Launch Sequencing and Market Prioritization in an Evolving Global Market

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The world is facing a multitude of governing and legislative changes that will directly affect pharmaceutical pricing in the coming years, with many of these changes exacerbated by the pandemic. As countries become increasingly interconnected, decisions in one pharmaceutical market will have ripple effects globally.

Reasons for traditional launch sequencing include market size, opportunity and accessibility, previous launch experiences, connections and market knowledge, and default or habitual launch sequencing approaches. However, recent trends are upending the traditional approaches to launch sequencing, and an opportunity exists for pharmaceutical companies to rethink market prioritization.

Multiple changes are occurring around the globe, driving the need to re-evaluate launch sequencing. In this article, we will detail those changes and the impact they are having, along with practical advice on how biopharmaceutical companies can rise to meet these challenges and plan now for future launch success.

CHANGE 1

UK Departure From the EU

Now that the UK has left the European Union, the Medicines and Healthcare Products Regulatory Agency (MHRA) is separate from the European Medicines Agency (EMA), which means the UK has the ability to approve products more quickly. This was seen in action with the emergency use authorization of the Pfizer/BioNTech and AstraZeneca COVID vaccines. We should expect to see more of this kind of speed of approval, particularly in oncology products and rare diseases.

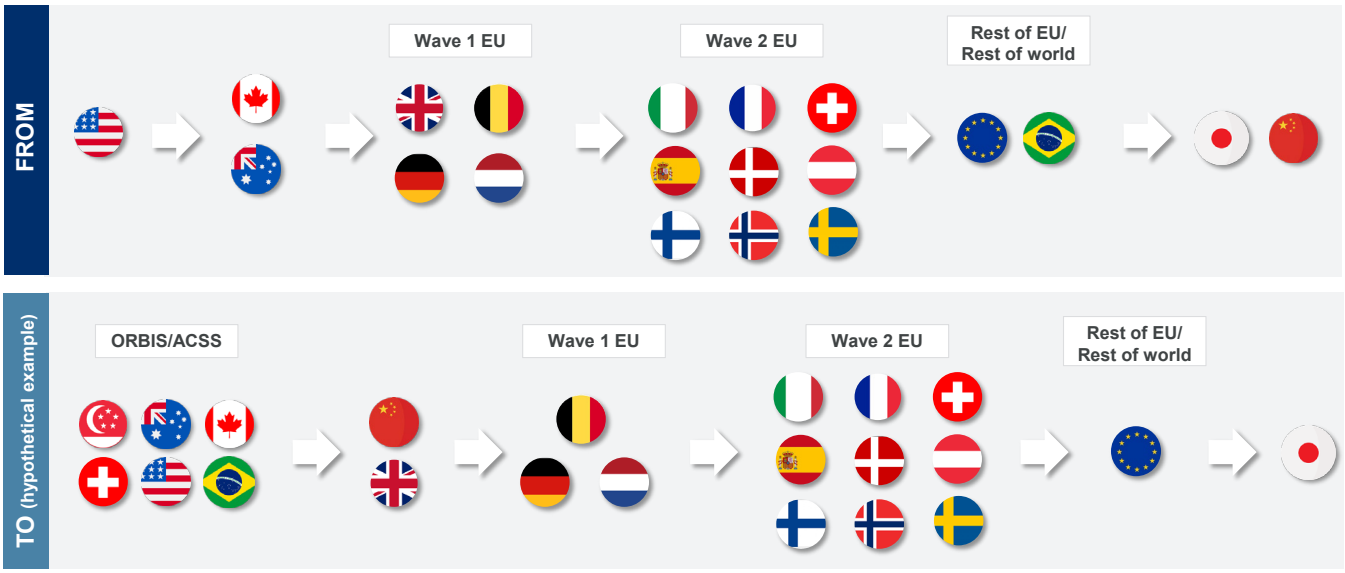
CHANGE 2

Rise of Non-Traditional Blocs to Approve Pharmaceuticals

Demonstrating the country's desire to separate itself from the EMEA, the UK joined the Australia-Canada-Singapore-Switzerland Consortium (ACSS) in October 2020. The Access Consortium is a medium-sized coalition of regulatory authorities that work together to promote greater regulatory collaboration and alignment of regulatory requirements. The move is tied to the UK government's goal to find more innovative approaches to approval.

