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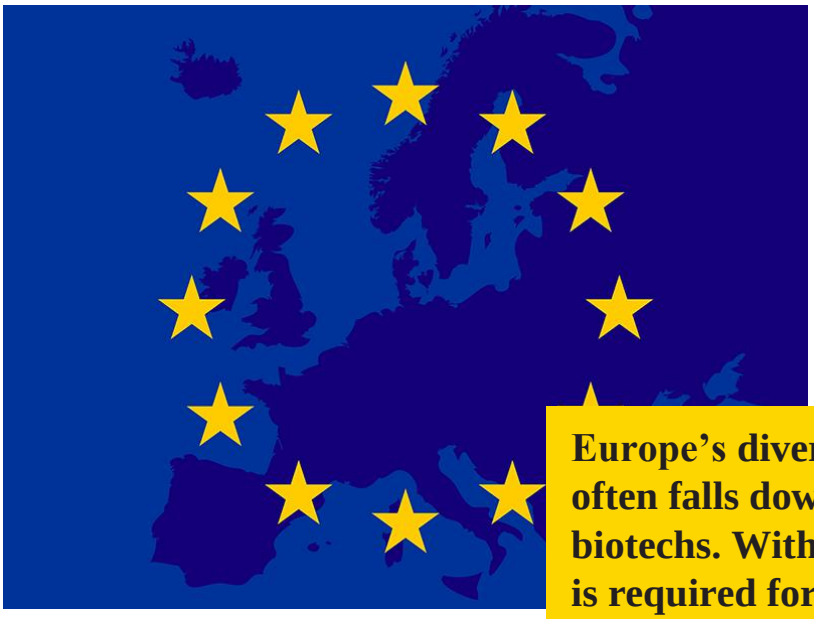
INSIGHTS

Crossing the Pond – How US Biotechs Can Succeed in Europe



Europe's diversity and complexity means it often falls down the priority list for US biotechs. With a solid understanding of what is required for success, the opportunity to make the most of the world's second biggest pharmaceutical market can be realised.

- *Europe is a collection of unique markets with a reputation for being difficult to the pharmaceutical industry, particularly with regards to pricing*
- *Each country decides its own market access and pricing leading to a level of complexity that non-European companies can find overwhelming – this is particularly true for US biotechs that are used to a homogenous market*
- *A range of options exist for US biotechs that seek to bring their product to Europe – a strategic collaboration with a well-established local player is frequently attractive*
- *Companies that choose to own commercialise need to invest both time and capital to understand the complexities of Europe if maximum value is to be created*

Europe is Diverse but has a Common Regulator

Europe can be defined based on geography alone, but for the purposes of pharmaceutical commercialisation, the European Union (EU) is what really counts. The EU is currently a group of 28 countries that operates as a cohesive economic and political block. Its 'four freedoms' – the free movement of goods, people, services and capital over boarders within the block – lie at its heart and are the basis for its multitude of laws and treaties. They are designed to remove trade barriers and harmonise national rules at an EU level. The EU has 24 official languages, a common currency which most, but not all countries use, and over 500 million citizens. It is worth noting that Switzerland, a major player in the global pharmaceutical market, whilst on the continent of Europe, is not part of the EU. Switzerland leverages and adheres to many of the EU regulations, but it remains fiercely independent with distinct laws and a separate currency. Norway, Liechtenstein and Iceland are other European countries not part of the EU. These countries sit within the European Economic Area (EEA), which enables them to trade with the EU and support the 'four freedoms' but excludes them from other laws and treaties, such as those involving agriculture or fishing.

The EU body that matters most to pharmaceutical companies looking to commercialise in Europe is the European Medicines Agency (EMA). It has a wide range of responsibilities including pharmacovigilance and facilitating early access to medicines. However, for companies looking to launch an asset, the EMA's role as a regulator is the most relevant. Approval of a medicine for human use can follow one of three pathways, with the 'centralised authorisation' procedure being the most common. In this procedure the company submits a single marketing authorisation application to the EMA, which if successful, enables the company to make the product available to all countries in the EU. The EMA's Committee for Medicinal products for Human Use (CHMP) conducts a scientific evaluation of the medicine and makes a recommendation on whether the product should be marketed or not. If approved, the product can be marketed in all EU states and those within the EEA.

