHWAYS

Several acts of legislation overhauled the regulatory process for drug approvals in the US and enabled the FDA to create expedited programs and special designations to stimulate and accelerate novel drug development (Table 1). Collectively, these programs and designations have become known in the industry as "accelerated pathways."

Different accelerated pathways focus on different characteristics of drugs and target indications, and drugs may qualify for more than one pathway. The focus and benefits of the different pathways are summarized in Table 2.

AstraZeneca's TAGRISSO® (osimertinib) is an example of how a manufacturer can use multiple pathways to significantly accelerate development timelines.

TAGRISSO® was granted four accelerated pathways (Figure 1). The IND for TAGRISSO® was filed in June 2013, and TAGRISSO® was awarded fast track designation in November 2013. Based on its Phase 1 data showing disease control in 94% of patients, TAGRISSO® was granted breakthrough designation in April 2014.[1] In September 2014, the FDA granted TAGRISSO® orphan drug designation. The NDA for TAGRISSO® was filed on a rolling basis, with the first portion submitted January 2015 and the third and final portion submitted in June 2015, and TAGRISSO® was awarded priority review. Finally, in November 2015, TAGRISSO® was granted accelerated approval for the treatment of EGFR T790M mutation-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.[2] Approval was granted based on two Phase II studies showing a complete or partial reduction in tumor size (i.e., objective response

Table 1. Legislation Establishing FDA Accelerated Pathways

	Orphan Drug Act 1983	PDUFA I 1992	FDAMA (under PDUFA II) 1997	FDASIA (under PDUFA V) 2012
Purpose	• To simulate interest in drug development for orphan diseases that affect <200,000 people	• To address "drug lag" in the US	• To recognize the changes in which FDA will operate in the 21st century	• To expand FDA's authorities, promote innovation, and increase stakeholder involvement
Key Elements	• Provided incentives to manufacturers: – Development grants – 50% tax credits for clinical trial expenses – 7 year market exclusivity	• Authorized collection of user fees to increase scientific staffing and upgrade information technology systems • Reauthorized every 5 years	• Established: – Clinicaltrials.gov – Biologic License Application (BLA)	• New user fees for generic and biosimilar drugs • Incentives for antibiotics (GAIN Act)
Accelerated Pathways Introduced	• Orphan drug designation	• Priority review	• Fast track designation	• Breakthrough designation • QIDP designation • Accelerated approval • Rare pediatric disease priority review voucher

Source: FDA Guidance on Expedited Programs for Serious Conditions, May 2014.

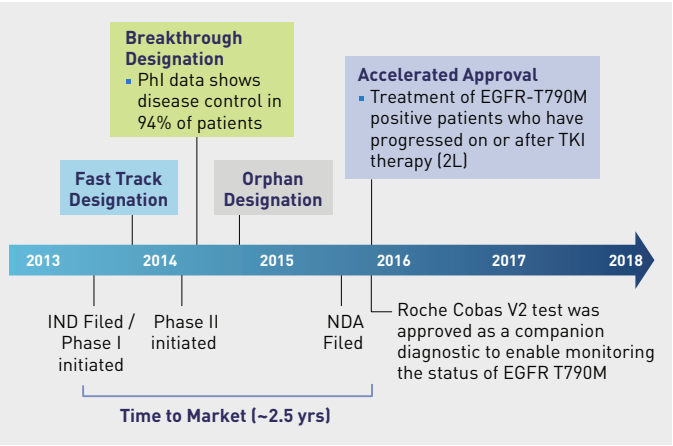
Table 2. Summary of FDA Accelerated Pathways

