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Seven Secret Ingredients for Successfully Launching and Commercializing a Biopharma's First Drug in Europe

Understanding What Drives a Product's Value and How to Fully Extract It

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The idea in short: Shifting gears to succeed

Transitioning from an R&D-focused biopharma company to a commercially viable operation is already a challenging endeavor, and the prospect of having to master complex European launch requirements while also steering US business makes this shift even more daunting. To help companies assess the general viability of such ventures, this Simon-Kucher whitepaper article identifies common characteristics among independent operations and carves out key managerial implications to enable business leaders to properly analyze, prepare for, and execute a successful launch for their company's first drug in Europe and also establish a fully integrated (bio-)pharmaceutical company (FIPCO).

Extensive quantitative and qualitative research, covering more than 20 company analog cases, approximately 4,500 data points, and 18 industry expert discussions, shows that unlocking significant price potential for the target asset is one of the key prerequisites to make this organizational leap. The primary factors driving a drug's price potential are a high level of unmet medical need, high disease severity, orphan drug status/relative rarity of the disease, a small but targeted patient population, and a significant therapeutic improvement, which, in turn, provide companies with a higher degree of freedom to shape and establish a new market environment or disease area.

However, our interviews with industry experts show that many emerging US-based, R&D-focused biopharma companies fail to understand the importance of these individual factors. Their planning is often insufficient and delayed, impeding orderly market entry that would otherwise enable them to shape the market/disease area of their first drug. As such, these companies must broaden their horizon beyond the US, sharpen their commercial focus, identify their assumptions, and debias their strategies early on. Eventually, they should set up an empowered European organization that is fully integrated within a multi-functional structure to align global strategies with country-tailored launches, regulatory (requirements), medical affairs/patient advocacy, marketing, pricing and market access, and life-cycle planning capabilities.

Introduction: Searching for the right opportunities ahead

For decades, the life sciences industry has been renowned as one of the most profitable and innovative industries in the world[1]. However, despite tireless research and development efforts, many diseases are still lacking treatment options or are in need of more effective and/or safer treatment alternatives[2]. Given these unmet needs and attractive business opportunities, many established companies as well as emerging biopharma startups have geared up to develop new drugs and treatment approaches.

After the US, Europe is considered the second most attractive market for serving patients' needs while extracting commercial value from innovative drugs to fund future innovation[3]. Yet, regardless of the commercial upsides, the region is also seen as significantly more challenging than the US in terms of entering the market and accessing patients.

For companies without any regional presence or experience, making the leap to Europe seems particularly daunting and complex. While Europe has one major central regulatory access point via the EMA, the 28 EU member states (and beyond[4]) each have their own approaches to pricing and market access and need tailored commercialization/go-to-market strategies.

Consequently, most emerging biopharma companies opt to out-license or partner with other companies, primarily big pharma, as seemingly easier commercialization strategies[5]. However, the desire for a safer go-to-market strategy may leave significant shareholder value, learning, and scaling opportunities on the table.

Due to our commitment to help the life sciences industry achieve sustainable TopLine Power® and extract maximum value out of its ventures, this Simon-Kucher whitepaper article aims to provide a better understanding of the key value drivers and success factors for companies launching their first drug in Europe.

By analyzing over 20 prominent first drug launches (2005 to 2019) by US-based companies in Europe, over 4,500 individual data points from independent launches, and one-on-one expert discussions with 18 senior (commercial) executives who have led or overseen the setup of commercial operations in Europe, this article investigates four areas of interest:

[1] Statista Research Department, 2019; Stalder, 2018
[2] VFA, 2019
[3] EFPIA, 2019; Aitken & Kleinrock, 2015
[4] For example, in Switzerland, Swissmedic is the regulatory access point and BAG is the respective payer party.
[5] Gilbert, Easton, & Breazzano, 2013

1. **Characteristics of first drug launches in Europe:** Drug, disease area, and company specifics that lay the foundation for successful independent launches in Europe

2. **Opportunities and reasons to commercialize:** Why companies consider launching a drug in Europe on their own?

3. **The seven secret ingredients for success:** How to maximize value when launching a first drug?

4. **The dos and don'ts:** What to consider before planning a company's first product launch in Europe?

1. Characteristics of first drug launches in Europe: Identifying common patterns

From 2005 to 2019, over 650 innovative medicinal products received (initial) marketing authorization from the EMA. Only a fraction of these launches (around three percent) were driven by companies that had to establish their own commercial operations in Europe for the first time.

Previous research by Gilbert, Easton, and Breazzano (2013) indicated that first drug launches increasingly target orphan diseases given the fewer/less demanding commercial infrastructure requirements.

However, launching an orphan drug also comes with other significant challenges, such as creating disease awareness, educating the market, and addressing the ever increasing cost consciousness of payers. Moreover, success is no longer guaranteed. With fewer stakeholders in the market to address, there are zero opportunities to make mistakes – effective performance is critical.

Building on the working hypothesis of Gilbert, Easton, and Breazzano, we analyzed further drug and indication characteristics of 20 first product launches by US-based companies from 2005 to 2019. These characteristics include indication size (prevalence), unmet medical need, severity of the disease, the drug's current and future competitive strength and differentiation potential, and achieved yearly price level of the drug. In addition, we assessed company characteristics, such as pipeline strength, finances, and strategic outlook, for each of the drug launches to understand value drivers behind the commercialization efforts.

16 out of 20 new drug launches (80 percent) analyzed had received an EMA orphan drug designation. In total, metabolic disorders and oncology were the most frequently targeted disease areas, accounting for 45 percent (9 out of 20) and 25 percent (5 out of 20) respectively. While the orphan drug status grants

certain regulatory benefits such as no/reduced regulatory fees, increased support (e.g. scientific advice on study protocols for a reduced fee), and market exclusivity for up to 10 years, making an independent launch more attractive, other underlying factors must be considered to draw a holistic picture and derive key value drivers for a successful, independent go-to-market strategy.

Ultimately, the decision to independently launch a drug depends on the way biopharma companies create value, and therefore, the financial/profit aspects they take into account. In simple terms, value/profit is given as revenue minus cost. These considerations are largely based on the achievable price tag for a new drug and the ultimately accessible patient population (revenue potential = price x volume) and the commercial infrastructure needed to extract this created value (i.e. cost). Consequently, the majority of drugs launched in disease areas with high disease severity and a high unmet need for innovative treatment options for a well-defined, distinct patient population. On average, the drugs analyzed target a patient population of only 2.6 patients per 10,000 people (prevalence) with average EU-5 treatment costs of around 150,000 euros per year (ex-manufacturer list price level)[6]. According to our expert panel, achieving a high price for these drugs is a key prerequisite in order to make the economics of establishing a fully integrated sales organization work.

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While the working hypothesis of Gilbert, Easton, and Breazzano has been confirmed, it is necessary to look beyond the orphan drug status. Figure 1 depicts the strong correlation between achievable price and disease prevalence for the product analogs considered. Although low prices are not reserved for technologies with high patient prevalence, very high prices (i.e. yearly treatment cost above 100,000 euros) are reserved for low prevalence treatments.