Countries are increasingly forming non-traditional blocs, such as ACSS, to approve pharmaceuticals. These blocs upend traditional launch sequencing for both new indications and new products.

A much more established bloc is Project ORBIS, an initiative of the FDA Oncology Center of Excellence (OCE), which provides a framework for concurrent submission and review of oncology products among international partners. Currently, ORBIS has been focused on oncology drugs. While it was originally set up by FDA, other markets are slowly joining, including the UK and Brazil. The focus has been on rapid approval of established drugs, but this changed in 2020 with Seattle



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Genetics' Rituxan, the first new drug to be approved by ORBIS. This has profound implications for how companies think about the approval of new medicines via these kinds of consortiums.

Meanwhile, the EU Commission has developed a comprehensive pharmaceutical strategy, with 11 flagship initiatives that are to be addressed beginning in 2021. It is the first time that the body has put pen to paper and developed a strategy for pharmaceuticals and has plans for the industry moving forward.

CHANGE 3

Increasing Pan-EU HTAs and Accelerating HTA Reviews

On June 22, 2021, the Council and the European Parliament enacted a new law to join EU member states' efforts on scientific consultations on health technology assessments (HTAs) through mandatory joint clinical assessments (JCAs). The aim is to reduce administrative burden on both HTA agencies and pharmaceutical companies, accelerate the HTA process, improve patient access to medicinal products/medical devices, and simplify the submission procedure for manufacturers. This could especially help smaller companies because they will need to submit data and evidence only once at the EU-level.

Meanwhile, parallel licensing and HTA for new medicines has significantly accelerated access for drugs participating in a pilot project in The Netherlands. Time to access for the first two drugs to complete the parallel process—Novo Nordisk's Rybelsus (semaglutide) and Insmed's Arikayce (amikacin liposome inhalation suspension)—was reduced by an average of three months, according to the *Vereniging Innovatieve Genessmiddelen* (VIG; Association of Innovative Medicines).

That time savings is particularly impressive given that The Netherlands is already one of the fastest countries in Europe to grant access to new medicines. Data from the EFPIA Patients WAIT Indicator Survey show that the mean time to access in The Netherlands was 213 days in 2020; only Germany, Switzerland and Denmark were quicker.

Under the parallel process the *College ter Beoordeling van Genessmiddelen* (CBG; Medicines Evaluation Board) and the *Zorginstituut Nederland* (ZIN; National Health Care Institute) conduct their assessments simultaneously. Ordinarily, ZIN begins its work only after a drug has received its marketing authorization.

Besides Rybelsus and Arikayce, four other drugs have thus far been registered for the pilot project: Astellas's Evrenzo (roxadustat), Bayer's finerenone, Vifor's avacopan, and Janssen-Cilag's ciltacabtagene autoleucel. The last of these products has attracted particular attention as the first inpatient treatment—and the first CAR T-cell therapy—to undergo the parallel process. Drugs that will be assessed by the Beneluxa Initiative or EUnetHTA are not eligible for the parallel process.

It remains to be seen whether the pilot project will lead to the permanent—and wider—implementation of the parallel process.

CHANGE 4

China Displacing Europe and Japan as Priority Markets

China will likely displace Europe and Japan as a priority market and is becoming a source of innovation in its own right. Once a traditionally later launch market, China is increasingly being prioritized by big pharma when determining launch sequence, primarily because of its size. While China has traditionally been viewed as a complicated market where approvals, access, and pricing tended to take longer, now big pharma is prepared to move significant resources to Chinese affiliates in order to get drugs to market quickly.

China is becoming more important not only from an opportunity perspective but also as a source of innovation. The government in China has put together a Made in China 2025 initiative, which is spurring investment and driving new launches, making the market a hub for innovation. China is looking to provide incentives for simultaneous launch with the U.S., which is going to force some difficult decisions when thinking about launch and launch sequence.

