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White paper

LAUNCH EXCELLENCE VI

Launch Excellence in a disrupted world: challenges and opportunity

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INTRODUCTION

It is now very clear that the global pharmaceutical industry is in a period of significant change, and with it the environment for innovative product launch. Molecular innovation is being supplemented, and in some instances could be replaced, by other forms of innovation, including highly individualised and procedure-like cell and gene therapies, prescription digital therapeutics, or innovation on existing, off-patent molecules.

The rise of specialty as the key value growth driver of the developed markets, has already created a situation where most launches, and almost 100% of the most successful launches, are for globally small, sometimes tiny, patient populations. 2018 was the first year in which both the FDA and the EMA approved more Orphan medicines, for rare diseases, than mainstream products. Mass market common, chronic diseases of the elderly don't drive pharmaceutical value growth anymore; increasingly, the pipeline, the launches, and the pharmaceutical industry's value growth is a product of high value therapies for small patient populations.

IQVIA is in the unique position of having the largest global database on past launch performance available, giving us an unmatched quantitative evidence base in research on Launch. In this white paper, we make extensive use of our core MIDAS database of global launch sales, as well as, when we search into the past of launch, the MIDAS based World Review. In all cases, note that the value figures provided are at list price, pre-rebates and discounts, and at ex-manufacturer level.

For our white paper, we focus on innovative, protected new products, defining these as New Active Substances (NAS). New Active Substances

Figure 1: How has the launch environment changed?

	Past	Present	Future
Stakeholder environment	Simple: Prescribers, then payers	Complex: interconnected web of multiple stakeholders, Payers dominant	Complex: personalised and patient journey based
Promotional model	Share of Voice, Rep lead	Multichannel, digital share higher for more successful launches	Orchestrated for individual prescriber journeys
Launch positioning	First line, mass market	Later line, segmentation	Companion diagnostic, biomarker, genotype defined or otherwise personalised
Payer focus	Price	Value, health technology assessment	Outcomes, Real World Evidence, new funding approaches
Launch type	Two types of launch: small molecule or biologic	Cell and gene therapies lead ATMPs, molecules joined by digital launches	Further new types of launch achieve commercial success
Company type	Most commercially successful launches by top 10 Pharma	Small/mid sized Pharma also launching successful specialty	Non-conventional pharma companies launch products

are novel and innovative active ingredients, small molecule, biologic or other, which have been launched on the global pharmaceutical market for the first time.

In our Launch Excellence series, we have defined the launch period as the first two years of a launch's commercial life in a country, from the point sales first appear in MIDAS. Some argue the launch period can only start once a certain level of market access is obtained, although since market access processes and outcomes are highly variable by country this makes objective agreement on when "proper" launch has started across countries complex. For Thought Leadership, we've chosen objectivity and simplicity. However, we accept that the two-year initial launch period is only the start of many launches, albeit, because of the six-month window of opportunity which we will discuss later, an extremely important one.

For multi-indicational products, launch is no longer a one-off event. In addition, faster approvals on earlier clinical data and longer journeys to full market access, because of extended real world assessment, create an extended launch period. There's also consideration of the full lifetime value of a pharmaceutical launch. Unusual patterns of uptake, as for Hepatitis C products, create spectacular early launch performance but also rapid declines in performance. These products may have the steepest uptakes ever, but they are not the most valuable launches ever.

The core of the Launch Excellence series examines the launches, which have been the most commercially successful in the recent timeframe, relative to their contemporaneous launch peers to each major launch country. By using largely consistent data and analytics since 2007 we build a unique, quantified view of the way in which commercial success has changed over years. Examining launches on a country by country basis means that we can understand the most common reasons why launches do not reach their full potential.

Of the top 20 products with the greatest life-time sales, 8 are primary care and 12 are specialty -- specialty is winning in the long term, even amongst older products.

THE PAST

THE MOST SUCCESSFUL LAUNCHES OF ALL TIME

What is the ultimate measure of a Launch's Excellence? Steep initial uptake curves, consistency of performance across major markets, and optimisation on the available opportunity are all extremely important. In the long view, however, the final assessment may be the total revenues the launch accrues during its full lifetime on the market. IQVIA can undertake this final assessment using its very long running World Review, published since the 1970s. More recent launches have an incomplete life, so we chose only launches for which we had a minimum of ten year's World Review recorded sales.

Despite the rise of specialty as the key launch value driver, it is still Lipitor, with an estimated $160bn of gross lifetime sales, that sits in the leader position of best-selling product of all time. But of the top 20, eight are primary care, and 12 specialty- even with these necessarily older products, specialty is winning in the long term. The world's current largest selling product, Humira, is second in absolute lifetime sales and a specialty product ($145bn).

Although the very best top sellers were also Excellent by our Launch Excellence criteria, the top sellers of all time can be either tortoises or hares - Launch Excellence uncovers, in the two-year evaluation period, the hares. Slower burn "tortoises" are also among the biggest selling products ever, notably Crestor, with an estimated

$75bn of gross lifetime sales. Very commercially successful "tortoises" fail on Excellence criteria most often on measures of promotional out-performance, suggesting exceptionally high levels of promotional investment in the first two years of launch. This investment may also be accompanied by significant investment elsewhere. Crestor was not, by our two-year uptake criteria of previously Launch Excellences, an excellent launch. Consistent, careful investment over a period of a decade, including the GALAXY series of clinical trials which was, at the time, the largest patient number set of trials around a single product, have, in the longer term, paid off. However, such a lengthy and sustained level of investment will delay profitability.

THE CLASS OF 2019

SPECIALTY DOMINATES ONCE MORE, IN BOTH ACHIEVEMENT AND IN RETURN ON (MEASURABLE) INVESTMENT

Over six Launch Excellence white papers we have sought balance between consistency of analysis and adaptation to the changing realities of the launch environment- the biggest change being the vertiginous rise in the number and commercial impact of specialty launches, especially oncologicals.

By Launch Excellence V, specialty products out-performed primary care launches on all Launch Excellence measures, and only specialty products were in the elite group of launches which performed consistently excellently across countries. Primary care launches operate in a far more constrained environment, and at present the overall opportunity for these products is often reduced. Nonetheless, unmet need still exists in primary care, innovation is possible and launches necessary, as outlined in detail in a recent IQVIA white paper[1]. In Launch Excellence VI we therefore decided to separate specialty from primary care launches, comparing Launch Excellence only within each group.

In previous Launch Excellence studies, we used launch's market share, quarter on quarter, as a basis for analysis. As specialty launches came to dominate, defining the market which the launch entered became increasingly challenging, and for many oncology launches, impossible.

Figure 2: Key parameters of the present launch environment

80%+ of launches don't improve on their first 6 months

Only 1 in 5 launches improve significantly between 6 months and 2 years

Only 1 in 10 or fewer of the remainder improve between 6 months and 5 years

<10% of launches are Excellent

By the IQVIA criteria, 2 years into launch, 8% of specialty launches demonstrate Excellence in 2 or more of the US, top 5 Europe and Japan, and only 5% of primary care launches

1 company has multiple launches with consistent Excellence

Historically, there's an inverse relationship between the number of launches a company has in a given period, and the percentage that are Excellent by the IQVIA criteria - one major exception

86% of launch sales from 7 countries

Two years into launch by country, 86% of sales value comes from the seven lead markets: US, top 5 Europe, Japan