Pathway	Focus	Benefits	Impact
Orphan Designation	• Drugs that target rare diseases or conditions affecting <200,000 people in the US	• FDA guidance on protocol development for clinical trials • Development grants • Small trial sizes • Eligibility for accelerated approval or priority review • PDUFA fees waiver • 7 years of market exclusivity • Tax credits • Priority review vouchers for rare pediatric disease approvals	• As of 2015, 437 drugs were approved with orphan designation (compared to 10 in 1982)
Priority Review[1]	• Drugs that provide a significant improvement in safety or effectiveness for a serious condition	• Shortened review of marketing application (6 months vs. 10-month standard review)	• Median time to approval was reduced from 19 (1993) to 10 months (2012)
Fast Track Designation	• Drugs that demonstrate the potential to address unmet medical needs for a serious or life-threatening disease or condition	• Frequent interactions with the FDA and the possibility for rolling review and/or priority review	• As of 2015, 114 drugs were approved with fast track
Breakthrough Designation	• Drugs that target a serious or life-threatening disease or condition, where preliminary clinical evidence indicates substantial improvement over existing therapies	• Intensive guidance on efficient clinical trial design, frequent interaction with the FDA, and the possibility for rolling review and/or priority review	• As of 2015, 22 drugs were approved with BTD
Qualified Infectious Disease Product (QIDP)[2]	• Antibacterial and antifungal drugs intended to treat serious and life-threatening infections	• Potential eligibility for fast track designation and, priority review upon submission of an NDA or supplement for that use	• As of 2015, 6 drugs were approved with QIDP
Accelerated Approval	• Drugs that target a serious or life-threatening disease or condition, where a surrogate endpoint is reasonably likely to predict clinical benefit	• Early approval based on an effect of the treatment on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• As of 2015, 74 drugs were approved with AA

1. Not explicitly an accelerated pathway, but strongly associated with use of accelerated pathways
2. Not analyzed in this paper since priority review is usually applied for at the time of NDA filing rather than during development

Source: FDA Guidance on Expedited Programs for Serious Conditions May 2014, PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2015/2016.

Figure 1. Regulatory Timeline for TAGRISSO®



Source: Health Advances analysis, FDA, company press releases.

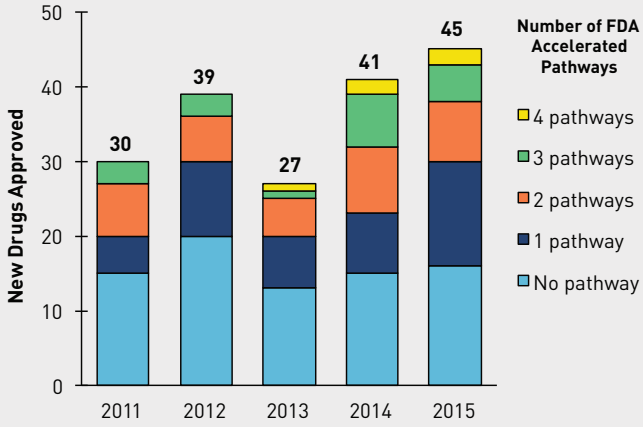
rate), a surrogate endpoint. By leveraging all possible accelerated pathways and executing a highly efficient development plan, TAGRISSO® was able to compress its clinical development and regulatory approval timelines, reaching the market only 2.5 years after IND filing, a remarkable achievement compared to the industry average of approximatley 8 years.

RECENT TRENDS IN THE USE OF ACCELERATED PATHWAYS

Of the 182 new drugs approved by the FDA between 2011 and 2015, 103 (57%) drugs participated in at least one of the FDA's accelerated pathways. 71 drugs received orphan drug status, 69 drugs received fast track designation, 23 drugs received accelerated approval, 22 drugs received breakthrough designation, and 6 drugs received QIDP designation.[3] The stacking of designations has increased over time, especially following the introduction of breakthrough designation in 2013 (Figure 2).

Oncology drugs, which account for a substantial share of new drug approvals in recent years, received the majority of accelerated pathway designations (Figure 3). Stacking multiple accelerated pathways was a common trend among oncology drugs. Among oncology drugs receiving accelerated approval, all but one (IBRANCE® (palbociclib) for ER+ breast cancer) were orphan drugs, and most also received fast track designation, breakthrough designation, or both. The disease areas in which accelerated pathways were the next most common were anti-infectives, reflecting FDA recognition of the need for more antibiotic options in the face of increasing drug resistance, followed by digestive and metabolic conditions.

Figure 2. Stacking of Accelerated Pathways among New Drug Approvals in FDA*



*Pathways tracked include orphan, fast track, breakthrough, qualified infectious disease product, and accelerated approval.