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CHANGE 5

Small Countries Approving Pharmaceuticals Ahead of Big Countries

Beyond the EU4+UK, an additional 25+ markets in Europe— especially Central and Eastern European countries—can provide unique opportunities. Smaller countries can be early launch markets that serve as a test bed for launch strategy, messaging, and positioning. Taking an alternative approach can expedite time to value, rather than focusing solely on the size of the opportunity. Companies can leverage smaller markets to gain traction, rapid revenue generation and, ultimately, quicker access. Reprioritizing markets can help generate physician experience prior to spring-boarding onto the larger, "more attractive" markets.

Brazil and the United Arab Emirates (UAE) are increasingly approving products before full approval has been achieved throughout the EU. Figure 1 provides a snapshot of some recent launches in the UAE vs. the last launch in the EU. Some of the differences are stark. PIQRAY, for example, had almost 300 days difference between the two, and that trend clearly has implications in terms of launch sequencing and also pricing as companies think about their overall sequencing.

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	Launch Date (date of last launch in EU)		
			
PIQRAY® (alpelisib) tablets	**10/11/2019**	296 days	**1/9/2020**
ADAKVEO® crizanlizumab-tmca FOR IV INFUSION	**29/7/2020**	125 days	**1/12/2020**
TALZENNA® talazoparib	**23/06/2019**	70 days	**1/9/2019**
MAYZENT® (siponimod) tablets 0.25 mg • 2 mg	**22/12/2019**	52 days	**12/02/2020**

CHANGE 6

Increasing Net Price Transparency

Companies need to think carefully about product adoption and launch sequence in the face of increasing net price transparency. For example, the Belgian Health Minister recently tweeted the prices the government paid for vaccines from Moderna and AstraZeneca, much to the disappointment and frustration of the companies involved.

In other European markets, such as Italy, there is an increasing drive for net price transparency. Companies need to think very carefully about the order in which they launch products to make sure that if the prices are divulged, they do not destroy value in other markets.

CHANGE 7

US Reference Pricing and Other Policy Changes

Though a packed legislative agenda may slow Democratic plans to review drug pricing in the U.S., pharma needs to be prepared for change. Policy changes we might expect to see include external

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reference pricing from comparable countries, limits on drug price increases, increased influence of ICER in determining market access, and allowing importation of drugs from other countries.

What Do These Changes Mean for the Pharmaceutical Industry?

Companies are re-evaluating their product launch sequence to respond to changes at a global level. Traditionally, launches have been built around a wave of markets, with an established way of thinking about them. Manufacturers would make some tweaks to their launch sequence and do some optimization as they got to the edge markets, but not so much with the wave one and wave two markets.

Now, however, this regional notion will start to disappear as we start to group countries based on how quickly the launch can be executed, how much reference pricing impact the countries have, and how much flexibility the countries give to launch in a manner that is manageable in terms of price risk.

The waves are no longer going to represent the traditional geographic notion. The way manufacturers think about sequencing is going to need to change. It will also require a change in how companies think about partnering, particularly for emerging companies that are yet to establish affiliates in these markets. All of this collectively puts a greater burden on the price and access functions when it comes to launching products on a global basis.

Launches are already a loosely controlled process, but they are going to become even more subject to chaotic adjustment as a result of these trends.

Flatter, more accelerated launches

Launches will be flatter, meaning manufacturers will need to enter more markets at the same time versus sequentially. Launches will also be accelerated in that not only will companies need to enter more markets at the same time, but the overall pace between markets and penetration into each region will be faster. In addition, while demand for new products to fill unmet needs is accelerating product launch, for a laggard or, me-too, product, that barrier may actually slow down access, especially post-COVID.

Not only can launches be accelerated, in some cases they must be accelerated. In countries like China, the risk of a late launch into that market means potentially facing an established competitor with significant share, something we as an industry did not face in many of these markets previously.