Still the case 5 years into launch

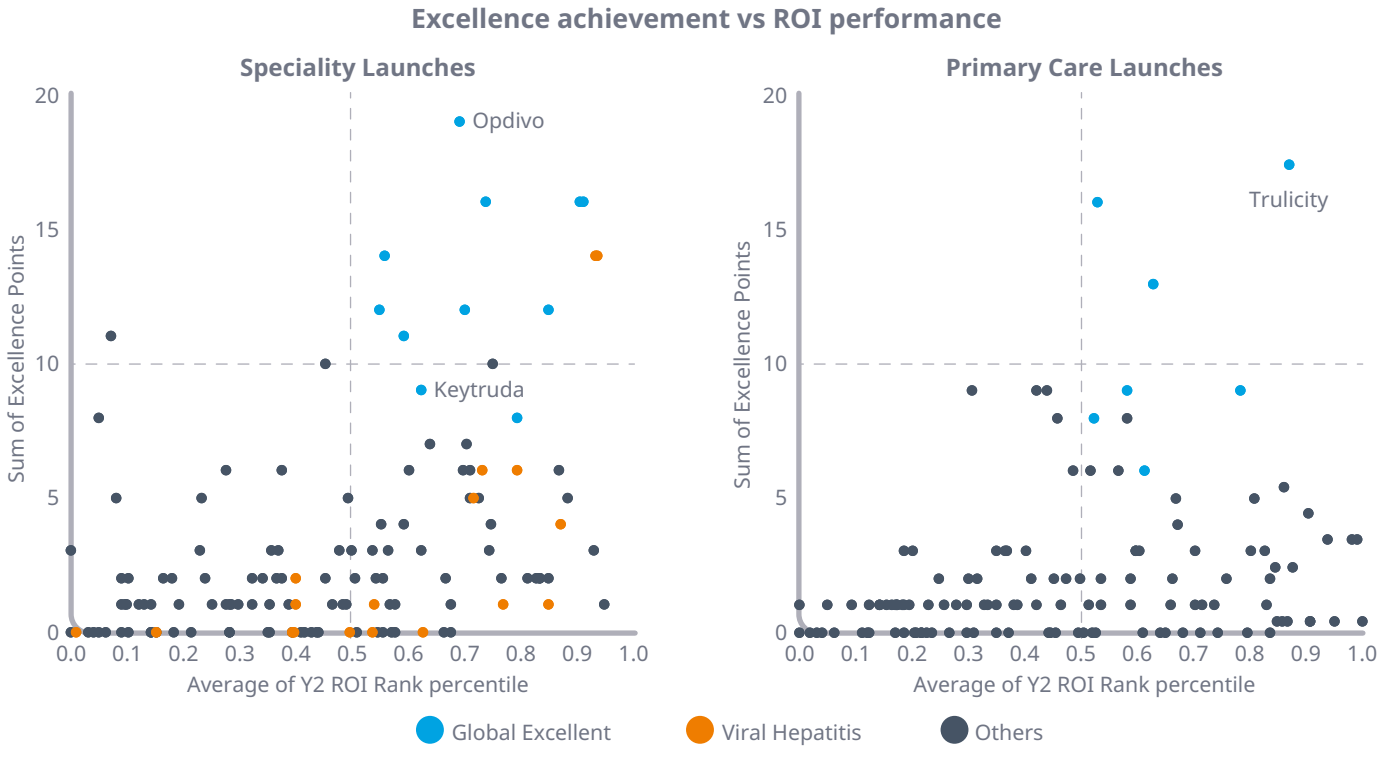
Therefore, for Launch Excellence VI, we have used absolute sales, quarter on quarter, as our analytic base. Analytics were adjusted to this new base measure, but the principles of the analysis remained the same; out-performance, relative to the usual launch behaviours in that country, on sales uptake, consistently high ranking in terms of absolute sales relative to other launches, and performance versus the number of promoted competitors. Separately, we also analysed performance relative to ChannelDynamics™ promotional investment to healthcare professionals. Further details of the methodology for Launch Excellence VI are provided in the appendix to this white paper.

Of the 136 specialty launches analysed across the seven countries, 8% (11 products) met our base three criteria in more than one country. Of the 146 primary care launches, 5% (7) did the same. Overall, 6% of the cohort of specialty and primary care launches met our three base criteria internationally. It is still extremely tough to achieve consistent Launch Excellence across countries. As Figure 2 shows, Launch Excellence, by the measures IQVIA has used across our white papers, remains tough to achieve.

6% of the cohort met our three base criteria internationally. It is still extremely tough to achieve consistent Launch Excellence across countries.

We also analyse the measurable element of launch investment, which is the promotional activities, non digital and digital, addressed to healthcare professionals, as measured by IQVIA's ChannelDynamics™ audit. True Launch Excellence should not be bought at any price- in Figure 3,

Figure 3: More specialty launches are excellent with a high RoI than traditional launches



Source: IQVIA European Thought Leadership; Launch Excellence VI

we address the relationship between Launch Excellence across countries and promotional return on investment. Excellence (shown on the Y axis) was assessed by calculating the total number of "Excellence Points" for each launch: a launch was awarded one Excellence point for every criterion it met within each country. To illustrate, a globally Excellent launch would have a minimum of 6 Excellence points as it would meet at least 3 criteria in 2 countries (3x2=6).

Return on Investment (RoI) is shown on the X-axis of Figure 3. The closer to 1, the higher (and better) the average ROI ranking performance. Each dot represents one brand. Viral Hepatitis brands, because of the very atypical nature of their uptake profile, were called out separately within the Specialty group.

Once again, the different economics of Primary versus Specialty care are clear: there are three Primary care launches in the upper right quadrant (high Excellence levels plus high return on investment) and nine (including Hepatitis C) Specialty brands- a greater proportion of specialty brands are both Excellent and have a high RoI. Each of the Excellent launches has their own story, and it is not our intention to make this paper an exhaustive collection of case studies- we will focus on one example of an Excellent launch in primary care with high RoI- Lilly's GLP-1, Trulicity, and a closely linked pair of Excellent launches in the specialty space, Opdivo and Keytruda.

The six-month window is an 80/20 rule - 20% of launches, on average, significantly improve on their first six-month trajectory; 80% don't.

THE SIX-MONTH WINDOW HOLDS – JUST

The first Launch Excellence white paper identified one of the most consistently compelling findings of the entire Launch Excellence series – the six-month window of opportunity. Before discussing the findings of this analysis it's worth revisiting what the six-month window is- and is not.

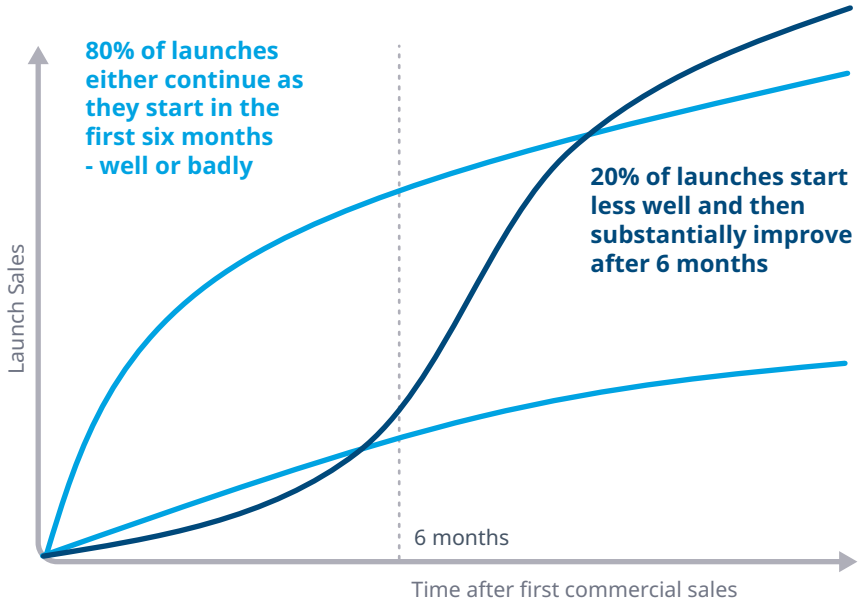
The six-month window analysis measures the degree to which launches change their country level sales trajectories between six months and two years.

