Prescient®

WHITE PAPER

US Biotech: 10 Key Essentials for Successful European Entry and Product Launch

The European market has opportunities, but the wrong approach will leave value on the table. Prescient's guide will steer you to make the best decisions for your asset.

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Introduction

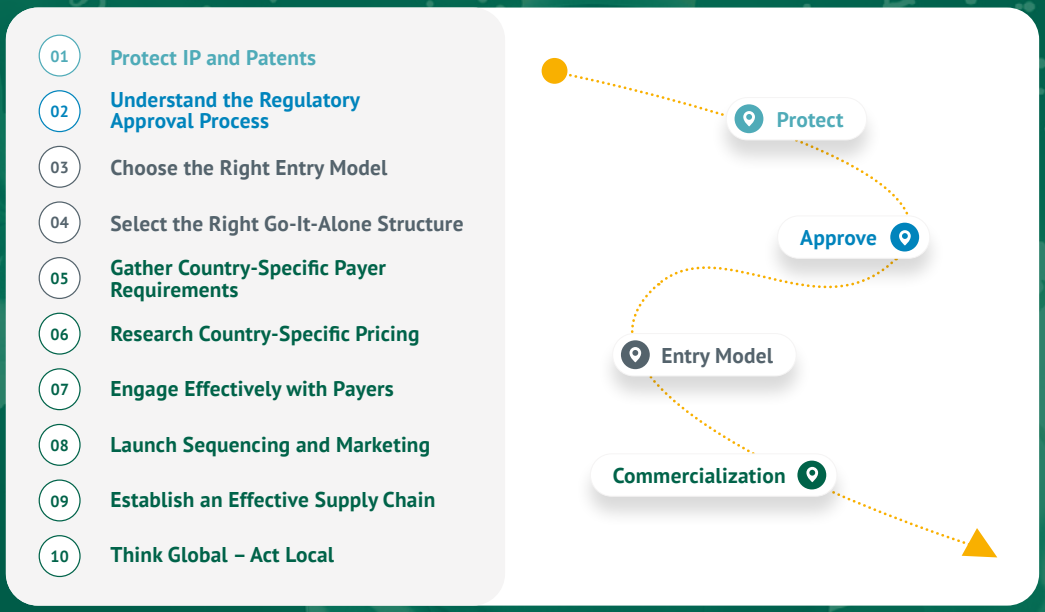
In any market, transitioning from an R&D company to a revenue-generating commercial organization is a daunting prospect and requires the company to build a significant number of new capabilities to ensure patients have access to its medicine. For US-based biopharmaceutical companies that are about to or have successfully launched in their domestic market, seeking geographical expansion is a natural and often essential next step to optimize the value of the asset and treat more patients.

The attractiveness of the European market, including non-EU countries like Norway, Switzerland and the UK, is well documented. It is the second-largest market for prescription drugs in terms of patient numbers and financial rewards, but the complexities are unique; successful entry, navigation and infrastructure building require a strategy that aligns with the company's aspirations.

Companies would be wise to dedicate significant time and resources in planning their entry strategies and road maps to increase the chances of successful launches, otherwise they may face cultural, political and access obstacles, not to mention damage to the brand and the company's reputation.

In this article, we examine 10 key essential elements that every US biotech company should consider when planning European market entry, as outlined in Figure 1 below.

Figure 1: 10 essential elements across four key launch attributes



01

Protect IP and Patents

Regardless of which market a US biotech is planning to enter, ensuring robust patents have been filed that will stand up to any challenges is essential to protect the life cycle opportunity and value of the asset. Generally, patents may be material-based and related to the specific product and process of manufacture, and they may cover data exclusivity or trademarks and copyrights for the brand. Twenty-year patent protection is common in the biopharmaceutical industry, which safeguards the originator from other companies genericizing the product.

Within Europe, mechanisms exist that can extend the longevity of the patent, including supplementary protection certificates (SPCs), which can add up to five years to the patent life, while a pediatric investigation plan (PIP) filing can offer an additional six months.

Data exclusivity can be sought to protect the originator from generic and biosimilar filing applications for eight years from marketing authorization. If the product is a new therapeutic indication or drug classification, it is possible to increase this period by one year if sufficient relevant data are submitted.

Market protection can be granted for up to 10 years from launch, preventing generic or biosimilar filing applications, with the possibility of extending the period by one additional year if the asset is filed for a new therapeutic indication and receives a marketing authorization.

Last but not least, the company should ensure brand rights are protected by securing trademarks and copyrights. In many instances, a different brand name from that used in the US is required in Europe as the acceptance criteria and search for similar sounding brands may differ; for example, Tostran® (a testosterone gel for hypogonadism) is the brand name in Europe, while in the US, it is supplied under the brand name Fortesta®.