The centralised procedure is *compulsory* for medicines that contain a new active substance to treat the following therapeutic areas:

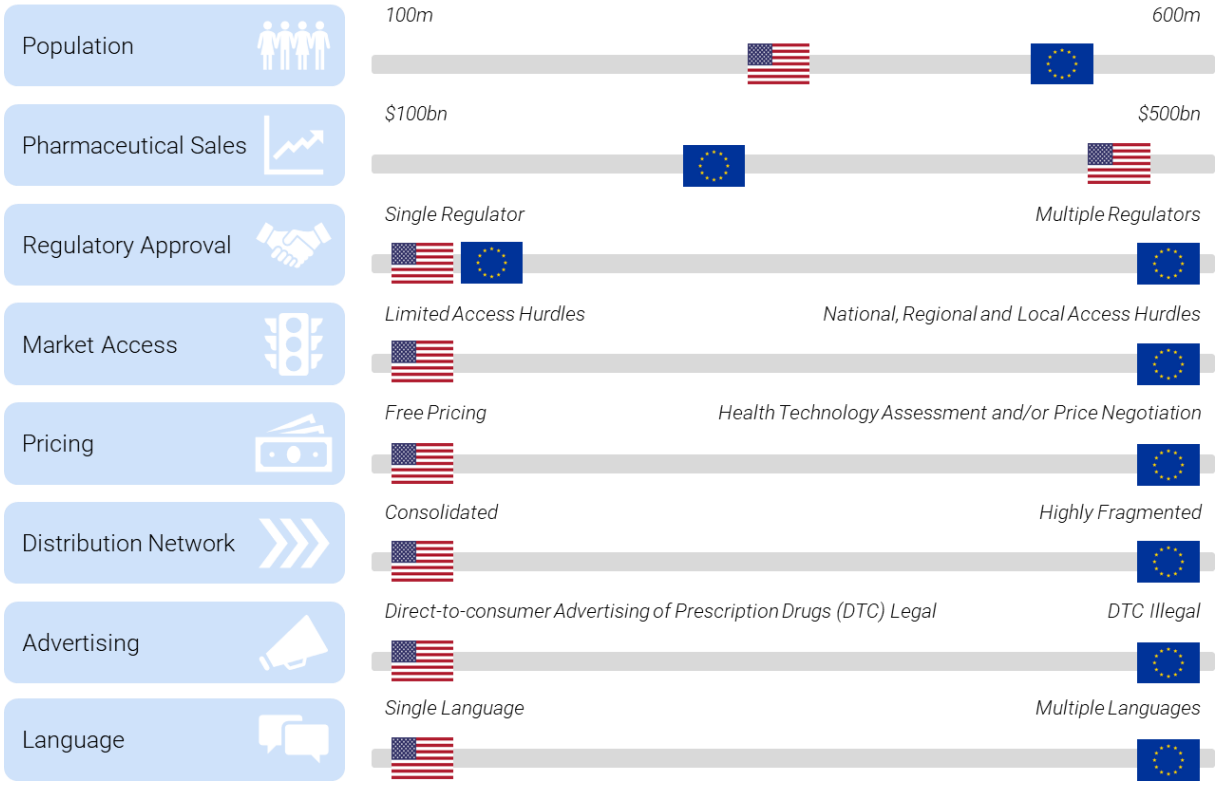
- Auto-immune and other immune dysfunctions
- Cancer
- Diabetes
- Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
- Neurodegenerative diseases
- Rare diseases (orphan medicines)
- Viral diseases

It is also compulsory for medicines derived from biotechnology processes, such as genetic engineering, and for advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines.

The centralised procedure is *optional* for other medicines, including those with a new active substance to treat a therapeutic area other than those above, or medicines which have a significant therapeutic, scientific or technical innovation. The centralised procedure can also be pursued for products for which authorisation at an EU level would be in the interest of public health.

If a company chooses not to pursue a centralised approach, it has two choices. It can either follow the mutual recognition procedure, whereby the marketing authorisation granted by a single country's regulator is recognised by other EU countries, or the decentralised procedure, for which a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU member states. Regardless of which route is chosen the data requirements and standards applied are the same.

Europe is a Large, Complex and Diverse Market Compared to the US



Each Country Decides its Own Market Access and Pricing

Although regulatory approval can be obtained at an EU level, each country has autonomy in relation to market access, pricing and reimbursement. This has profound implications for companies seeking to enter Europe, as each country is different and requires a bespoke approach. 'Free' pricing exists in some countries, such as Germany, for one year post

launch, and the UK. However, new medicine can also face a health technology assessment to establish whether the price is cost effective for the therapeutic benefit it provides; if not, price negotiations will follow. In other markets, such as Italy, pricing is more restricted and requires in-depth negotiations with government bodies that consider factors such as therapeutic benefit, budget impact and comparator medicine prices.