A steep, sustained uptake curve is the goal for all launches, but is not always achieved. Launches can falter, seeing initial early growth moderate. They can fail to ignite at all in the first two years. They can, in some cases, convert an initially modest performance in their first two quarters into significant improvement. The six-month window simply measures the percentage of launches that manage to achieve this last reversal- convert an initially modest launch uptake into something significantly better. IQVIA measures this by ranking the sales of all launches in a country by quarter and then grouping them into deciles based on share rank. Launches which, between six months and two years on the market manage to jump at least two deciles up in ranking, are deemed to have significantly improved, as Figure 4 shows

The six-month window does NOT say that no launch can improve its trajectory after six months on the market- in fact, an average of 20% of them do improve

Users of the IQVIA Launch Excellence white papers have sometimes interpreted the six-month window as a 100% rule – 100% of launches have their trajectory determined in the first six months. It's not. It is an 80/20 rule- 20% of launches, on average, significantly improve on their first six months. 80%, on average, do not – they either remain in the same decile, move up or down only to the one adjacent. Roughly 20% of launches in fact drop two or more deciles between six months and two years on the market.

Figure 4: The Launch Excellence six-month window explained: it's an 80/20 rule



- The majority of launches have their longer term fate determined in the first six months of their commercial life
- It is possible to improve after the six month window – 20% of launches do
- The 80/20 rule has been consistent since the first 2007 Launch Excellence study, over time and countries despite the rise of Health Technology Assessments and payer power
- In Launch Excellence VI we have analysed using absolute rather than relative rankings, but the 80/20 rule mostly remains

Source: IQVIA European Thought Leadership

The Launch Excellence VI analysis of the six-month window used the same decile approach as previous Launch Excellences, but applied to quarterly rankings of absolute sales, rather than share of therapeutic markets. The findings are also presented separately for traditional (primary care) launches and specialty care launches. As Figure 5 shows, on average across the countries, the 80/20 rule holds,

Figure 5: It is still the case that on average only 20% of launches significantly improve between 6 months and 2 years

Only 20% of launches are able to improve their trajectory between 6 months and 2 years, this is even less likely to 5 years

	Specialty	Primary Care
6M 2Y	20%	20%

Average share of launches jumping up 2 or more deciles

2Y 5Y	10%	3%

Source: IQVIA European Thought Leadership; Launch Excellence VI

both for primary care and specialty. However, within individual countries, there are breaches: for primary care, Germany, Italy and Japan see more than 20% of launches improve, and for specialty the UK, Italy, Japan and France see more than 20% of launches improve. In all cases, the percentage of launches that improve significantly is still lower than 33% and mostly lower than 20%.

The longer-term prognosis for launches that fail to improve in their first six months is more challenging. We took the group of launches that had not made significant improvements between the first six months and two years, and looked, for those launches, at whether they improved their trajectories significantly between two years and five. The percentage of the remainder that do improve is only 10% of remaining specialty launches and 3% of remaining primary care. There are exceptions, but for most the rule is that early performance, good or bad, is strongly influential.

WHAT DOES THE SIX-MONTH WINDOW TEACH US?

IQVIA's six-month window insight has been interrogated closely over the 12 years - but it has stood up to scrutiny, and over time (having been repeated, with different launch cohorts, in every single one of our Launch Excellence white papers, and always with the same conclusion). In Launch Excellence VI a slightly different methodology, using absolute sales rather than market shares, yields very similar results across both primary care and specialty products.

Multiple factors influence post launch sales trajectories – new indications can add incremental patient opportunities, market access decisions, which could be taken a year or more post launch, can boost or kill early sales trajectories. More rarely, launches could turn around with a change of strategy- new promotional investment, pricing or positioning. The six-month window shows that these factors improve the shape of the uptake curve for only a minority of launches- albeit a reasonably sizeable one.

The key lessons from the six-month window:

There is no substitute for effective pre-launch preparation – ever

The 80/20 rule of the six-month window dictates that every launch should be prepared as if it were destined to be in the 80%, not the 20%. "In-flight" course correction cannot be a substitute for early, systematic, high quality launch preparation, country by country, function by function. Companies know this, but sometimes still leave preparations too late or under-invested. The reasons for this do not change: the pressures of delivering on sales from the existing portfolio, uncertainties on when and if launches will enter a country, and these will never disappear. What can be solved for is the structure and process for launch preparation.

See the wood for the trees

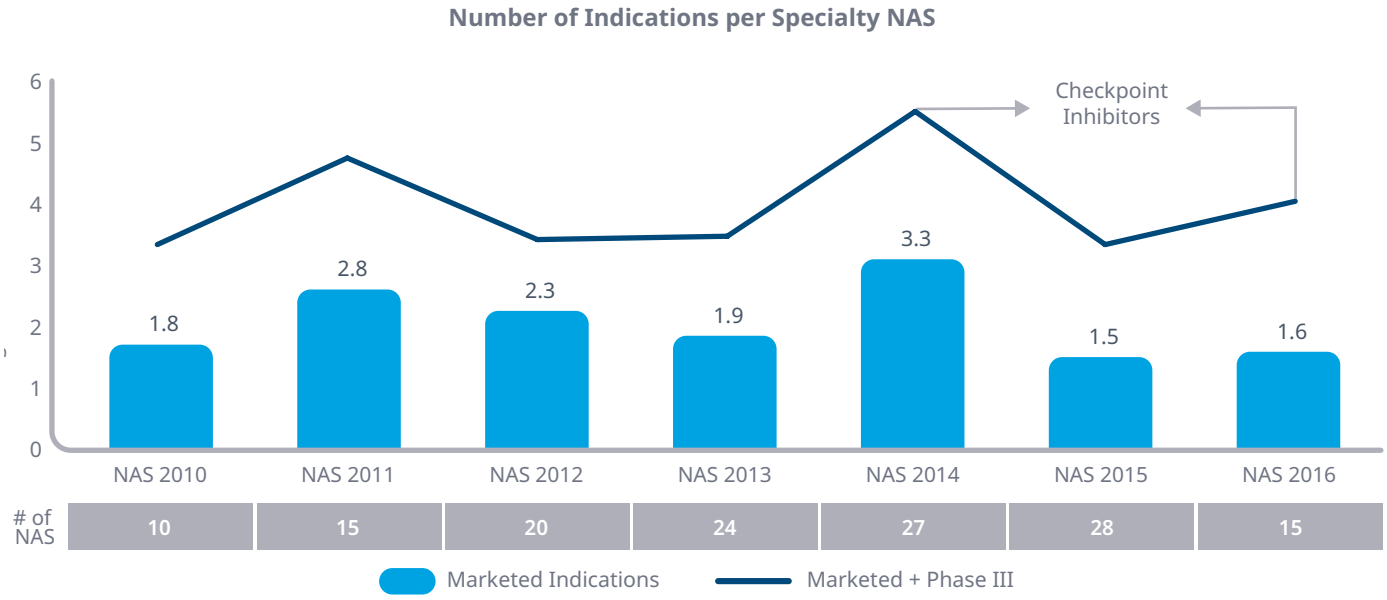
Launch Preparation plans can be formidable documents, with hundreds of tasks spread across Gantt chats of great complexity. Comprehensive Launch Preparation plans, covering all the tasks necessary for an effective launch have an essential role, but as Launch Preparation documents grow, there's the danger they become the purpose rather than the means to achieve the purpose. Seeing the wood for the trees is about the smarter use of Launch Preparation planning. Be comprehensive, but discriminate between the tasks that are mission-critical for that specific launch's Critical Success Factors, and therefore need priority and resource, country by country, and the other necessary but not critical tasks.

SPECIALTY LAUNCH EXCELLENCE

MULTI-INDICATIONALITY AND LAUNCH

Traditional single indication launches, such as Lipitor, were a sprint with huge focus on the early years. However, as companies recognised the potential of the "fulfilling life" a product can achieve, investment became long and sustained throughout the product life-cycle. While Lipitor has just two

Figure 6: Multi-indicationality is not a generalised trend, but led by fundamental mechanisms of action – e.g. Checkpoint inhibitors



Source: IQVIA European Thought Leadership, Innovative, Branded Specialty New Active Substances launched globally between 2010-2016. Indication information from IQVIA Pipeline Intelligence

indications, Humira in contrast has 10[2], and was referred to as a "pipeline in a product" during its launch years.