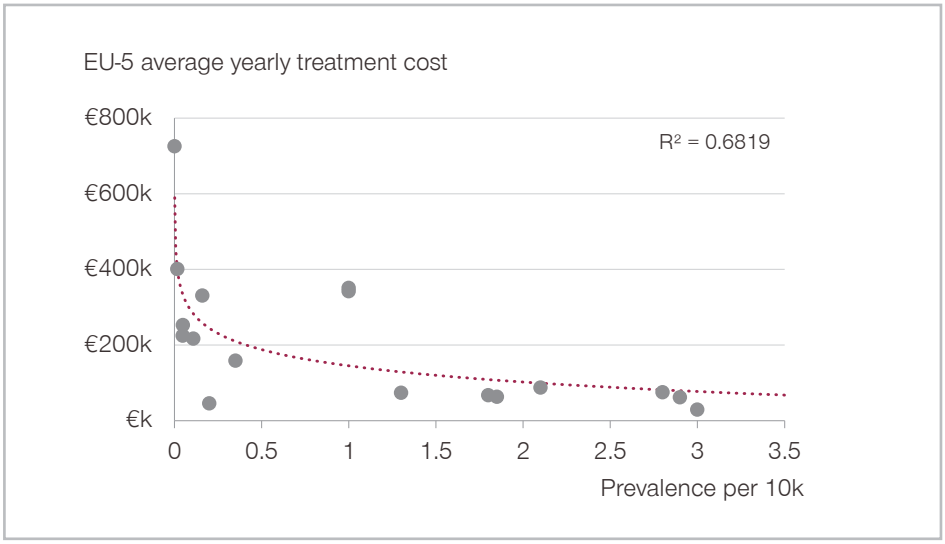


Figure 1: Achieved target price of drug depending on disease prevalence

[6] Excluding one drug having only launched in Germany with no negotiated price available; inclusion of this drug would lead to average treatment cost of around 180,000 euros.

When patient numbers are low, prices tend to be higher; however, incremental (perceived) therapeutic improvement, age of affected patients (pediatric vs. elderly), and unmet need/disease burden are important variables in determining price beyond prevalence. A multiple linear regression assessing price depending on size and age of patient population, unmet need, severity of disease, and therapeutic improvement underlines the relationship between these variables (r: 0, 78; R^2: 0.61). Achievable drug prices are not calculated; they are ultimately the result of many different factors, including the subjective value perception of payers and the negotiation excellence of the respective biopharma company. Therefore, the calculated linear relation of R^2:0.61 (R^2 in figure 1 is logarithmic) seems very reasonable, and the variables size of patient population, age of patients, unmet need, severity of disease, and (perceived) therapeutic improvement can be considered sensible factors in determining a drug's price potential and, in turn, its overall revenue potential.

From a purely financial viewpoint, these observations are also in line with the abovementioned working hypothesis. Generating considerable (annual) income from just a few hundred patients in a treatment space where basically no competition exists is much more attractive than having to prevail against numerous competitors trying to reach thousands of patients with relatively low yearly treatment costs.

Nevertheless, this assessment cannot be taken for granted. There are numerous examples of similar drugs that end up being out-licensed or distributed through partnering agreements in Europe. The (managerial) reasons for opting for an independent launch are therefore manifold. The arguments in support of an independent launch given by our external experts are discussed in the next section.

2. Opportunities and reasons to commercialize: Striving for increased shareholder value

In addition to putting patients at the core of all actions, emerging biopharma companies also strive to perform well financially in the long term and create shareholder value. Therefore, the key reason to globalize and enter new markets, such as those in Europe, is mostly economics. Other motivations for an independent launch include the desire to establish a platform for subsequent drug launches, the flexibility of having full control over an asset, and unforeseen circumstances that force the company to do it alone, e.g. if the company has not found another viable go-to-market route, such as out-licensing or partnering the product in question. Our external experts revealed that most of the time, a combination of economic value and other factors (see above) ultimately drove the "do-it-yourself" decision.

If executed properly, going it alone can offer significant financial upside and offset the considerable investment cost. In order to succeed in the long term, it is necessary to accept short-term losses. According to our internal Simon-Kucher project experience and expert interviews, establishing operations in the EU-5 and other markets via a country-clustering approach (e.g. Nordic countries) can be expected to generate costs of between 60 and 120 million euros per year (incurred mainly during ramp-up and launch)[7]. As such, it is not surprising that the companies in scope had average cash positions of around 389 million euros[8] one year prior to EMA approval. Of course, potential cost and revenue heavily depend on indication, therapeutic value offered by the drug, and managerial implementation excellence. However, if costs are managed efficiently and offset by future expected revenues, launching in Europe can offer positive 10-year NPVs of several hundred million euros. This financial upside comes with significantly higher risk than partnering or out-licensing. However, partnering and out-licensing both tend to increase complexity and may significantly limit the company's shareholder value extraction, for example, if a licensing deal was primarily structured around defined milestone payments.

The additional effort also allows companies to maintain full control over the commercial development of the drug. This includes key steps such as positioning, branding, value messaging, pricing and market access strategies, and commercialization. Therefore, pricing and market access processes can be planned and implemented in a way that they optimize potential international price referencing (IPR) inside and outside of Europe, and the global brand plan can be aligned and tailored where necessary in terms of messaging and posi-

[7] Please note that these figures are directional and take a certain forward-looking aspect into account. It is possible to operate very lean and more centralized organizations with less monetary efforts.

[8] Converted using applicable yearly average exchange rate from Thomson Reuters Eikon.

tioning. In addition to controlling the clinical and commercial development of the drug, all participants also appreciated being able to maintain control over hiring in order to get the right talent on board to implement their commercial/go-to-market strategy.

Almost 90 percent of our study participants believe that it is not worth the effort to become an international biopharma company for a single product only

The efforts to establish independent European operations provide monetary upsides and significant learning opportunities that can be leveraged for subsequent indication expansions or new product launches. Almost 90 percent of our study participants believe that it is not worth the effort to become an international biopharma company for a single product only. Our experts state that a major indication expansion or an additional product launch is needed every three to four years in order to fully exploit an organization's commercial capacity. This is also reflected by the pipeline profiles of the companies assessed. While size and quality of the pipeline vary, 80 percent of companies had at least one additional product or indication expansion undergoing pivotal trials.

At the time this industry study was initiated, the plan was to solely focus on US-based companies that wanted to commercialize their lead drug in Europe following an initial launch in the US. This approach, however, would have left out interesting analog cases, which is why the scope was broadened to all US-based companies launching their first drug independently in Europe. These companies may do so for a number of reasons. The two most frequent are delays in the FDA registration procedure (e.g. InterMune with Esbriet, Amicus with Galafold) and executive decisions by managers of US-based companies with European roots/experience who want to launch on their "home turf" first. This observation is underlined by more than half of our participants stating that the executive team was responsible for interpreting the NPV calculation and that the overall decision lays in their hands. Therefore, having the will and vision to transform into an internationally operating company is often a prerequisite. An initial launch in Europe (before the US) was seen in 25 percent of observed cases. For the remaining 75 percent, the time difference between FDA approval and EMA approval was approximately 14.2 months.

Lastly, some of the companies had no choice but to launch on their own, since they were unable to find a suitable commercialization or licensing partner. A recent example of this was seen with a US-based biotech in the allergy space that was expected by analysts to seek a partner agreement and seemed to be doing so actively. Yet, over time, the narrative changed from "being open to anyone approaching them for partnering" to most likely launching in the EU-5+ on their own.

As stated above, a company launching its first (orphan) drug is not guaranteed to succeed. For every excellent example of successful launches with subsequent acquisitions by big pharma and sky-rocketing share prices, there are

other examples where companies could not fulfill their own high expectations or those of their shareholders. The reasons for these unsuccessful ventures included limited robustness and quality of clinical evidence for the drug, a lack of engagement with key medical and payer stakeholders at regional, national, and local levels, an inadequate pricing and market access strategy, and a mismatch between the value the company perceives the drug to offer and the value perceived by European payers, resulting in a mismatch between the organizational setup and scale vs. actual achievable revenue. As such, the potential (financial) upsides must be critically assessed in terms of their likelihood to occur and the investments required to extract the product's overall value need to be continuously challenged. Ultimately, success is anchored in having the right drug to fill a significant perceived unmet need for patients and payers. Therefore, the decision on whether to go it alone or seek a partnership should start long before FDA/EMA approval is received. Continuous, unbiased assessment of the opportunities as well as the will and vision to fully execute the strategic leap is needed in order to build a robust organization and implement the commercialization strategy appropriately across multiple regions. The following pages highlight the seven key factors that can favorably influence the outcome of a launch.