Unlike in the US, such country pricing and market access negotiations can cause substantial delays for European patients to access new medicines following regulatory approval. EFPIA's (European Federation of Pharmaceutical Industries and Associations) 2018 Patient WAIT (Waiting to Access Innovative Therapies) study indicates that patients in Northern and Western Europe see average delays of three to seven months, and patients in Southern and Eastern Europe see average delays of 20 to 33 months following EMA approval.

Reference pricing across European markets is commonplace and another feature of national price negotiation which requires in-depth strategic planning on pricing and launch sequencing. Price differentials between markets are typically unavoidable, resulting in 'parallel trade', where distributors buy medicines in one EU member state and resell them in another, where the price is higher. This requires close supply chain management but cannot be restricted by a company as it is part of one of the EU's fundamental freedoms – the free movement of goods.

It is also worth noting that within some countries, there are local access restrictions. This can mean that even when country access has been achieved, enabling a product to be prescribed in a hospital may require another hurdle to be overcome, such as with a tailored value proposition or discount negotiation.

Company Ambition Determines Route to Market

The complexity of Europe as a collection of unique markets and a common focus on the opportunity in the US, which accounts for ~40% of global pharmaceutical market sales, means Europe can be an afterthought or deemed 'too difficult'. For US biotechs, there are several important considerations when contemplating geographic expansion or product launch in Europe:

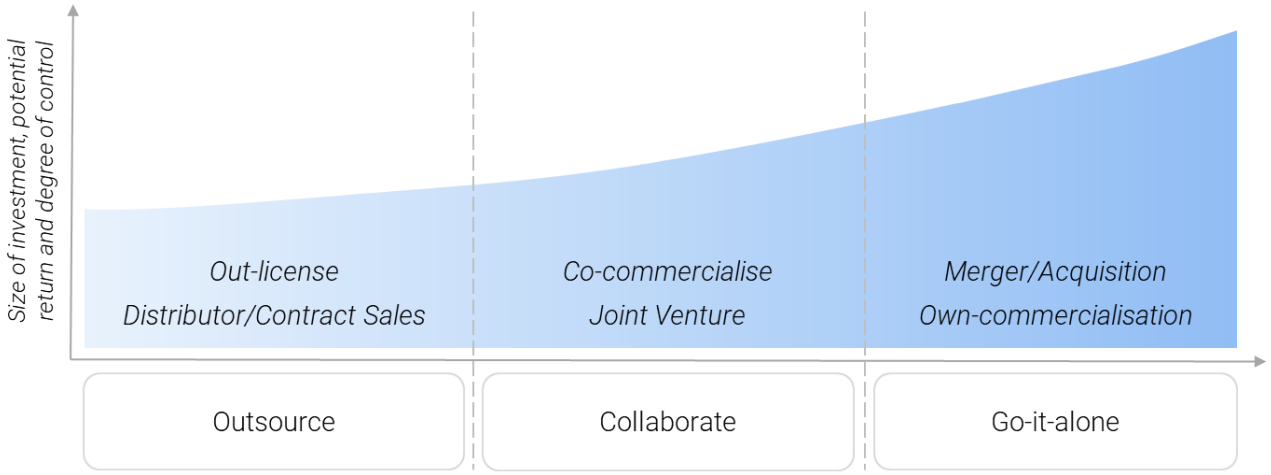
- *How can a value proposition and data generated for the US market be used to meet European regulator, payer, physician and patient needs?*
- *How can the difficulty and cost of navigating a disparate and more restrictive market access and pricing environment be managed?*
- *How can a complex supply chain across multiple markets be navigated?*
- *How can country-specific needs and differences be addressed (e.g. cultures, laws, regulations, stakeholders)?*

The best companies consider these questions early. For example, thinking about Europe at the clinical planning stage enables the development of a value proposition that is applicable worldwide. However, navigating these hurdles can seem daunting, and at its most extreme, some companies choose to reject Europe completely. For those willing to invest, the rewards are there. In a market that places value demonstration at its core, there is a substantial opportunity for innovators with truly differentiated products. With the US moving towards a more value-based approach, the experience of Europe can also inform plans in the home market. Companies can also take comfort from the availability of a range of routes to market. This helps to shift the mindset from 'Should I invest in Europe?" to "Which model is right for me to access the opportunity in Europe?"