Overall, the number of new launches that are multi-indicational has not increased systematically. As Figure 6 shows, the average number of marketed and Phase III indications has fluctuated for specialty NAS, and growth is driven by the launch of highly multi-indicational products, such as immuno-oncologics, specifically checkpoint inhibitors.

Specialty medicines are often developed for a broad range of potential indications as they tend to target a key biological process. Oncology as a therapy area lends itself well to the multi-indication "long launch", as shown in Figure 7. One key example is the advent of Immuno-Oncology (IO) products which took multi-indicationality to a whole new level by targeting a key hallmark of cancer that is present across multiple tumour types – the ability to avoid immune destruction.

WHAT DRIVES EXCELLENCE IN MULTI-INDICATION LAUNCHES – IT'S NOT JUST A SPRINT ANYMORE, IT'S ALSO A MARATHON

Brands which launch into multiple indications will require evolutions of Launch behaviours, budgets, and performance management.

Multi-indicational launches do, however, expose the stresses of launch preparation and execution complexity.

- Stretched and competing budget priorities
- Maintaining continuity and focus
- Maintaining energy and communication across countries

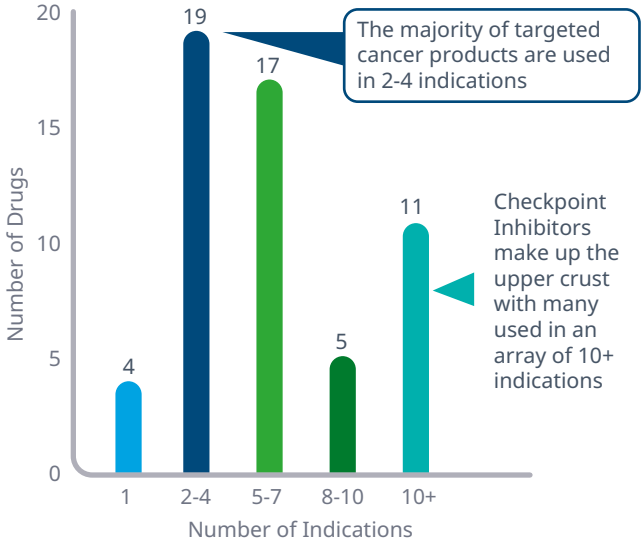
KEYTRUDA: AN EXAMPLE OF WHERE THE "LONG LAUNCH" AND A HIGHLY EFFECTIVE INDICATIONS STRATEGY PAID OFF

Keytruda, Merck, Sharpe and Dohme (MSD)'s immuno-oncology treatment, was first launched for melanoma in 2014. In the same year, Bristol-Myers Squibb (BMS) launched its own immuno-oncological, Opdivo. Both launches are Excellent

by our two years Launch Excellence criteria, but while both launches have a very similar and novel mechanism of action, blocking inhibitory checkpoints in the immune system to allow it to more effectively attack cancer cells, BMS and MSD pursued different initial launch strategies, based on their initial target patient populations. Programmed Death-Ligand 1 (PD-L1) is a protein which plays a key role in suppressing elements of the immune system. Tumours express this protein to varying degrees, high PD-L1 expression is associated with more aggressive tumours, and PD-L1 is a target for checkpoint inhibitors. When launching Keytruda, Merck chose a conservative approach to targeting, focusing on patients with high PD-L1 expression arguing the greatest benefit would be seen there. In contrast, BMS chose a maximalist approach at launch, targeting patients based on tumour, regardless of PD-L1 expression levels.

Initially, as Figure 8 shows, BMS's Opdivo pulled ahead, with an approval for all second line lung cancer patients, in contrast to Keytruda's approval only for those with high levels of PD-L1 expression.

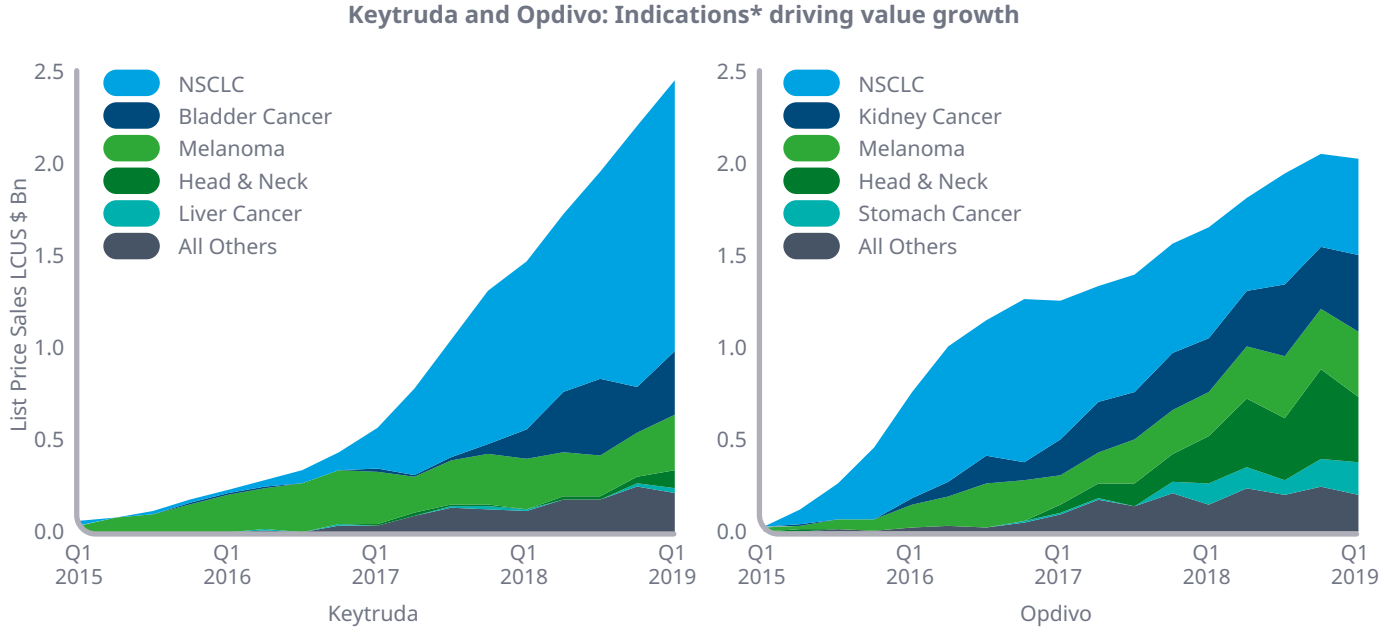
Figure 7: Targeted Oncology Products and Multi-Indicationality



Source: IQVIA European Thought Leadership, IQVIA Oncology Dynamics, MAT Q1 2019, Patient Level Oncology Survey, EU5, JP, CN, KR, Excludes patients participating in Clinical Trials & products with less then 50 sample patients globally

The maximalist approach to patient strategy, not segmenting by biomarkers, appeared to pay off. For oncologicals, the "long launch" is very much an arms race of clinical and real-world evidence.