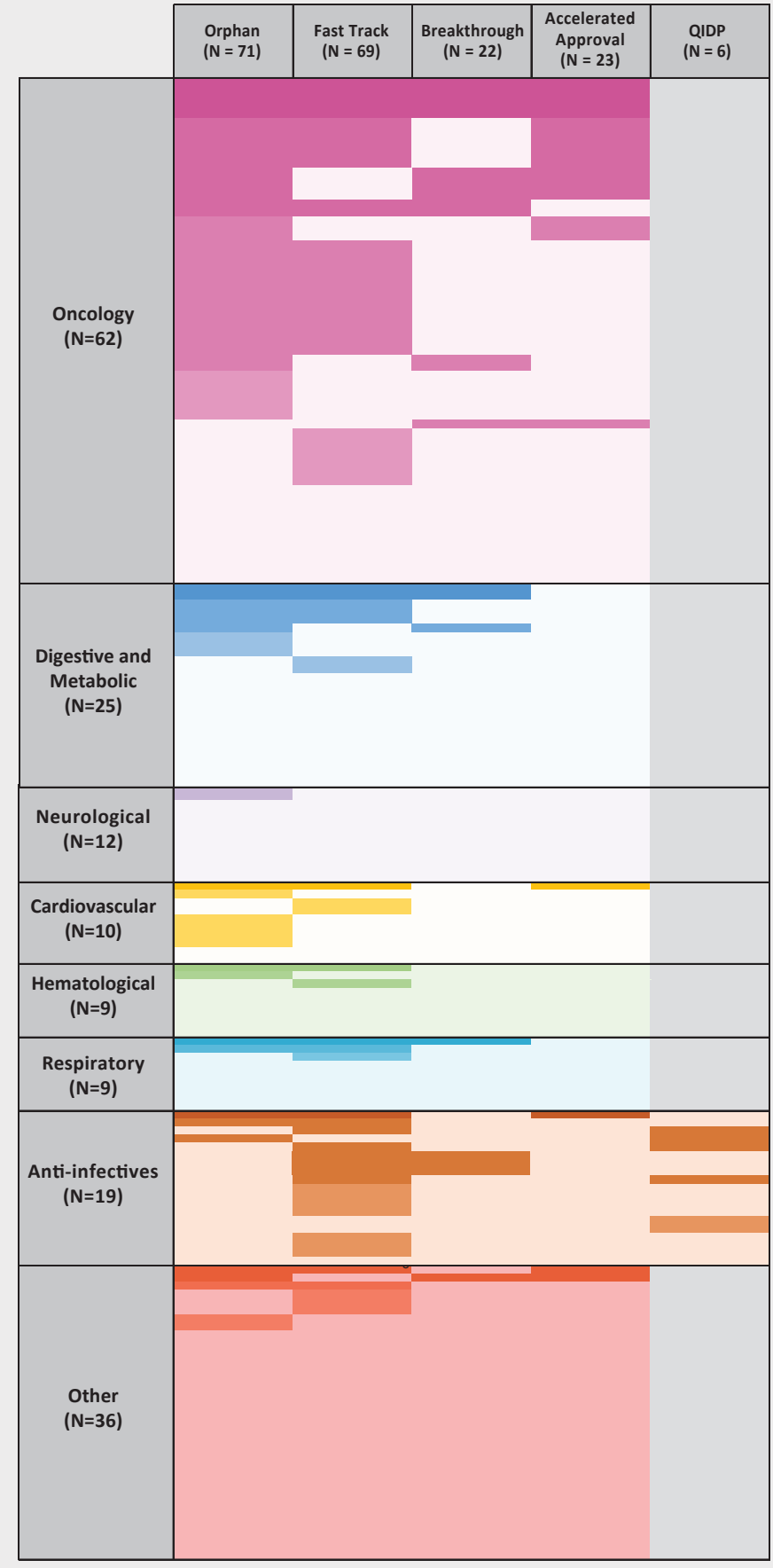
Source: Health Advances analysis, FDA New Drug Summary (2011-2015).