3. The seven secret ingredients for success: Pursuing the full extraction of a drug's economic value

Considering that the majority of first drug launches target small patient populations with a high unmet medical need and/or high disease burden, the commercial opportunities are significant.

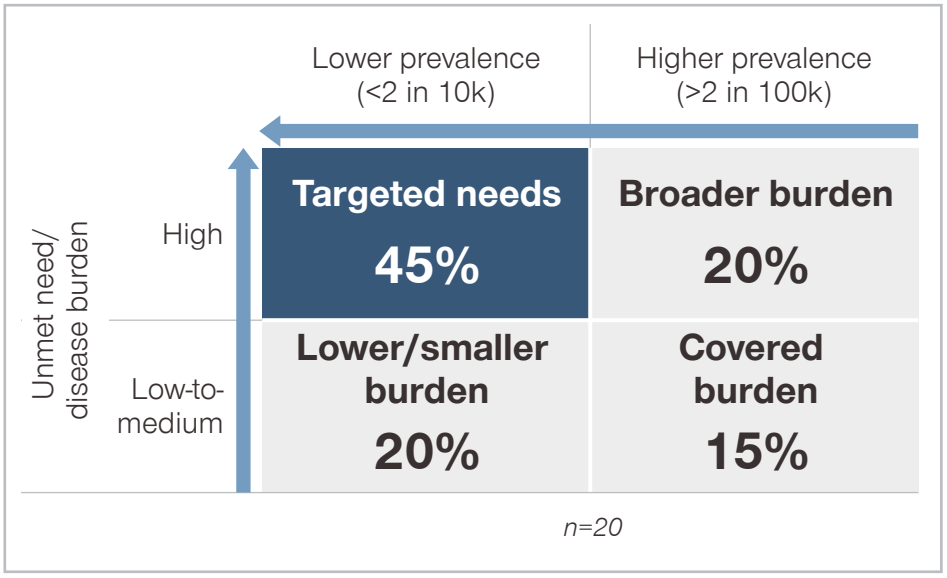


Figure 2: Characteristics of drugs in analyzed sample (n=20)

Nearly 90 percent of the industry experts interviewed believe that companies, especially those based in the US, fail to plan properly for a timely, regionally tailored, and well-executed launch in Europe

To tap these "targeted needs" and the commercial potential in Europe, companies must broaden their horizons beyond the US early on. They need to be able to steer the development and positioning of the drug and lay the foundations for a commercially successful launch in both regions. They must consider both clinical and organizational prerequisites. However, nearly 90 percent of the industry experts interviewed believe that companies, especially those based in the US, fail to plan properly for a timely, regionally tailored, and well-executed launch in Europe. Based on their own first-hand experiences, our expert panel has identified seven secret ingredients beyond product characteristics for companies launching their first drug in Europe (Figure 3):

Figure 3: Seven secret ingredients for successfully launching and commercializing a company's first drug in Europe

Secret #1: Gain new perspectives (early on)

All of our experts were concerned about a common trait shared by the senior executives of emerging biopharma companies. Either they are too focused on the scientific quality of their work (research-focused) and do not take commercial considerations into account during the development of their drug (e.g. formulation/application, appropriate trial design in terms of clinical endpoints or study location) or they are too focused on only excelling in US markets and fail to understand the global potential (e.g. the European market) and requirements for tapping this potential early enough.

As pointed out by our experts, commercial aspects need to be considered at a much earlier stage. Company executives need to broaden their outlook regarding the commercial attractiveness of their drug in worldwide markets, ideally at the very beginning of the process or, at the latest, prior to setting up pivotal clinical trials. This can be facilitated by bringing on board a chief commercial officer at an early stage to help assess commercial viability and, if necessary,

by seeking the support of a VP for commercial affairs/P&MA with European or global experience to provide guidance on the full potential and the regulatory and clinical requirements of the drug[9].

Secret #2: Debias your assumptions; be a challenger

"Often, there are one to three executives who drive global strategies and decide on critical steps all by themselves." (VP for market access, US-based biotech)

Behavioral psychology not only plays a significant role in managing stock portfolios; our experts have witnessed two common errors in thinking among the executives of emerging biopharma companies:

- **Mustering courage:** Executives overestimate the therapeutic improvement of their drug based on false assumptions and/or fail to identify other differentiation opportunities
- **Conservatism:** Executives are reluctant to update their beliefs in the face of new evidence, such as the viability and attractiveness of launching in certain markets or payer requirements regarding trial design and clinical data

Although the analyzed companies employ an average of 473 FTEs (globally) one year prior to their drug's European launch, such errors in thinking are likely to have a greater impact at earlier stages. When companies have much less FTEs and the executive team mainly makes all their decisions on their own: The smaller the company is or the more power its executives have, the greater the impact these errors can have in the long term.

The first step is to realize that these and other biases exist. Further, executives and their direct reports must create a collaborative atmosphere characterized by an open exchange of ideas without specific constraints. In addition, all of our industry study participants, regardless of whether they had worked with Simon-Kucher in the past, acknowledged the importance of external consultancies in bringing in new perspectives or challenging existing mindsets. The nature and depth of this collaboration should increase with each development stage of a drug, from high-level market sizing in preclinical stages, to payer-rationalized clinical trial design and (early) pricing and reimbursement assessment for Phase II/pivotal trials, to sophisticated market forecasting, to commercialization/go-to-market due diligences, to market entry strategies and NPV exercises, and finally to launch readiness programs.

[9] The converse also applies; Europe-focused companies or commercially oriented executives should broaden their horizons in the opposite direction.

Our experts specifically and unanimously highlighted the critical importance of running thorough (and externally performed) commercial due diligences to identify and evaluate options regarding market entry strategies

Given that the decision to go to Europe ultimately depends on financial considerations, our experts specifically and unanimously highlighted the critical importance of running thorough (and externally performed) commercial due diligences to identify and evaluate options regarding market entry strategies. Commercial due diligence derives different scenarios comparing pricing potential against physician prescribing behavior given expected payer/reimbursement restrictions to costs associated with commercializing a drug (i.e. no sunk cost) and assesses risk-adjusted NPVs from these different scenarios and strategies to determine the most favorable one and then pursue the specific market entry strategy in a dedicated manner (Figure 4).