Figure 8: Keytruda: an example of where the "long launch" and highly effective indications strategy paid off



Source: IQVIA European Thought Leadership, MIDAS Q1 2015 – Q1 2019, LCUS $, Global Sales- list price, pre-rebate and discount
Indication Split: IQVIA Oncology Dynamics Q1 2017-Q1 2019, Patient Level Oncology Survey, EU5, JP, CN, KR, Oncology Analyzer Q1 2015-Q1 2016, EU5, JP, CN, KR
*Patient Split from said countries applied globally to estimate sales by indication, list price, pre rebates and discounts

MSD's focus on patients with high PD-L1 expression levels resulted in approval for first line lung cancer patients with tumours expressing high levels of PD-L1, opening the larger first line market to Keytruda. At the same time, the FDA allowed Keytruda to be used for second line lung cancer patients regardless of level of PD-L1 expression- the same label as BMS's Opdivo had entered that market with. MSD, therefore ended up with the larger market potential, and BMS failed to catch up as Opdivo did not meet clinical endpoints as a monotherapy in first-line treatment. In 2017, the FDA granted Keytruda a label for any unresectable or metastatic solid tumours identified as having a biomarker, referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This is the first instance of an oncology launch receiving a label that is tumour site agnostic and genetically specific. The Keytruda/Opdivo story is by no means finished, but a current (2019) analysis of this story shows an interesting evolution. Keytruda, in combination with chemotherapy, is showing results which benefit patients regardless of PD-L1 expression levels, and the product, which started narrow in terms of target patients, is now able to broaden out. BMS has shown Opdivo combinations meanwhile, benefitting high TMB patients, an independent biomarker from PD-L1 status. In other words, Opdivo strategy has shifted to a narrower patient population focus, at least in some trials.

SEGMENTATION ANXIETY REVISITED

In the first Launch Excellence, the choice in the classic dilemma of launch -whether to start with a narrow population segment where a highly differentiated benefit can be proven, and subsequently broaden out- or to start broad in the first place, was so obviously tilted in favour of the latter that we referred to the dismissal of more focussed approaches as "segmentation anxiety". After all, the logic went, starting narrow only meant missed opportunity. Times change – in more primary care, mass market disease areas the option to go in broad has simply been taken off the table by the existence of perfectly effective generics. But for specialty areas, with high unmet need, especially with a very innovative mechanism of action, the temptation to go in broad still exists- should it be resisted? In the past, there have been highly successful launches (Avastin, launched 2004, the most notable) which have not had a companion diagnostic, but their success was achieved in a very different era of the oncology market. In today's oncology market, the question is resolved in favour of narrow by Keytruda and by other successful oncological launches. Where they are possible, companion diagnostics should be built into the development and launch of oncologics, defining the populations where the greatest benefit can be demonstrated.

Segmentation is now almost always the future for Launch Excellence, because regulators and payers are seeking certainty of superior outcomes and on budget impact, which is much more difficult to deliver initially in broader populations and with less mature data.

THE ELUSIVE PRIMARY CARE SUCCESS

TRULICITY AS AN EXCELLENT LAUNCH

In the time-period studied, Trulicity, a member of the GLP-1 class of injectable diabetes treatments, has been the most successful primary care launch in terms of the number of times it has achieved our Excellence criteria across the seven markets studied. Trulicity also achieved this position as the fifth GLP-1 to market as it was launched in late 2014 in the US, four years after the market leader, Victoza, launched in the US 2010 and Europe 2009. The first member of the GLP-1 class, Byetta, was in fact launched in 2005, but Victoza, an Excellent launch in previous Launch Excellence studies, rapidly eclipsed Byetta with a combination of specific clinical advantages and promotional focus. Lilly, when launching Trulicity, faced an entrenched market leader that had already beaten other competitors. By 2018, just four full

years in the market, Trulicity had overtaken Victoza in value market share in the seven Launch Excellence markets- with 43% of market value versus Victoza's 41%.

Trulicity is a once weekly product with a superior, patient friendly device, whereas Victoza is once daily: this core difference translates into a convenience of administration and ease of use advantage, a simple, patient focused message. Trulicity was not, however, the only once-weekly product, and once daily Victoza had successfully contained the challenge from other longer acting products. Lilly's launch strategy in the US was superficially counter-intuitive: even though Trulicity's advantage was patient centred, Lilly spent a year working first with payer and then endocrinologist prescriber stakeholders before active patient engagement, in the form of a Direct to Consumer (DTC) launch, was rolled out. This apparently back-to-front approach to stakeholder engagement – starting with the stakeholders who arguably cared least about Trulicity's key differentiaton, but were essential to remove barriers to prescription – meant that, as payers and prescribers were engaged and onside, the DTC launch, when it came, had maximum impact. Messages to patients focused on Trulicity not being an insulin, and its once weekly, convenient administration, with a pen that required no dose dialling, mixing or reconstitution, and had a pre-attached needle which was hidden from the patient's view. These messages were reinforced to physicians, and Trulicity had a highly consistent physician recall of its core messages.

THE FUNDAMENTALS OF ACHIEVING AN EXCELLENT LAUNCH

We have always described the foundational success factors of Launch Excellence as "Easy to say, difficult to achieve". They are also consistently relevant across launch types, countries, and throughout our Launch Excellence studies. To reprise, our foundational success factors are:

A POWERFUL AND PERTINENT VALUE PROPOSITION

When a launch enters commercialisation, generally early in Phase III, many of the clinical decisions which shape the final product will have been made, but by no means all. Multi-indicational products may still have clinical development strategy to be executed post initial launch. For all products, continued development of Real-World Evidence during and post launch is now an essential element of building a powerful and pertinent value proposition.

IQVIA's Launch Archetyping methodology categorises launches using a detailed, objective approach, by how differentiated they are, and the level of unmet need of the therapeutic area into which they will launch. When we examine the success of launches categorised into these archetypes, unsurprisingly, there's a greater proportion of commercially successful launches falling into the highly differentiated into high unmet need market quadrant than elsewhere. However, not all highly differentiated products launching into high unmet need areas are as commercially successful as they should be, and some launches (albeit a smaller proportion) archetyped as low differentiation into areas of low unmet need are commercially successful. The difference here is in the stakeholder engagement and the alignment behind the execution of the launch.

EFFECTIVE AND EFFICIENT STAKEHOLDER ENGAGEMENT

Companies start preparing Excellent launches with a carefully researched stakeholder map, built country by country. They create an investment and activity plan against each stakeholder to have the optimal awareness and perception of the launch product, and readiness to act on that perception, at the time of launch.

AN ALIGNED AND PREPARED ORGANISATION

The most important foundational success factor of all is an aligned and prepared organisation. It is also the most difficult to achieve, for a single launch, let alone for multiple launches, which is what companies increasingly must accomplish, Excellently.

ARE COMPANIES NOW MORE EXCELLENT AT MULTIPLE LAUNCH?

In Launch Excellence IV, published 2013, we made a very important finding: the more launches a company made in the time-period covered by the Launch Excellence cohort, the lower the percentage of those launches that were Excellent by our classification. Or, more succinctly, the more you launch the less (proportionately) excellent you get. There were two responses to this finding: the first argued that the finding must be incorrect – companies launching more products should be learning from their experience, honing their approaches and becoming more formidable launch machines as a result. The proportion of a company's launches that are Excellent should, consequently, improve. The counter argument is that the finding is true because multiple launches compete for budgets, management attention, priority and focus. Companies fail to manage that competition effectively- after all, a single launch is a hugely complex, multifunctional, multinational endeavour; multiply that by four or five and you have a tremendous challenge. Consequently, the chances of a launch becoming Excellent in a company consumed by multiple launches becomes lower.

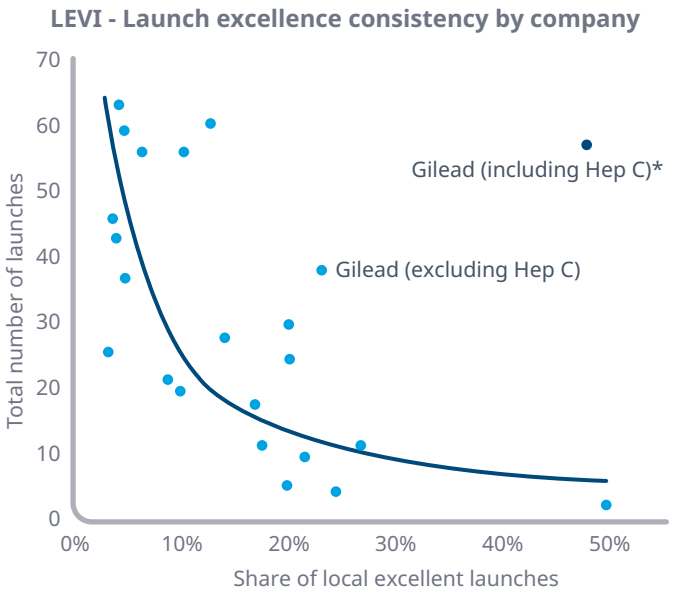
In practice, IQVIA's experience with companies addressing multiple launch is that both drivers happen- a multiple launch situation will never cease to be an extraordinarily complex challenge, but the best companies recognise this and have structures and processes in place which seek to address it. Four years later, and for Launch Excellence VI, seems an appropriate time to revisit this analysis – what we found was the same inverse relationship: it's still the more you launch, the less excellent you get. It is, clearly, still extremely tough to break out of the inverse relationship.