Selecting the most appropriate route to market starts with a clearly defined ambition for what a company wants to achieve by expanding to or launching in Europe. That ambition also needs to align with the company's risk appetite and any capital constraints, in addition to the size of the opportunity for its asset or portfolio.

An ambition to reinforce or achieve a market leading position and become a truly global player is more likely to take a company down the route of own commercialisation. Indeed, own commercialisation is becoming increasingly attractive to US biotechs as capital is now available in the public markets to do so. This is particularly the case for companies developing assets for niche patient populations. The focus on a small, clearly defined patient population can facilitate a company's ability to demonstrate value, an important factor for success in Europe, and minimises the investment and operational footprint required to serve its customers. Conversely an ambition to maintain a strategic focus on the US and generate revenue to support US operations is more likely to take a company down the route of out-licensing or seeking a partner to drive entry to Europe. There is not one single key to the kingdom and companies successfully deploy different routes to market based on their ambition and product portfolio or pipeline.

The Best Route to Market Depends on Investment and Risk Appetite



Strategic Collaborations Balance Risk and Value Creation

Organisations can reinforce their focus through a strategic collaboration. Rather than being a simple cash transaction, they are an opportunity to trade assets and capabilities with like-minded partners for mutual benefit. Even for a US biotech with a strategic focus on the US, a collaboration with a European pharma company can create significant value by providing non-dilutive capital, access to expertise and further validation of a technology or asset to support future fund raising or revenue growth.

An organisation's ability to leverage its assets and capabilities is key to a strategic collaboration. This may be through an out-licensing deal with a strategically aligned partner, a strategic 'swap', where companies trade complementary assets and capabilities, a Joint Venture, where partnering companies combine to create a new entity, or other types of creative structured deals. Regeneron and Sanofi's antibody collaboration, which ran from 2007 to 2017, is a standout example of a lengthy and highly successful discovery, development and commercialisation collaboration between a US biotech and a European headquartered pharma partner. The two companies established a second collaboration in 2015 focused on immuno-oncology, which highlights the value of finding a well-matched partner.

The rising cost of M&A and the increasing difficulty of developing a sustainable R&D pipeline of internally sourced assets means companies are actively searching for such collaboration opportunities. European mid-sized pharma companies are particularly active in this space. These companies often have limited breadth in product portfolios and face difficulties in acquiring assets owing to recent price rises and the buying power of larger competitors. In our experience, the European MidPharma companies are open to creative ways to collaborate for scale, focus, and sustained profitability. They are therefore a rich source of opportunity for US biotechs, allowing both access to the commercial opportunity in Europe and the maintenance of a strategic focus on the US market.

The incremental commercial opportunity provided by Europe should not be ignored. Strategic collaborations not only provide an effective route into Europe, they also provide a powerful opportunity to create transformational value – helping US biotechs to stimulate innovation, deepen strategic focus and, ultimately, grow more quickly.

Own Commercialisation Can Create the Greatest Value

Own commercialisation requires a level of investment and commitment that US biotechs should not take lightly. However, those that do are likely to reap the greatest rewards. Unlike in the past, own commercialisation is increasingly the route of choice for US biotechs because of a focus on specialised therapies requiring smaller commercial footprints for success.

Gilead stands out as a company that pursued own commercialisation at a time when few companies took such an approach – now it is a $22bn revenue company with a string of successful products. More recent examples include Amicus Therapeutics and Intercept Pharmaceuticals.

For US biotechs that choose the own commercialisation route, the greatest risk to success is taking a 'one size fits all' approach. It is critical for leaders to realise and accept that the countries within Europe are not only different from the US, they are different from *each other*. Employing team members who have extensive experience in each country and trusting them to get on with the job is critical to creating maximum value. Oversight on progress and delivery against performance milestones is important but micro-management of specifics is detrimental to success.

Timing is another important factor. Companies should have a physical presence at least 2 years ahead of achieving marketing authorisation. This enables team members to be recruited to deliver the launch, as recruitment can take longer than expected, owing to nuances around employment law, notice periods and benefits. It also allows for the market environment to be shaped through policy activities and relationship building with key stakeholders such as KOLs and payers. This is particularly important for innovative medicines which may be first-to-market and face regulatory and payer pathways that are not fully formed.

There are Many Ways to Cross the Pond

Europe represents a complex commercial opportunity with large potential rewards for US biotechs. Clarity on ambition is required to determine the most appropriate route to market. There are many ways to cross the pond and ambitious US biotechs are expected to take the plunge.

Novasecta is a specialist strategy consulting firm for pharmaceutical companies.

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