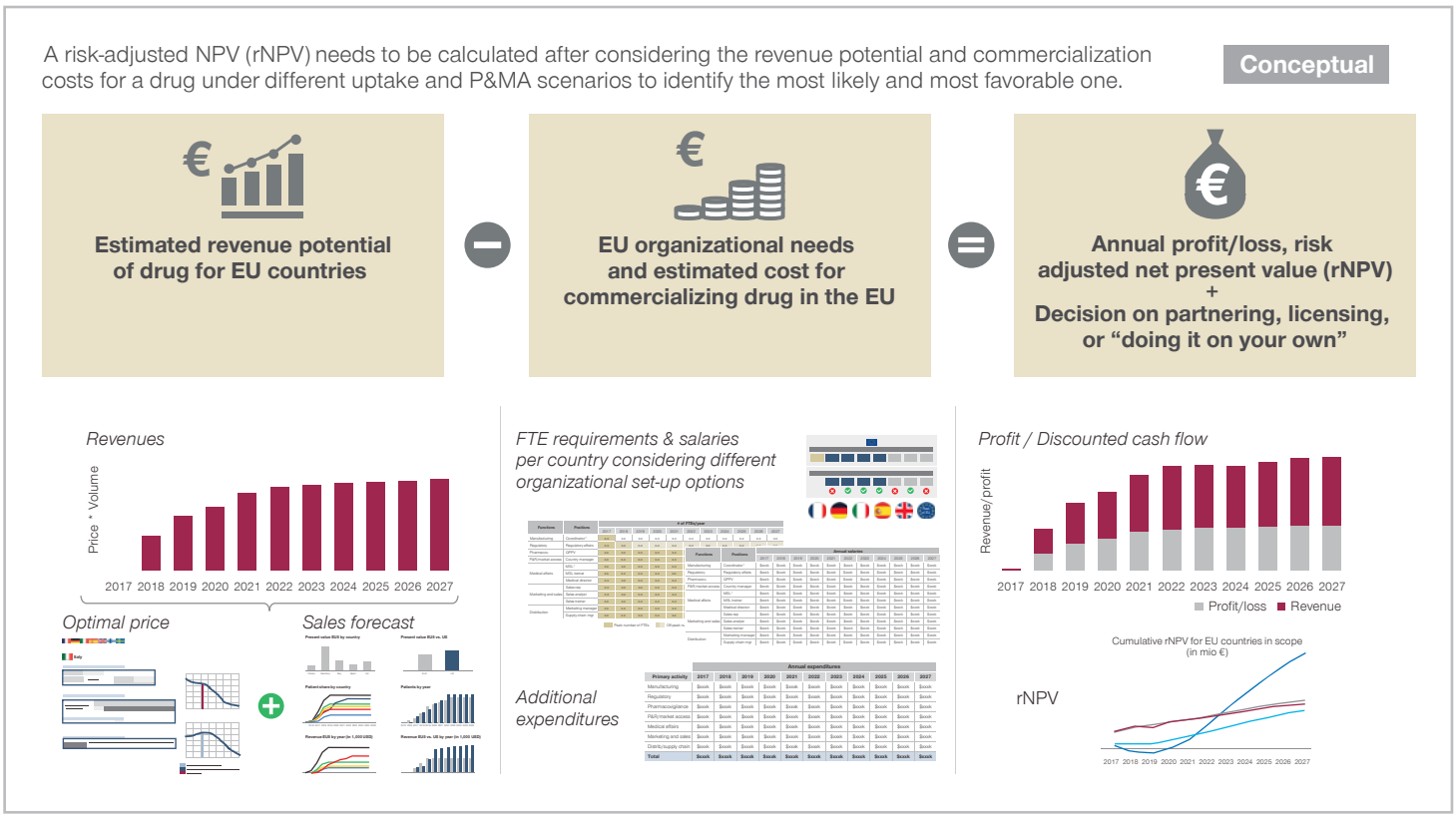


Figure 4: Conceptual commercial due diligence approach

Secret #3: Tear down existing silos

Nearly 80 percent of respondents highlighted the importance of close collaboration between R&D, medical, P&MA, marketing, and other departments (e.g. patient services, supply chain, manufacturing) at global, regional, and local levels

Launching in Europe is daunting and complex. It is necessary to fulfill regulatory requirements and come to an agreement with five (EU-5), 28 (EU) or even 44 (Europe) different country-specific health authorities to be granted potential market access. The boundaries between key stakeholders are diminishing due to the significant influence of patient advocacy groups on the outcome of regulatory assessments as well as the shift in decision-making away from physicians toward payer-supported treatment guidelines/algorithms. In this context, nearly 80 percent of the respondents highlighted the importance of close collaboration between R&D, medical, P&MA, marketing, and other departments (e.g. patient services, supply chain, manufacturing) at global, regional, and local levels.

The importance of R&D, medical, P&MA, and marketing are obvious and were considered essential to a company's success by all of our participants (with prompting). However, a fully integrated commercial strategy is one that aligns global marketing and launch capabilities with pricing, market access, and new product planning. It should also consider the specifics of global markets and the R&D organization to ensure that the drug can deliver value for all of its stakeholders: patients, physicians, payers, and policymakers. A well-known best practice to break up silos and identify assumptions is to engage early on with regional regulatory bodies (e.g. EMA) and country-specific payer authorities (e.g. NICE in the UK, TC in France, and G-BA in Germany) to understand key requirements for the ideal clinical trial design and successful approaches to pricing and market access.

The value of breaking up silos is highlighted by an anecdotal experience from one of our experts. When conducting the initial commercial due diligence cross-functionally for their innovative biological product, they realized their manufacturing and supply chain capabilities were insufficient to cater for full commercial scale and were able to adjust capacity before they ran into stocking issues. Running out of stock hurts a company's reputation as well as its top and bottom lines and dramatically impacts the lives of patients.

Secret #4: Build a tailored operational model for Europe

A company's operating model is the link between strategy ("making the leap") and its proper implementation ("succeeding"). It cannot simply be a copy of global structures; instead, it should be specifically tailored to European markets, suit the company's requirements and capabilities, and most importantly, enable collaboration between and within global, regional, and country-affiliate divisions.

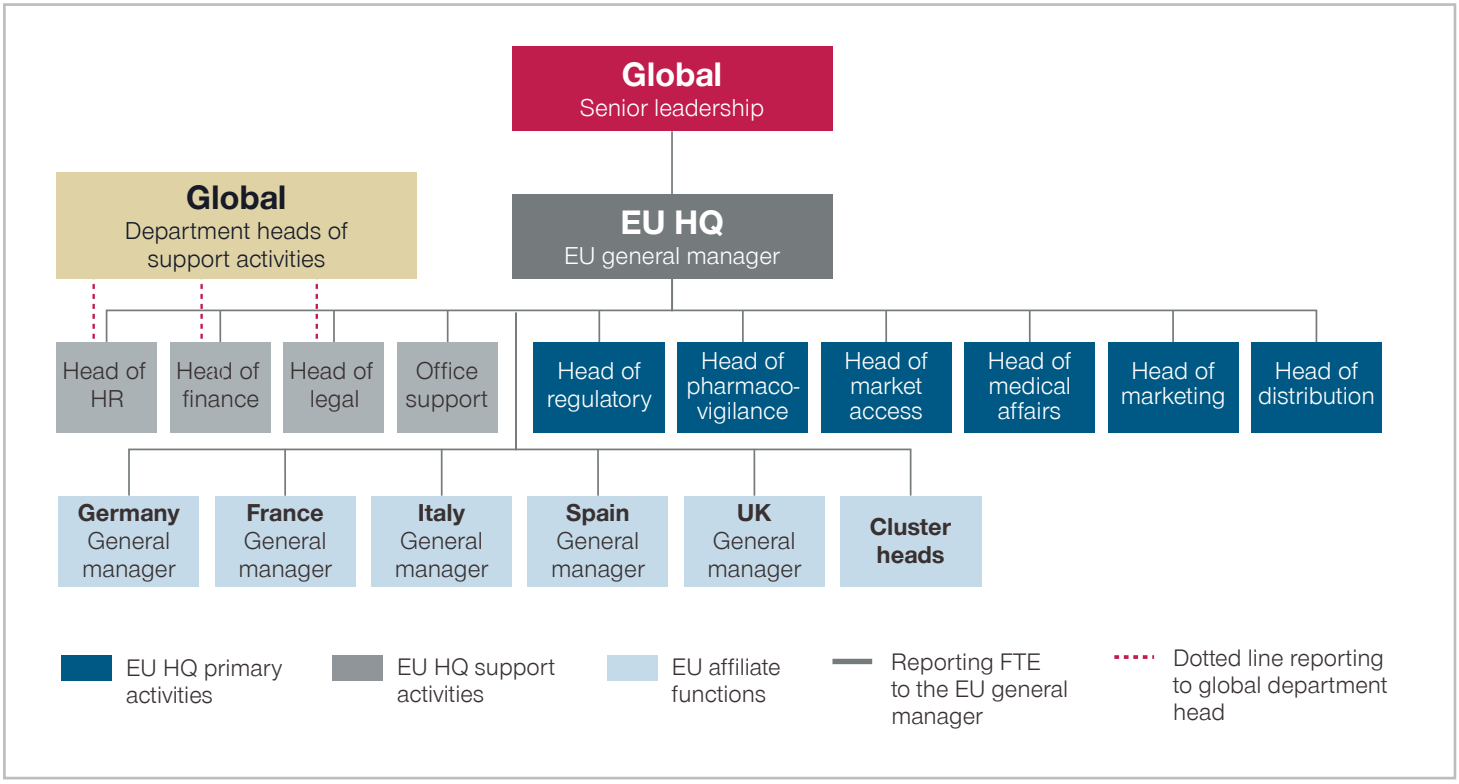
A. Structure: The first building block is setting up the right organizational structure to define lines of business and accountability, shared services, and coordination between functions and countries. Although in theory there are numerous ways to structure an organization, all but two participants favored a structure with regional headquarters in a location where the company could