A flatter and faster launch means that the timeline compresses, and the time it takes to get to certain key markets is faster. Not all markets may move their timelines the same as other markets, creating differences in traditional sequencing. Also, differences exist in who references whom and when. Knowing the details of that referencing and how they influence each other is critical, especially in a number of bridge or key markets that get referenced around the world. Canada, for example, is referenced in every geography, and Brazil also has significant impact in that not only is it referenced by emerging markets, but it is referenced across all geographies.

In many cases, traditionally low net-price markets came very late in the launch sequence. If they are accelerated, it becomes critical to think about strong distribution agreements upfront. It will be difficult to fix any of these issues after the fact.

Qarziba is one example of a product that has done a good job of this, with Eastern European prices that are on par with their German prices at a list price level, minimizing their risk to policy changes and other effects. Flatter list price corridors are achievable if a company is willing to think outside the box, manage the approach differently from a negotiation standpoint, and think in terms of the new world that we are in. No longer can a brand start to erode the price differential as it gets into later countries in the launch and think that it is not going to reference back directly to the early launch markets. That world is going away.

Higher risk launches

The trends outlined above increase the risk of a suboptimal launch. For example, a company may be ready to launch with a plan based on the current set of policies, but those policies—such as reference price rules—can change quickly, as when Saudi Arabia started referencing Brazil in January 2021. If an organization did not have intelligence and insight

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into this change, it could wreak havoc.

The key is to develop an outstanding monitoring plan and to push for a high, consistent list price. Even if it does not affect the net, a high consistent list price can minimize impacts. It is also important to be prepared to delay countries that do not fit the corridor.

The same is true for U.S. referencing. A change in U.S. referencing rules can impact an in-process launch. For ex-U.S. markets that are part of a potential basket, one must take action to give them the highest scrutiny. If New Zealand is part of the U.S. basket, for example, it cannot be treated as a minor market because today it is not referenced and is a small market. It must be treated seriously because it could become part of a reference basket for the world's largest market, and the decision must be treated as such and take that risk into consideration.

Transparent prices

The intentional or unintentional release of pricing information is a growing risk. This will impact negotiations in other markets and cause renegotiation of existing launch markets, which might cause delays. Some of the existing markets that choose to renegotiate may change their list prices, all of which can upset assumptions.

Manufacturers should assume that their net prices will become transparent and therefore plan with consistent guidelines around how they set net prices, eliminating one-offs. Tools are available to simulate what a visible net price impact would be. It is necessary to be strong in distribution agreements, especially in the ex-EU, where the barriers are a little higher but not nonexistent, in order to have net prices that are larger and different in many of these markets.

Conclusion

Instead of thinking of a static launch sequence with the possibility of reacting if there is a suboptimal negotiation, manufacturers must have a strategy that has optionality built into it. This will allow them to assess many different sensitivities to something going wrong in the launch and what it means, so one can know before the launch what must be done differently if something goes awry, such as a policy change or a price becoming transparent. Collectively, these steps must be taken to prepare for a better launch and a more agile reaction to unfolding events.

Many companies put a great amount of effort into the launch and then breathe a sigh of relief. However, just because a brand has launched does not mean it is time to relax. That is when the work really starts. One must continually monitor the landscape and be prepared to challenge existing thinking. A decision framework to which all layers of management can anchor themselves when determining launch sequencing is needed. Finally, companies must ensure robust global price governance, and above all, be agile.

KEY TAKEAWAYS

Challenge internal launch assumptions and plans
Strong monitoring and intelligence is required. Larger firms may already have these capabilities, but smaller firms will need to find an agile partner that can help them understand shifting market events.

Flattened launch price corridors
As much as possible, assume prices are going to become transparent. In the next three years, we could be in a very different price transparency world. Make all discounts defensible to all parties today.

Deepen capabilities around China
Educate the organization on the Reimbursement Drug List (RDL), early launch, and the value and risks that provides.

Establish and maintain a robust global price governance
Many firms still try to manage prices on a regional basis, but that is an outmoded way of doing business. It is no longer advisable to have an EU team focused on EU reference pricing and an emerging-markets team focused on emerging markets. They need to talk to each other.

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