In future this will matter more, because most companies will be faced with more, but smaller launches, driven by two trends:

- Opportunity fragmentation (eg median sales in oncology falling; innovation focusing on smaller sub-populations while high prices are coming under pressure), but companies must still deliver absolute growth targets.
- Multi-indicationality, if different indications target different healthcare professional universes (eg rheumatologists vs gastroenterologists).

As Figure 9 shows, some companies have performed better than others at multiple launch – in Launch Excellence VI the standout company is Gilead. Even without their Hepatitis C products, with their HIV launches, Gilead shows higher proportion of

Figure 9: The inverse launch law still applied to companies with multiple launches in Launch Excellence VI



[t]All Hep C launches considered excellent for the purpose of this analysis

Source: IQVIA European Thought Leadership; Launch Excellence VI; Takeda includes Shire

launches that are Excellent, relative to the number launched. Reasons for this are multiple, but could include:

- Gilead has always been focused exclusively on specialty products- whether HIV, Hepatitis C or oncology. This means Gilead has never had the high headcount sales force that was necessary to support primary care products, and no primary care legacy to support.
- Gilead is a leading pharmaceutical company by IQVIA MIDAS reported Rx sales. The average number of employees for a top 10 Pharma company is 80,000 – although for diverse companies not all will be employed in pharma. Nevertheless, Gilead's headcount, at 11,000 employees worldwide, is the lowest by some margin, and is more typical of a small to medium sized pharma company. Gilead is widely described in the industry as having a notably "lean" structure, more akin to an Emerging Biopharma..
- Gilead has been very driven by the science and depth of knowledge– John C. Martin, Gilead's CEO from 1996 to 2016, the era of Atripla and Sovaldi, was formerly VP for R&D, and came from an antiviral research heritage.
- The launch of Sovaldi, post the 2012 $11bn purchase of Pharmasset, was a case study in a bold vision, led from the top, paying dividends because of very rapid and effective launch preparation and roll out. Sovaldi was approved in December 2013, a mere two years after the Pharmasset purchase was announced in November 2011.

Specialist focus, a lean organisation, strong, focused leadership and highly disciplined execution all undoubtedly played a role in Gilead's outperformance.

In previous iterations of this analysis, the standout company was Johnson & Johnson, which remains a relatively strong performer, although less of a standout than formerly. J&J is quite a different company to Gilead- at approximately 135,000 employees (not all in Pharma) it is the largest of the top 10 in headcount, and whilst it is increasingly specialty focused, in the Launch Excellence study period it launched both primary care and specialty care products. What J&J has in common with Gilead is focus and discipline- a consistent approach to launch preparation across functions, countries and launches.

THE FUTURE OF LAUNCH

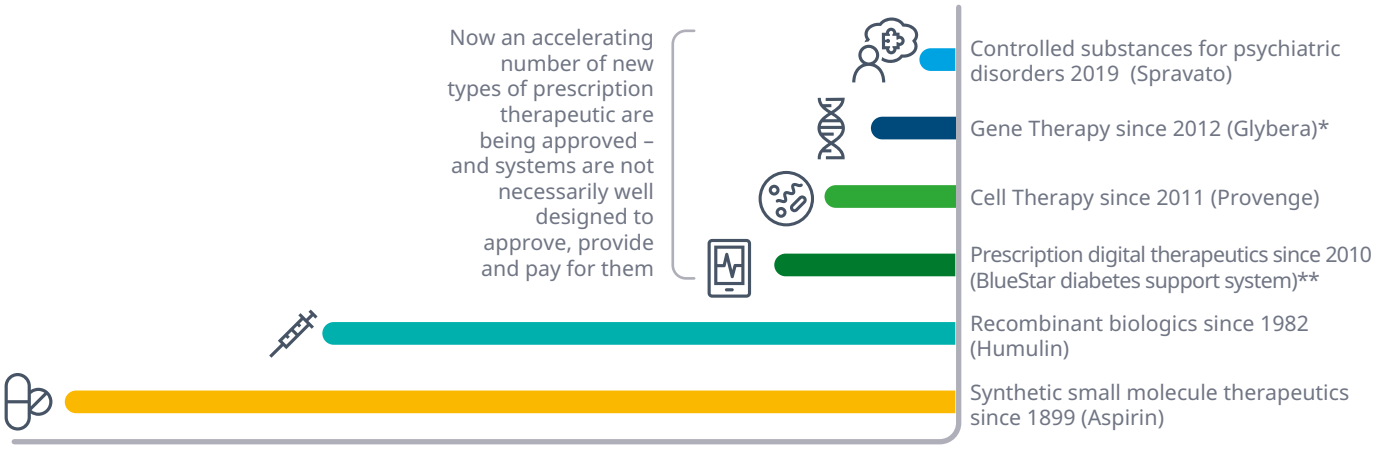
The prescription medicines industry has always been driven by innovation, and that innovation has, until very recently, focused almost exclusively on the molecule. In fact, for more than the first century of the modern pharmaceutical industry's existence[3] innovation was focused on the molecule and came in two basic types- small or biologic. This is changing, rapidly, as Figure 10 shows.

LAUNCH OF THE FIRST ADVANCED THERAPY MEDICINAL PRODUCTS: CELL AND GENE THERAPIES

From 2010, with Provenge (sipuleucel-T), pharmacotherapies involving modified cells launched commercially. Provenge, a prostate cancer treatment, failed to achieve commercial success, largely for non-clinical reasons. Subsequent launches of Kymriah, (tisagenleleucel) for acute lymphoblastic leukaemia and diffuse large B-cell lymphoma, and Yescarta (axicabtagene ciloleucel), also for large B-cell lymphoma from 2017 onwards have proven more successful and laid the foundations for a sustainable commercially successful sector in cell therapies.

Gene therapies had been performed experimentally since the 1980s, with patchy and partial success, until the 2012 approval of the first gene therapy treatment by a major regulatory agency, the European Medicines Agency, with Glybera. Once again, the pioneer commercial therapy was not a commercial success, and it was a subsequent gene therapy launch, in 2016, Spinraza (nusinersen) for Spinal Muscular Atrophy, which became the first truly commercially successful gene therapy launch[4].

Figure 10: Prescription launch offering types have multiplied since 2010- as will launch challenges



Until 2010 there were only two types of innovative prescription medicine to launch: small molecule of biologic, into systems designed to approve, provide and pay for them.

Notes: *Gendicine was approved in China in 2003, but Glybera was first gene therapy approved by EMA and FDA
**First standalone prescription digital therapeutic (reSET) approved by FDA November 2018

For these launches, solving manufacturing and logistics questions moves from background and support very much into the foreground.