Figure 5: Value chain matrix in the life science industry

seek tax and cluster benefits, maintain a good connection to the US headquarters, and attract talent while also having affiliates in the EU-5 and strategic cluster approaches throughout the region (e.g. Nordics, Benelux, Iberia). The decision of whether to partner with another company or target smaller markets should be made on a case-by-case basis, taking into account financial and non-financial risks and benefits.

Organizational structure is based on the value chain in the life science industry (Figure 5). The activities required to commercialize a product in Europe vary from case to case and also depend on the need for certain skills within a company. However, there are certain requirements that our experts believe to be essential for establishing operations in Europe. Next to the European GM, each of the key functions (P&MA, medical, commercial, and pharmacovigilance/clinical trial operations) must be represented by a VP or head of department (Figure 6). Despite the extra cost, all participants believe that these functions and decisions cannot be made solely from the US and warn that adding extra work on top of the US-focused activities will demotivate and frustrate US employees. Only regulatory could be handled mostly from the US if the launches are in sequence. All participants, regardless of whether they had manufacturing in Europe or were following a centralized warehouse/CMO approach, recommend having a single person who is responsible for overseeing the whole supply chain/manufacturing/distribution process with operating vendors in place.

Figure 6: Conceptual European operational set-up



Viewpoints were mixed regarding outsourcing other support functions, such as finance, HR, IT, and legal. Most frequently, participants told us that the majority of these support functions were initially outsourced but then staff were gradually hired internally. Two support functions that may require direct internal FTEs are legal and HR. None of our respondents believed it would make sense to execute nonstrategic tasks like payroll management or dossier writing (not strategy development) internally.

At a country-level, especially in the EU-5, market specifics require a minimum number of leading medical, P&MA, and marketing functions. Depending on how lean the structure is kept, those functions could be potentially shared by FTEs, e.g. the GM acts as GM and head of market access. In any case, it is likely that the actual tasks will be broader than the typical role description would suggest. In addition, the lead functions are supported by customer-facing MSLs and sales reps in the field to shape the market actively. Depending on the requirements, other analysis (e.g. financial analysts) and support functions (e.g. HR) may also be needed.

Finding and empowering the right talent was identified by over 80 percent of our industry experts as a key success factor to pay attention to

Ultimately, the organizational structure should support the go-to-market strategy and financial objectives but must be the right size to serve the different disease areas and stakeholders as effectively as possible.

B. Capabilities and mindset: It is obvious that securing the right talent can be the difference between winning and losing in an increasingly fierce and competitive market. Finding and empowering the right talent was identified by over 80 percent of our industry experts as a key success factor to pay attention to. However, one third of the experts raised the concern that hiring timelines are often too short to enable proper selection in terms of skills, local experience, personal fit, and drive. As one of our participants put it: “Often, too much focus is put on experience and hiring excellent senior people. We need people who are not only able to tell others how to get things done but actually get it done by themselves.” It is thus recommended to not only consider what people have done in the past, but also what they will achieve in the future. Hiring the European GM is a matter for the CEO, as the European GM must ensure that individuals with these qualities are recruited from day one. Again, this will require time, since the GM not only has to find the right people for the job but also create an environment that is appealing to the desired talent while preparing initial launch steps. One former European GM from a US-based biotech stated that he had spent nearly 50 percent of his time meeting and selecting suitable candidates. Further, the prospect of creating a company from scratch may not always draw in the desired talent, so companies must be prepared and willing to make their offering financially attractive such as by offering performance based share compensation.

Often, too much focus is put on experience and hiring excellent senior people. We need people who are not only able to tell others how to get things done but actually get it done by themselves

C. Empowerment: *"You hire all these experienced and talented people only to not listen to them? Regional and global executives can only direct effectively if they want to know what is happening in the markets and region." (Chief commercial officer, US-based biotech)*

Broadening perspectives also means understanding that the company vision can be best executed by the hired experts. Therefore, companies must balance regional and global decision-making as well as local and regional responsibilities. The objective is to create a collaborative environment with engaged employees that can work and provide input across functions and countries.

A key pillar for this kind of collaboration and empowerment is to create a governance structure that allows for rapid decision-making in a cross-functional setup and incorporates the input and perspectives of regional and local divisions. However, the majority of our industry experts believe that providing input should not necessarily be equated with decision-making. The final decision maker at the country-affiliate level is the GM who reports (along with regional heads and VPs) to the European GM who, in turn, is accountable for the overall success in the region of Europe. Other means to enable exchange include setting up cross-functional roles. Many of our industry study participants who are or were (affiliate) GMs by title were actually executing cross-functional roles, e.g. operating as head of P&MA and country GM.

D. Flexibility: The operating model does not have to be fully staffed from the get-go and can be added to over time according to local and regional demands. Furthermore, depending on the launch/commercialization status of the drug in the US, the entity may be burning cash. The financial impact of when and how to staff another entity must be considered. However, in general, key regional lead functions (medical affairs, P&MA, regulatory, and commercial) must be filled first. In regard to which functions to hire first, our experts had different opinions. Although the sequence varies, most commonly P&MA, medical affairs, and regulatory are considered the first key hires. The ideal timeline to start hiring is two to three years prior to launch (e.g. the regional GM), since this leaves enough time to fill key regional functions in order to map out and engage early on with key stakeholders at national, regional, and local levels as well as drive and prepare local market access and reimbursement (e.g. dossier strategy development) (Figure 7).