MARKET ADVANTAGES OF ACCELERATED PATHWAYS

Regression analysis of all oncology drugs approved between 2011 and 2015 shows that breakthrough designation is associated with commercial benefits in terms of shorter time to market, defined as time from IND filing to FDA approval, and higher projected peak sales, based on EvaluatePharma® projections (Figure 4). Specifically, breakthrough designation is associated with higher projected peak sales of over $1.0B ($p<0.01$) and reduced time to market by ~2.8 years ($p=0.04$). Fast track designations also have positive effects, but these are not statistically significant. Accelerated approval does not show statistically measurable effects, but this is likely due to designation stacking: at least 86% of breakthrough designation oncology drugs also received fast track designation, accelerated approval, or both, so the benefits of accelerated approval are captured in the benefits ascribed to the other pathways.[4]

When the stacking of accelerated pathways was considered, oncology drugs that received fast track designation, breakthrough designation, and accelerated approval were associated with higher projected peak sales of nearly $1.4B ($p = 0.01$) relative to drugs without these stacked designations. The stacking of breakthrough designation and accelerated approval was associated with shorter time to market than oncology drugs without this stacking by ~4.4 years ($p=0.03$). For example, KEYTRUDA® (pembrolizumab), which received

Figure 3. Accelerated Pathways and Combinations for New Drug Approvals, By Disease Area



Source: Health Advances analysis, FDA New Drug Summary (2011-2015).

both breakthrough designation and accelerated approval, is projected to attain sales of ~$6B by 2022, and it obtained FDA approval within 3.7 years of IND filing. Another oncology drug, IMBRUVICA®, which received fast track designation, breakthrough designation, and accelerated approval, is projected to attain sales of ~$4B by 2022, and it received FDA approval within 5.2 years of IND filing.[5]

USE OF ACCELERATED PATHWAYS FOR MARKET ADVANTAGE: CASE STUDY OF PD-1 DRUGS

The strategic application and sequencing of accelerated pathways can provide market advantage in situations where competitor products cannot be easily differentiated. One example is the class of PD-1/PD-L1 checkpoint inhibitors, breakthrough immuno-oncology therapies that can significantly improve patient survival and tumor response rates relative to current regimens. While several PD-1 drugs are marketed or are in development, studies to-date have suggested roughly comparable efficacy among competing agents in this class.

The two leading anti-PD-1 agents, BMS' OPDIVO® (nivolumab) and Merck's KEYTRUDA® (pembrolizumab), were able to stack multiple accelerated pathways to reach the market more quickly and obtain competitive advantage over other anti-PD-1 drugs in the key indications of melanoma and NSCLC. KEYTRUDA® and OPDIVO® received accelerated approvals for melanoma within a few months of each other in 2014.[6] During clinical development, both drugs received breakthrough designations based on preliminary clinical evidence that the drugs provided substantial

Table 3. PD-1 Drugs in Development with a Breakthrough Designation for their Lead Indication

Drug	Manufacturer	Lead Indications	BTD Date	Expected Approval Timeline
Avelumab	Pfizer	Merkel cell carcinoma	November 2015	Expected NDAfiling: H2 2016
Durvalumab	AstraZeneca	Bladder cancer	February 2016	Phase III primary completion: November 2017

*Only represents indications that received breakthrough designation; does not include all indications in development.

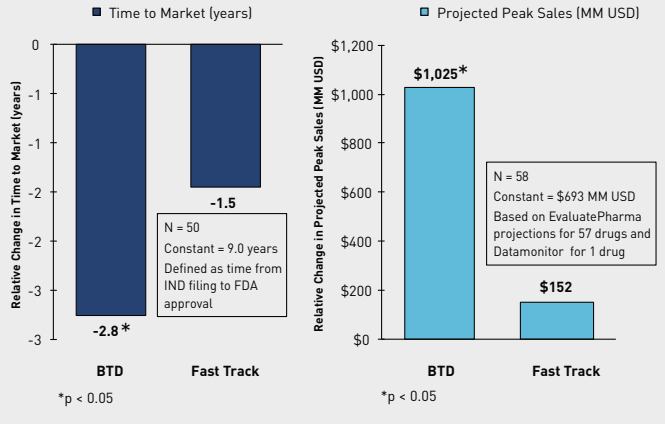
Source: FDA, company press releases and investor reports.