- **Location of manufacturing facilities choices must be made early and carefully** – the cell therapy area has many restrictions on the testing and export of human cells which mean that international launch could be complicated and slowed by where manufacturing is allowed. Unsurprisingly both Kymriah and Yescarta started with manufacturing facilities in the US, and serviced their initial European use out of those facilities, although European facilities will come on line. Other countries require earlier planning – China does not permit the export of human cells and therefore cell therapies must be manufactured locally. As a consequence, Novartis announced in 2H 2018 it would be partnering with a local Chinese Biotech, Cellular BioMedicine Group. This moves China very rapidly up the sequence of launch focus, compared to the traditional playbook.
- **Cost of goods is significant and cost reduction a challenge. The companies which most successfully address this challenge will also be most successful in long term launch.** Localisation of manufacturing facilities may be necessary from a legal standpoint, and may also improve logistics (eliminating transatlantic shipments to tight deadlines, for example), but could pressure costs which are already high, and do not gain economies of scale for autologous cell therapies, the currently launched cell therapies, where the patient's own cells are processed to create the treatment. Compared to the processes for manufacturing conventional biologic medicines, cell therapy manufacturing is labour intensive and, initially, unautomated. Estimates of manufacturing cost using the original, manual processes have been in the order of $100k per patient[5]. Full or partial automation of cell therapy manufacturing processes will be pursued, and may successfully address the cost challenge, although as patient numbers ramp up from scant hundreds to thousands other formidable challenges of consistent quality, demand management and capacity will come to the fore. What's clear is manufacturing strategy is a key element of autologous cell therapy launch success.

PRESCRIPTION DIGITAL THERAPEUTICS (PDTs)

In November 2018, Pear Therapeutics' prescription digital therapeutic reSET, was approved by the FDA for patients with substance use disorders in the US. This FDA approved prescription treatment consists of a 12-week series of interactive treatment modules delivering cognitive behavioural therapy, to be used in conjunction with outpatient care. This launch was rapidly (January 2019) followed by the US launch Pear's reSET-O for Opioid use disorder. This is not first digital therapeutic to receive FDA approval. WellDoc has received FDA clearances for its BlueStar digital support system for diabetes management since 2010, when the offering was approved for prescription use to track blood glucose and support patient self-management, to January 2017, when the system was approved for non-prescription use. Proteus Digital Health's Digital Feedback Device, a miniaturised, wearable sensor and Proteus/ Otsuka's Abilify MyCite, a drug/device combination to track ingestion of Otsuka's atypical neuroleptic for schizophrenia, have also received multiple FDA clearances since 2012. However, what has been approved and by which pathway differs- Pear Therapeutics' reSET is indeed the first prescribable software claiming specific therapeutic benefits, supported by clinical trial results.

Digital therapeutics are, therefore, a broad and evolving group of offerings, but Pear Therapeutic's offerings mark a new stage, where Prescription Digital Therapeutics (PDTs) have the potential for genuine equivalence to molecular therapeutics.

Substantial barriers remain before PDTs are routinely prescribed and reimbursed. Prescription cannot automatically follow the well-established path of molecular therapeutics- in fact, there are four potential routes to prescription:

- The traditional, paper-based channel- service request form sent to the PDT provider's patient support hub – this route it entirely possible, but bureaucratic and slow
- Access to a dedicated portal by the clinician - but clinicians will dislike the need to log in to different portals for different companies' PDT offerings – "Portalitis" would be an inhibitor for PDTs as a class
- Accessing multi provider digital prescribing and monitoring platform. These already exist; IQVIA's AppScript is an example that is a digital therapeutic agnostic, EHR compliant portal. As of mid-2019, 58% of UK General Practitioners have access to the AppScript portal to recommend and prescribe apps and other digital therapeutics (although not yet PDTs such as Pear's). AppScript is also available in the US and certain Middle Eastern countries. Such a solution provides the convenience of a single portal for a wide range of digital therapeutics.
- Electronic Health Records with a prescribing module to prescribe PDTs using a recognised, reimbursable code.

The prescription element of PDT infrastructure is in its infancy. Reimbursement, the next challenge to successful launch, is also developing. WellDoc secured reimbursed access to BlueStar for employees of several major companies, emphasising the savings that use of the programme bring to the management of diabetics. In the UK, digital therapeutics delivered via AppScript can already be funded by parts of the UK's National Health Service (for some this is free, for others this is as a one-time fee set at the level of the prescription charge – ie £9, and for a third category costs are individually priced). However, debate on appropriate price points for digital therapeutics is in its infancy. The UK's Health Technology assessor, NICE, has undertaken (2017) a technology evaluation for Sleepio, a sleep improvement digital program, and published the first evidence standard framework for Digital Health Technologies in March 2019- the start of a more explicit discussion on how to evaluate investment and return.

Digital therapeutics, and PDTs within them, also exemplify the launch challenges of creating new types of therapeutic launch. The market is not a global one- different countries are at quite different stages of development. New infrastructures for prescription, pricing, reimbursement, delivery of molecular therapeutics must be developed- existing ones may not be ideal or may not work at all. In short, creating new markets is a lengthy process, requiring activities and investments over and above the established challenges of Excellent Launch.

LAUNCHING WHILE CREATING A NEW MARKET

Frequently quoted studies suggest that a minority of launches achieve the sales predicted pre-launch- commentators use this as evidence that launch execution is poor. That's a misleading interpretation, because it presumes that the sales targets were set correctly 100% of the time, and the failure is to meet them. Actually, it's the sales targets that are more often wrongly set- there's too many incentives to over-state. A careful, comprehensive externally researched set of perspectives on the true archetype for the launch, as perceived by each of the stakeholders that matter, is the essential first step.

The nature of launches will continue to evolve, faster than ever before, but the fundamentals of Launch Excellence remain the same.

At the heart of all Excellent launch preparation, whether for a single or for multiple launch, is a focused, actionable, aligned, realistic group of critical success factors tailored for that launch, which have been identified as the critical factors necessary to exist in the launch period for optimal success. As figure 11 outlines, these must be defined and limited in number, actionable and aligned across the organisation, and aspirational but realistic. The nature of launches will continue to evolve, faster than it ever has before, but the fundamentals of Launch Excellence at heart remain the same.

Figure 11: Be FAAR sighted

Focused	Critical Success Factors (CSFs) should be no more than 5-8 key circumstances, activities, perceptions or behaviours which must exist during the launch period for the launch to be a success
Actionable	CSFs must be addressable by actions the launching company can undertake- what those actions are, when they should start, internationally and by country, and the level of investment required should be specified
Aligned	the CSFs should be agreed across functions and countries. There will be nuances and variation in how addressing CSFs plays out by country and function, but alignment on the core CSFs is vital.
Realistic	CSFs should be built on a clear-sighted view of the launch's archetype- the level of differentiation and degree of unmet need in the eyes of the key stakeholders

APPENDIX

BACKGROUND TO LAUNCH EXCELLENCE AND METHODOLOGY

IQVIA has undertaken six Launch Excellence studies since 2007, maintaining the same top level approach whilst adjusting details in response to both changes in data and in the Launch Environment. This unique "long view" of launch means we understand the long term trends driving the launch environment.

IQVIA believes that Launch Excellence is built country by country, and therefore we focus first on determining Excellence within a country and subsequently Excellence across countries. In our previous white papers we determined that the overwhelming majority of New Active Substance sales in the early years of launch come from just seven countries. As the analysis in Figure 12 shows, the most recent New Active Substances still derive over 85% of their first two- and five- year sales from the US, top five Europe and Japan combined (all sales have been normalised to account for later launches in some countries). Therefore, for global Excellence, success in these six countries is the first priority.