In regard to which functions to hire first, our experts had different opinions. Although the sequence varies, most commonly P&MA, medical affairs, and regulatory are considered the first key hires

For affiliates with longer P&MA timelines or potentially delayed P&MA decisions, such as Spain, GMs should plan the commercial affiliate organization conservatively to account for delays and other unforeseen events. For these affiliates, it is important not to drain the bottom line too much while no commercial sales are being made. At the same time, companies must be ready to

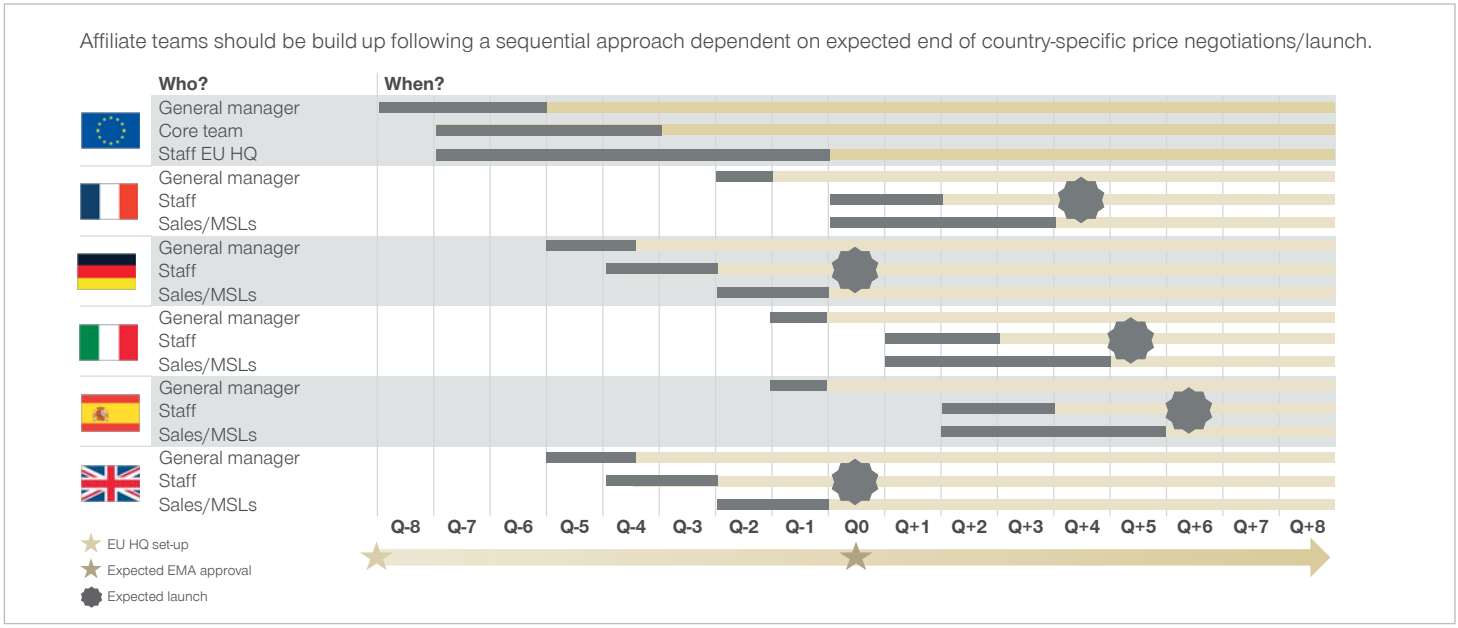


Figure 7: Exemplary FTE ramp-up for EU HQ + EU-5 affiliates

switch to launch mode quickly to boost the top line as soon as possible after a successful pricing and market access negotiation in a particular market.

First-year losses are inevitable when setting up an operating model, especially during the ramp-up phase. However, our experts have reported various methodologies to estimate the financial viability of setting up an operating model. They include challenging the feasibility of achieving positive operating income (without cost allocation of global spending, e.g. R&D) within three years after launch, requiring ~around one million euros in sales per FTE, relative maximum costs of 10 to 20 percent of peak revenues, or absolute estimates of 60 to 120 million euros per year (incl. non-FTE spending but without global cost allocation). On the revenue side the estimates/requirements are similar (yet mirrored to cost expectations). However, minimum expected revenues in the range of 200 to 400 million euros coupled with the favorable long-term perspective of a bolstered pipeline are considered a robust prerequisite to make such ventures commercially attractive. Nevertheless, each case requires a sophisticated and individual commercial due diligence assessment for the drug, disease area, and financial and organizational requirements (optimal set-up and FTE requirements) of establishing the regional (and country-affiliate) organization(s).

Secret #5: Create awareness and differentiate

A frequently mentioned success factor for all activities was "starting early."

A frequently mentioned success factor for all activities was "starting early." For most orphan drugs with a small patient population suffering from a severe disease that most payers and even some physicians are unaware of, timely preparation is key. Companies need to be patient-centric and fully understand the patients' disease experience and patient journey in order to properly address their needs, create awareness about the disease, train professionals, and ensure patients get sufficient access to the medication they need.

Regulators, HTA agencies, and payers often turn to patient advocacy groups and KOLs to gain insight into the actual incremental benefit of a drug and rely on their input. Particularly for orphan drugs, these stakeholders can be the decisive factor in terms of market authorization, pricing, and speed to market access and must therefore be seen as key partners. To ensure access, it is important companies understand patients' needs and treatment pathways and are able to communicate their product's benefits within the framework of patients' experience in a differentiated way to direct and indirect decision makers at national, regional, and local levels. The fact that emerging biopharma companies are now specifically hiring heads of patient advocacy at a regional level demonstrates how important this competency is.

Further, due to the smaller patient population sizes involved, simply increasing the number of sales reps will not drive up sales proportionally. Instead, companies should address the market through a multi-channel approach where MSLs ensure acceptance and endorsement from KOLs and patient advocacies, sales reps act as key account managers for treatment centers, and the overall company engages as an integrated (service) partner for patients. Therefore, the key touchpoints and components of medical excellence are engagement, patient advocacy, KOL/physician education, ensuring proper diagnosis, access to treatment (see next section), and patient support and retention.

Secret #6: Excel in P&MA – If you make it there, you can make it everywhere

Given that deciding to make the organizational leap to Europe ideally depends to a large extent on performing a thorough commercial due diligence assessment and understanding of a drug's pricing and market access potential, there is a high need to excel in pricing and market entry in terms of planning, execution, and final price negotiations in each European target market.

First, it is important to assess and understand a drug's country-specific market access potential. This involves bringing together product-specific, indication-specific, and country-specific factors that determine the perceived value and price potential of a drug. It is key for companies to:

1. Gain a comprehensive understanding of the asset's advantages, disadvantages, and perceived therapeutic value among payers and clinical stakeholders
2. Understand the strategic implications of treatment pathways and respective funding flows (e.g. identify key P&MA stakeholders)
3. Incorporate these observations and bring them together in a cross-country assessment of pricing potential that includes clinical and market access scenarios tailored to the specific nature of the drug

"Traditional pricing models, such as fixed price per pill or injection, will not help mitigate the clinical limitations your drug might come with, and payers will try to leverage this during price negotiations. We must find solutions to monetize our innovations properly and in a sustainable way." (Global head of P&MA, US-based biotech)

Drugs for "targeted needs" often come with clinical limitations (e.g. only Phase I/II data, limited trial population, short trial durations, new treatment approaches with safety/tolerability concerns), which cause financial concerns for payers despite the patient populations often being smaller. In these cases, a detour from traditional pricing can help address the challenges commonly faced by such paradigm-shifting therapies. Innovative access agreements, such as payment by results, risk-sharing or annuity payments, have made headlines several times and are widely discussed among different payer stakeholders. To make such agreements happen, manufacturers must not only convince payers of the benefits of their drug but also be willing to collect and grant access to real world evidence (RWE) within legal boundaries.

Further, it is important to consider country-optimal pricing strategies in an international context due to formal and informal international price referencing/re-referencing. In Europe, a large number of countries use formal international price referencing rules when determining the achievable price for a new drug in their market. Moreover, the threat of price information being exchanged among payer colleagues on an informal basis needs to be considered. Therefore, not only must the "story" (i.e. value story, branding, pricing strategy) be aligned across countries to ensure harmonized P&MA outcomes, for certain markets, it may also mean deviating from the country-individual optimal price strategy in order to optimize P&MA across the entire European region or defining a specific country launch sequence that best preserves overall achievable revenue for the region (Figure 8).