clinical improvement over available therapies (Figure 5). Breakthrough designation enabled the companies to obtain more intensive FDA guidance on clinical trial design. For example, both OPDIVO® and KEYTRUDA® received accelerated approvals in advanced melanoma based on substantial improvements observed in surrogate endpoints such as overall response rate (ORR).[7] Additionally, the FDA advised on the use of biomarkers, such as the approval of KEYTRUDA® for the treatment of PD-L1 positive NSCLC patients with a companion diagnostic to monitor PD-L1 status in patients. This high level of FDA engagement was likely a key factor to enable accelerated approval based on surrogate endpoints, which saved at least 2 years in time to market. Both drugs also received orphan designations in patients with advanced melanoma with disease progression despite initial treatment with either YERVOY® (ipilimumab) or a BRAF inhibitor (for BRAF V600 positive patients).[8]

Since KEYTRUDA® and OPDIVO® have been approved for melanoma and NSCLC, any new drugs that seek to enter these indications face a higher barrier to entry. Thus, later PD-1 entrants such Merck KGaA and Pfizer's avelumab and AstraZeneca's durvalumab are currently leveraging breakthrough designations in different indications (Table 3). For example, durvalumab obtained breakthrough designation in bladder cancer, while avelumab obtained breakthrough designation in Merkel cell carcinoma based on early efficacy data in these high unmet need conditions.

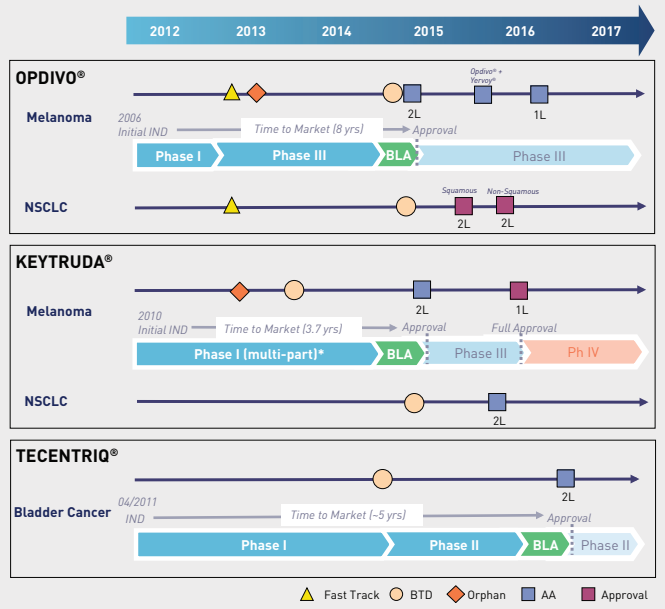
While market factors could affect the sustainability of market advantage, accelerated pathways have certainly helped prime the commercial success of breakthrough drugs in the PD-1 class.

Figure 4. Regression Analysis of Commercial Benefits for New Drug Approvals (2011-2015)



Source: Health Advances analysis, FDA New Drug Summaries (2011-2015), FDA Summary Review Documents, Sales Projections from EvaluatePharma®.

Figure 5. PD-1 Drugs that were FDA Approved with Multiple Accelerated Pathways*



* In addition, OPDIVO® has been approved in second-line (2L) renal cell carcinoma and 2L Hodgkin lymphoma, and it is currently in development for head and neck cancer. KEYTRUDA® is currently in development for colorectal cancer and classical Hodgkin lymphoma. TECENTRIQ® is currently in development for NSCLC.

Source: FDA Summary Review Documents, company press releases.

FUTURE CONSIDERATIONS

In conclusion, companies developing breakthrough oncology drugs have been able to successfully leverage the FDA's accelerated pathways to reach the market more quickly and to enhance their commercial prospects. The lessons learned from the PD-1 class will be important for several emerging breakthrough

therapies in oncology such as CAR-T, as well as novel therapies in multiple indications that utilize gene editing such as through CRISPR. Companies developing new drugs may be able to accelerate time to market and achieve first-mover advantage through a carefully-crafted strategy of prioritizing indications with greater potential to leverage accelerated pathways.

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