The US is by far the largest launch contributor, between 7 and 8 times larger than the next country, Japan. This analysis is at list price, and of course, substantial rebates and discounts can

Figure 12: IQVIA has undertaken six major studies on Launch Excellence

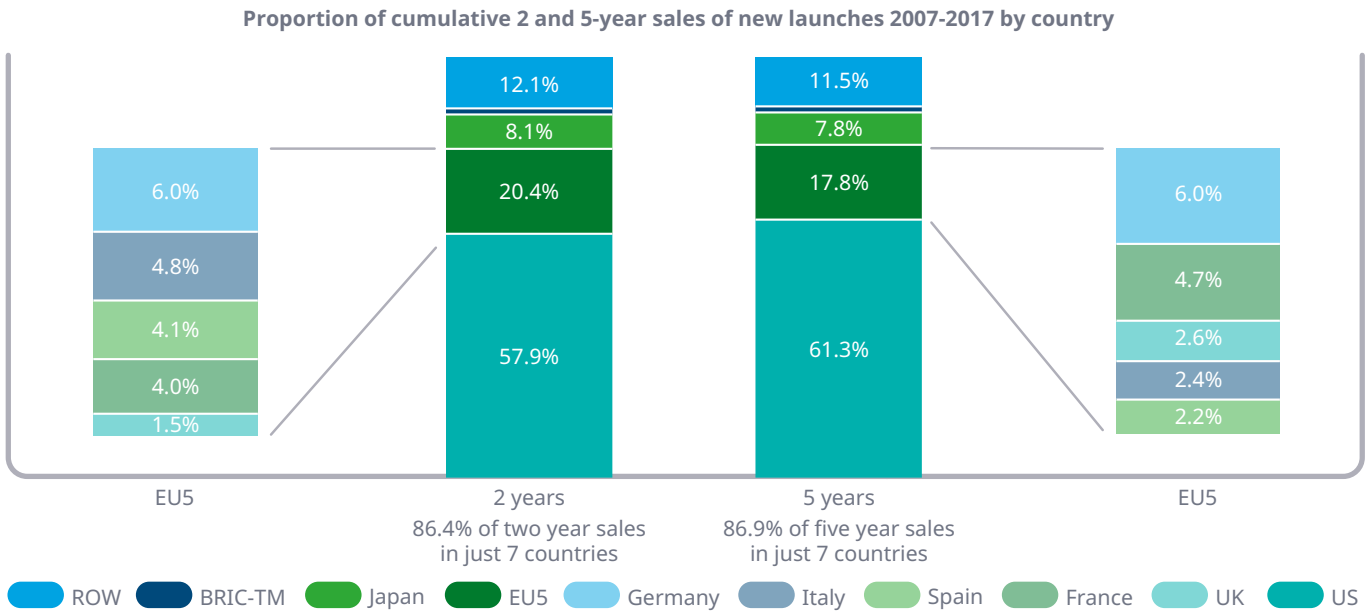
				Stricter inclusion criteria, same Launch Excellence criteria	Launch Excellence criteria modified to better address specialty launch
Launch Excellence 1	**Launch Excellence 2**	**Launch Excellence 3**	**Launch Excellence 4**	**Launch Excellence 5**	**Launch Excellence 6**
4,225 promoted launches 71 therapy areas 8 countries, 8 years	**3,081 promoted launches** 64 therapy areas 8 countries, launches from '00-'05, followed to '07	**1,388 promoted launches** 94 therapy areas 8 countries, launches from '06-Q1'09, followed to Q3'09	**1,309 promoted launches** 126 therapy areas 8 countries, launches from Q1'09 - Q3'11, followed to Q1'12	**360 promoted launches*** 8 countries, launches from Q4 '11 – Q1 '15, **Brands are counted once across markets; Promo data unavailable for Japan*	**299 promoted launches*** 7 countries, NAS launches from Q4 '10 – Q4 '16, followed to Q4 2018 **Launches were assessed within product segment (specialty vs traditional)*
88 (2%) outperform in one or more countries	68 (2%) outperform in one or more countries	19 (1%) outperform in one or more countries	18 (1%) outperform in one or more countries	55 (15%) outperform in one or more countries	22 (16%) specialty & 21 (14%) traditional launches outperform in one or more countries
35 (0.8%) outperform in two or more countries	21 (0.7%) outperform in two or more countries	8 (0.6%) outperform in two or more countries	10 (0.8%) outperform in two or more countries	36 (10%) outperform in two or more countries	11 (8%) specialty & 7 (5%) traditional launches outperform in two or more countries
Decline in detail impact Six month window Market expanders	Rise of payer as customer 3 month dynamic window Available market for launch declining	Pre-launch preparation: timing, organisation and quality Alignment and incentivisation	Where does "winner take all" operate? The dominance of the specialist launch Can companies cope with a larger number of smaller launches?	The continued rise of the speciality launch on a global level and the implications of low patient #s/high cost/patient	The "long launch"; multi-indicationality and Launch beyond the small molecule/biologic paradigm

Notes: *For studies 1-3, the market share period was 18-24 months; for studies 4 and 5, the market share period was 12 months. Launch Excellence V covered launches between Q4 2011 and Q1 2015. Promotional data is not included for LEV in Japan. LEV operated a stricter definition of launch which reduced the total size of the launch cohort and increased the % success for excellence. Canada was not included for Launch Excellence VI.

take net launch sales below these figures, but even were this accounted for (and because of lack of transparency and comparability on discounts and rebates across countries we do not) the US would still lead by a substantial amount. Nevertheless, we do not weight evaluation of Excellence by country contribution, because this would lead to success in the US being the only success criterion.

Figure 14 shows how we adapted the IQVIA Launch Excellence methodology to the realities of today's launch environment. The principles of outstanding uptake relative to usual country launch performance, a strong start in launch or rapid improvement, and strong performance versus competitors were all retained.

Figure 13: 7 countries account for >86% of total launch sales in years 2 and 5



Notes: Country contribution is calculated based on the accumulative sales of NAS (new active substances) launches from 2007 to 2017. Values are pre-rebates and discounts.
Source: IQVIA European Thought Leadership, MIDAS LC US $ Q4 2007-Q4 2018.

Figure 14: In Launch Excellence VI, we adapted our methodology to reflect the realities of a specialty dominated launch environment

Uptake

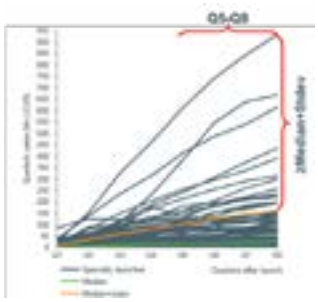
- Quarterly sales for Q5-Q8 post launch must be >= to 1 STDEV above the median (within country and segment*)

Ranking performance

- Launches were ranked by absolute quarterly sales within country and segment in Q2 and Q8 and deciled according to rank
- Excellent products must have jumped up one or more deciles between Q2 and Q8, or remained consistently within the top decile

Competitive intensity

- Launches were categorised into markets based on ATC3/4
- ChannelDynamics™ was used to determine number of promoted products within each market at latest date, excluding products with global promotional spend of less than $100k in MAT Q4 2018.
- Launches were then ranked within country and segment based on Q8 sales and this ranking was normalised to the number of promoted competitors
- Launch was considered excellent if ranked in top 20%



Product	Rank Q2	Rank Q8	Decile Q2	Decile Q8
HARVONI	1	1	0.1	0.1
SOVALDI	2	3	0.1	0.1
INCIVEK	3	14	0.1	0.2
...			...	
ZYTIGA	15	24	0.2	0.2
KADCYLA	16	41	0.2	0.4
KYPROLIS	17	36	0.2	0.3
...			...	
STRIBILD	27	10	0.3	0.1
OFEV	28	25	0.3	0.2
COMETRIQ	29	30	0.3	0.3

Product	Rank Q8	Competitors	Rank / Competitor
HARVONI	1	9	0.111
GENVOYA	2	31	0.065
SOVALDI	3	9	0.333
OPDIVO	4	6	0.667
IBRANCE	5	4	1.250
EPCLUSA	6	9	0.667
TRIUMEQ	7	31	0.226
DESCOVY	8	31	0.258
ODEFSEY	9	31	0.290
STRIBILD	10	31	0.323
...	...	...	...

Product	Normalised Rank
GENVOYA	1
HARVONI	2
TRIUMEQ	3
DESCOVY	4
ODEFSEY	5
STRIBILD	6
SOVALDI	7
OPDIVO	8.5
EPCLUSA	8.5
TIVICAY	10
...	...

Top 20%

Example shown : US Specialty launches

Source: IQVIA European Thought Leadership *Segment=primary/traditional or Specialty

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