It is important to consider country-optimal pricing strategies in an international context due to formal and informal international price referencing/re-referencing

Upon approval, each affiliate (with regional support) must prepare and best defend a company's price and access strategy effectively to ultimately prevail and succeed in P&MA. Country-individual preparation for P&MA negotiations

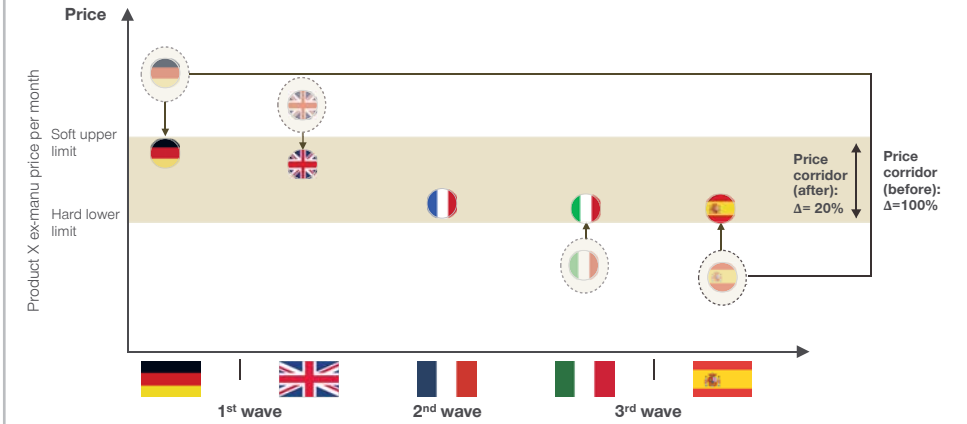


Figure 8: Conceptual launch timeline and price strategy considerations

with payers by developing negotiation strategies and tactics that include the necessary tools and supporting content is key. For example, an unfavorable G-BA benefit assessment in Germany or low ASMR rating in France can have a severe negative impact on price (negotiations) and utilization in these markets and beyond and is often the key reason for unsuccessful launches overall, not only from a P&MA perspective but also from the commercial side.

Secret #7: Leverage alternative access programs to support your P&MA and commercial strategy

Alternative access programs (AAP) can create true value for patients and grant patients access to an urgently needed treatment outside of the standard reimbursement pathways. The most common types of programs are early access or compassionate use programs.

These programs also provide significant (financial) upsides to the manufacturer, regardless of whether the alternative access pathways are reimbursed like France's ATU program or non-reimbursed ones like the law decree 1015/2009 (compassionate use) in Spain.

AAPs allow companies to build up a patient base that will become fully commercially viable upon reimbursement. From a medical and P&MA perspective, AAPs allow RWE to be collected, which is key for many different reasons. RWE can influence future therapy management and algorithms, which will become key decision drivers, making RWE increasingly important for P&MA decisions and drug reassessments, especially for orphan drugs pursuing innovative pricing schemes (see secret #6). In addition, RWE registries can (partially) replace randomized controlled trials for such drugs.

Moreover, AAPs help create awareness and goodwill among key (clinical) stakeholders which not only helps maintain healthy collaborative relationships

between patients and prescribers but, indirectly, may positively impact payer and regulatory discussions and decisions.

Lastly, according to our industry experts, AAPs are a good opportunity to test existing operations, by getting patients into treatment, overseeing and executing the supply chain, collecting RWE/safety data, and providing an excellent learning opportunity for the manufacturer prior to launch.

4. Conclusion: The dos and don'ts – Hunting for advice

All of our study participants believe that it was the right decision for their current or previous companies to commercialize their lead drug on their own in Europe. Despite the risks and, in some cases, roadblocks, they believe they were able to create significant patient value, lay the foundation for future launches, and support the international growth of their companies as well as increase their shareholder value.

All of the participants' contexts, products, and market situations were different and any future biopharma market situation will also be unique. Nevertheless, a few managerial implications and considerations hold true for any emerging biopharma company to apply the seven secret ingredients for success to their commercialization strategies of its first drug in Europe.

Do

i. Assess and incorporate the implications of a European commercialization strategy early on

ii. Understand the product's pricing and commercial value, potential hurdles, and key stakeholders to address in Europe

iii. Understand the importance of finding and empowering the right talent; be willing to relinquish some control in order to enable a tailored execution of their strategy

iv. Plan ahead and determine how to leverage the future commercial organization

Don't

v. Don't rely on experience and old assumptions; constantly challenge them and allow them to be challenged; seek expert help from a trusted advisor, if needed

vi. Don't underestimate the operational and financial requirements for making the commercial/organizational leap to Europe

vii. Don't overestimate your drug's potential or the company's European capabilities; make reasonable, fact-based decisions

viii. Don't copy and paste other companies' approaches; design a unique commercialization/go-to-market strategy tailored to your specific drug and venture

ix. Don't commercialize on your own at all cost; certain markets are better left to third parties

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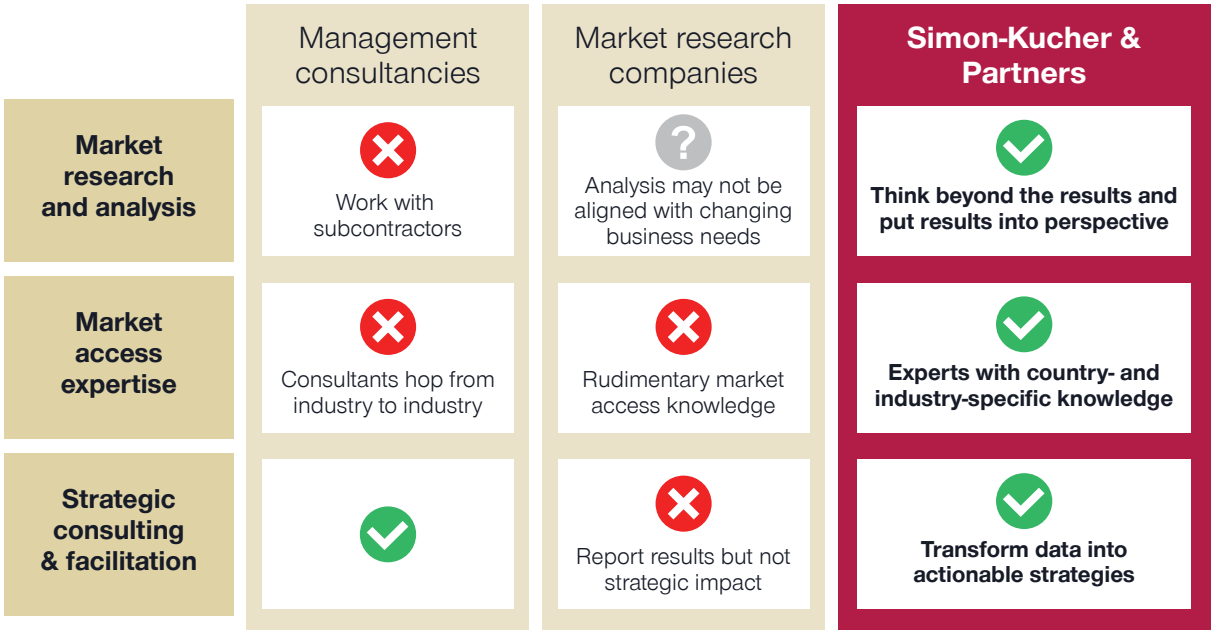

"This is what sets Simon-Kucher apart from all the vendors out there."

- Market access representative from a mid-sized biotech company

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Annex: List of drugs/companies included in study

Drug	Inn	Company	Indication	Year of EMA approval	Orphan designation	Comment
Mepsevii	vestronidase alfa	Ultagenyx	Mucupolysaccharidosis VII	2018	✓	At time of publication: Only launched in GER w/o no negotiated price
Onpattro	patisiran	Alnylam	hATTR, Stage 1 or 2	2018	✓	
Rubraca	rucaparib	Clovis Oncology	Ovarianc Cancer 3L+(BRCA/platinum sensitive)	2018	✗	Had their EMA approval in 2018 but only launched in Mar 2019 with two indications (3L and maintenance)
Tegsedi	inotersen	Akcea	hATTR, Stage 1 or 2	2018	✓	
Zejula	Niraparib	Tesaro (during late-stage of launch GSK)	Maintenance ovarian cancer platinum-sensitive	2017	✓	Included because advance stage of commercialization at M&A with GSK in contrast to other companies (e.g. Onyx)
Galafold	migalastat	Amicus	Fabry disease with an amenable mutation	2016	✓	
Ocaliva	obeticholic acid	Intercept Pharma	Biliary cholangitis	2016	✓	
Hetlioz	tasimelteon	Vanda Pharmaceuticals	Non-24-Hour Sleep-Wake Disorder	2015	✓	
Translarna	ataluren	PTC Therapeutics International	Duchenne muscular dystrophy	2014	✓	
Iclusig	ponatinib	Ariad Pharmaceuticals	CML or PH+ ALL	2013	✓	
Provenge	sipuleucel-T	Dendreon	Asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer	2013	✗	
Kalydeco	ivacaftor	Vertex Pharmaceuticals	Cystic fibrosis (one copy of the G551D mutation)	2012	✓	
Revestive	teduglutide	NPS Pharmaceuticals	Short Bowel Syndrome	2012	✓	
Cinryze	C1 inhibitor	Viropharma	Angioedema attacks	2011	✓	
Esbriet	pirfenidone	Intermune	Mild to moderate idiopathic pulmonary fibrosis	2011	✓	
Abraxane	nab-paclitaxel	Abraxis Bioscience	Metastatic carcinoma of the breast	2008	✗	
Revlimid	lenalidomid	Celgene	2L+multiple myeloma (+ dexamethasone)	2007	✓	
Soliris	eculizumab	Alexion	Paroxysmal nocturnal haemoglobinuria (PNH)	2007	✓	Expansion to children happened later
Naglazyme	galsulfase	Biomarin	Mucopolysaccharidosis VI	2006	✓	
Scenesse	afamelanotide	Clinuvel UK	Erythropoietic protoporphyria (EPP)	2014	✓	Australia-based company. Included due similar context: Ex-European, English-speaking

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Christian Schuler is a Senior Partner in the Life Sciences division of Simon-Kucher, working for the past six years out of the company's office in San Francisco, USA and has recently relocated to Munich, Germany. Previously, he worked for eight years in the company's headquarters in Bonn, Germany.

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Lukas Hirn was a Senior Consultant in the Life Science division of Simon-Kucher & Partners in Munich, Germany from 2014 until September 2019. While maintaining an international focus, he mainly worked within the European and German markets.

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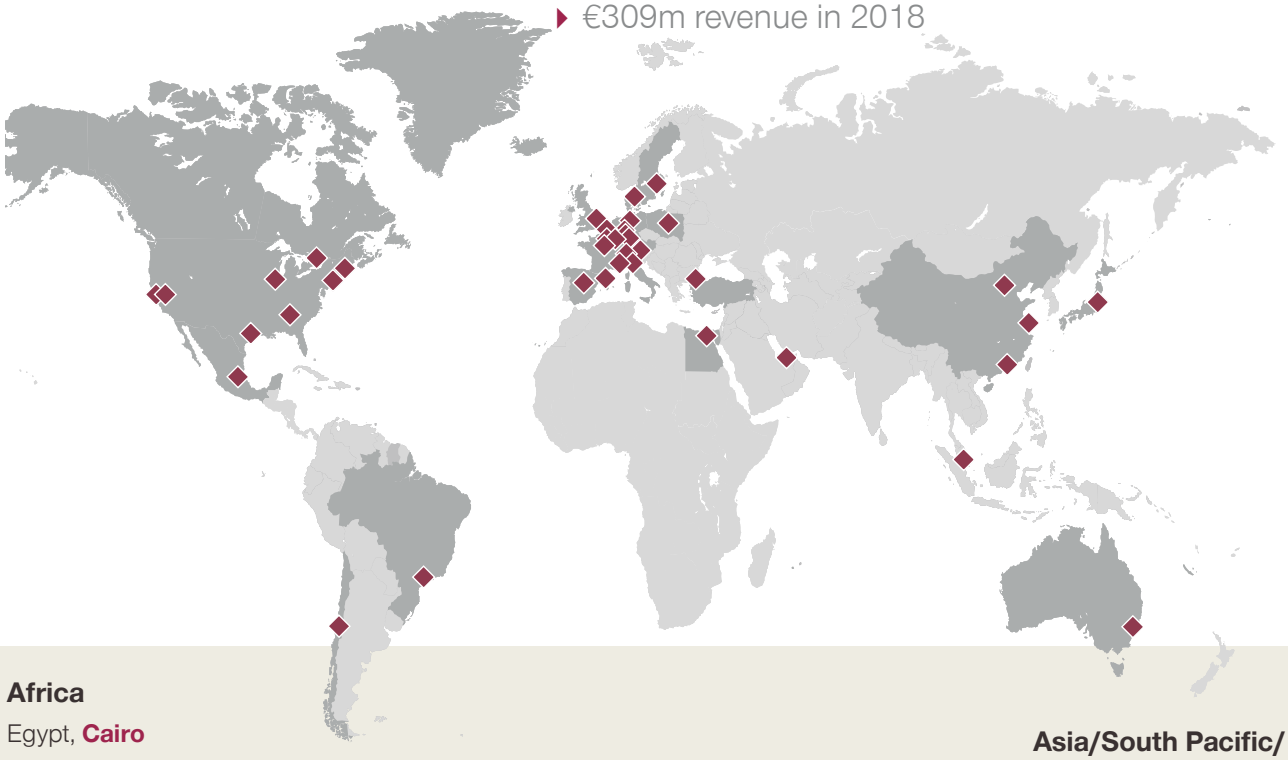

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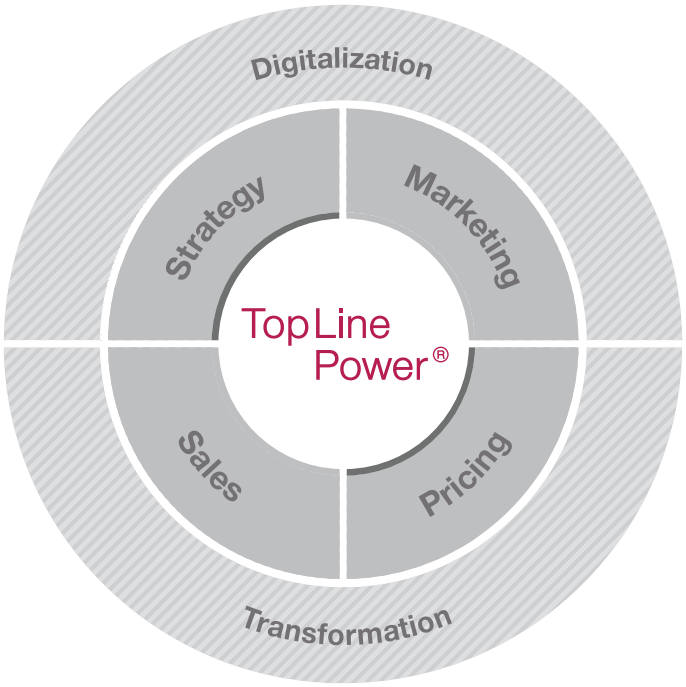

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