02

Understand the Regulatory Approval Process

The most common and, in many cases, mandatory way for a US biotech company to submit a regulatory submission in Europe is through the standard centralized procedure. Coordination of filing is done through the European Medicines Agency (EMA) and covers 27 EU states. Norway also accepts the application, although it is not part of the EU, while the UK Medicines and Healthcare Products Regulatory Agency (MHRA) appears to be adopting a similar mechanism through the EU-UK Trade and Cooperation Agreement. The actual marketing authorization is granted by the EMA's Committee for Medicinal Products for Human Use (CHMP), with engagement managed through two appointed countries to act as representatives for all member states (rapporteur and co-rapporteur).

Other approaches for filing in Europe include the decentralized procedure, where an application is sought across a number of member states at the same time as the appointment of one reference member state, although this is not applicable for biological products; a national license application for individual member states, which is less common and would not necessarily unlock the commercial potential of the asset; and the mutual recognition procedure, which follows from a national application and allows other member states to gain approval without the need for a new dossier.

As with new drug applications (NDAs) in the US, the EU centralized procedure requires the submission of a structured dossier that covers the safety, efficacy and quality data for the medicine. Proactive early engagement with the EMA is welcomed, particularly for novel treatments that have the potential to change the standard of care (SoC). For companies pursuing the approval of medicines in rare diseases or those with a high unmet need and burden of disease, accelerated and conditional approval pathways are potential options, while early access to the medicine is possible through a variety of country-specific compassionate and managed access programs. In some cases – most notably France, with its cohort and nominative temporary authorization for use (*Autorisation Temporaire d'Utilisation*, ATU) programs – it is possible for companies to be reimbursed for treatment.

"The EU centralized procedure requires the submission of a structured dossier that covers the safety, efficacy and quality data for the medicine."

03

Choose the Right Entry Model

Broadly speaking, the choice of European entry model can be categorized into three options:

Going it alone is where a company is committed to commercializing its asset by itself and wishes to establish a physical presence in the market. Investment is higher than the other options, with the benefit of potentially higher returns; however, going it alone carries a higher risk compared to partnering or out-licensing, as the company moves beyond its core competency set, so there is the possibility of overlooking aspects needed to secure a successful launch. This option is often used for core European markets, like the EU4, UK, Benelux and Nordics, whereas partnering options like distribution agreements may be more suitable for lower-value eastern European markets. More importantly, this option should not be based solely on financial metrics, such as a strong, positive rNPV, as it must also align with the company's ambition and strategic long-term plan. Having a light infrastructure already established in Europe will help facilitate the commercial build if there are additional indications or products that may be launched in Europe in the future.

Partnering can take different forms that will have slightly different terms and conditions: Distribution agreements, co-marketing or co-promotional agreements, or active licensing where the rights to the asset are owned by the selected partner. While partnering offers lower investment compared to going it alone, it will also lead to lower returns, as the partnering company takes a portion of the upside revenue. In many cases, the strength and ability of the partner to effectively negotiate will lead to a better deal. Conversely, if the partner is strong – perhaps a "big pharma" company – it will negotiate a larger return. This option allows the originating company to pool resources and learn from its partner about the market and what works well in individual countries. As a cautionary word: Ensure the right partner is selected, one that knows the therapeutic area, key physicians and local nuances of each country.

Out-licensing is the lowest investment option. Depending on the upfront, milestone and royalty structure of the agreement, this option may yield a modestly higher rNPV than some partnering options, such as a distribution agreement where the originating company has no control over sales and marketing activities but obtains ownership and future commercialization rights. Out-licensing allows the company to focus on its core domestic market while generating a relatively quick revenue stream from Europe that can be used to further the development pipeline. Provided the chosen out-licensed company is selected wisely, this option offers the lowest amount of risk with a potentially acceptable rNPV and may be a good strategy if the indication is not related to the company's core therapeutic areas; however, it should be noted that ambitious US companies may feel this opportunity gives away a significant share of their assets and does not provide any infrastructure for future launches.

Figure 2: The relationship between investment vs. risk and the returns achievable for each European market entry strategy

04

Select the Right Go-It-Alone Structure

For companies that prefer to maximize the returns of their assets without relinquishing any value and are prepared to accept the associated risks, a go-it-alone model is the most attractive. Depending on the therapeutic area, number of treatment centers, country reimbursement likelihood and available investment, companies should first choose a suitable structure for their European HQ. The decision for this should be driven by several key factors, including:

- Access to talent
- Tax laws
- Labor laws
- Proximity to other biopharma companies
- Local transport infrastructure
- Quality of life

Prescient's analysis has identified three distinct options for a company to consider:

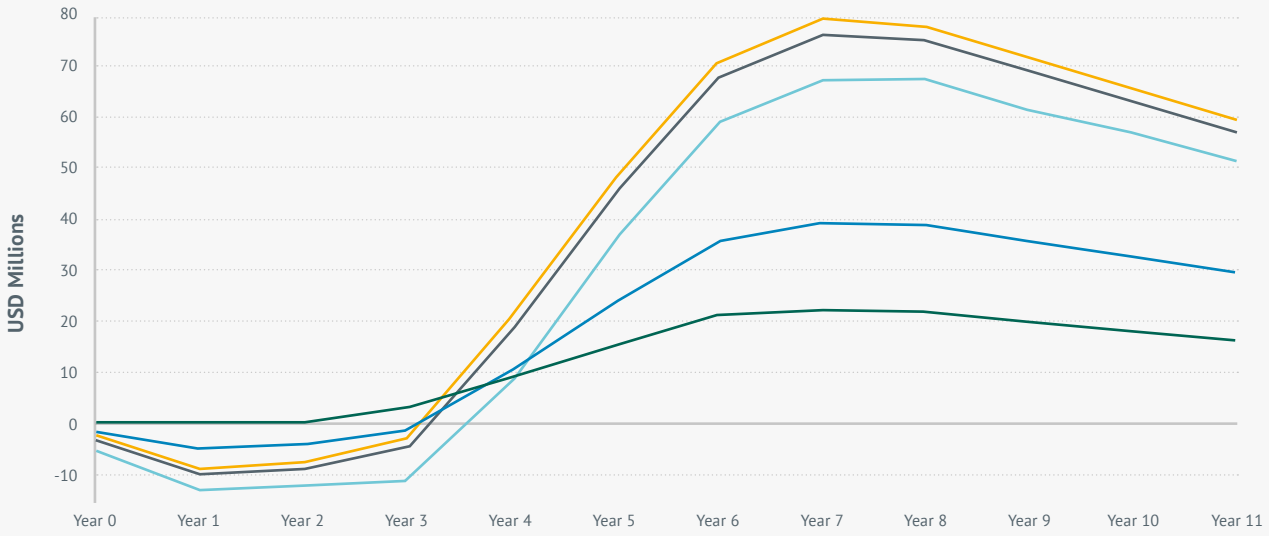
Centralized Structure:
Not to be confused with the centralized regulatory process, this term refers to a model whereby a European HQ is established with key senior appointments and exercises the largest degree of control over affiliates. Affiliates comprise key field-based experienced talent with no physical premises, reporting directly back to the European HQ. This talent is likely to be medical during the pre-launch phase to avoid any seeding of the market through commercially focused engagement. Closer to the launch, commercial and market access hires can be considered. This model works very well for rare and ultra-rare diseases, where treatment center numbers are low while per patient revenue is high.

Hybrid Structure:
This structure is a middle-of-the-road approach and assumes a reasonable degree of central control from a European HQ. A physical office is established and staffed with locally experienced medical and commercial employees who provide local leadership. These country businesses are semi-autonomous; however, European coordination and control still reside in the European HQ, particularly for functions that may not have been built yet, such as supply chain, regulatory, pharmacovigilance, legal and HR. This structure can be seen as a springboard for future buildouts while managing risk in case the newly launched product faces delays or uptake is slower than planned. This structure works well for rare diseases and for those companies that want to take a more cautious approach and expect country-specific challenges or delays.

Decentralized Structure:
This structure represents a more aggressive buildout where a European HQ is still established. The goal is to build autonomous country affiliates with full P&L responsibilities as quickly as possible, with all the backroom staff and functions to support a fully-fledged commercial business. Coordination of branding and pricing governance will likely still occur at the European HQ, but all other asset-related commercial decisions will be taken at the affiliate level. Essentially, each affiliate replicates the leadership team and function mix found within the European HQ. This model may be preferred for high-volume, lower-priced medicines that are used in many treatment centers or in primary care practices where a large field force is required to provide sufficient geographical coverage.

Figure 3: Illustrative cumulative rNPV curves over a 12-year product commercialization life cycle (pre launch through patent expiration) for EU entry strategies (in USD millions).

NB: assumes a baseline level of resources capable of reaching revenue forecast.



Key Takeaways to Consider:

- Due to it having the lowest cost, a centralized structure offers the highest rNPV potential; one caveat, however, is that this assumes the forecast can be achieved with minimum infrastructure
- The differences between the three go-it-alone models are related to differences in office costs and headcounts
- The financial returns between going it alone and partnering will be influenced by the degree of investment required based on the size of the indication, expected deal terms achieved in a partnership and degree of risk associated with achieving the forecast
- Although out-licensing represents the lowest rNPV, provided the company that in-licenses the asset for Europe can achieve the forecast, this still offers an attractive revenue stream for the originator with a lower level of risk compared to partnering and going it alone

05

Gather Country-Specific Payer Requirements

One of the key differences between the approval of medicines in the US and Europe is that, for the former, placebo-controlled studies are often acceptable and health economic data to support pricing are not required. For the latter, however, comparator data are needed to secure competitive pricing and reimbursement to support the commercial launch. Pharmacoeconomic data are often seen as the final hurdle in Europe after regulatory approval.

Importantly, European countries vary in their requirements. Germany, for example, requires comparative data to measure "added benefits" and wants to see data in German patients; Spain and Italy are notoriously driven by clinical budget impacts; and the UK and Sweden require health technology appraisals that include health economic modeling with cost per quality-adjusted life year (QALY) and incremental cost effectiveness ratio (ICER) calculations. If comparative data have not been collected within a Phase III study (i.e., a placebo-controlled trial rather than a head-to-head study), these data need to be obtained from real world evidence (RWE) generation or investigator-sponsored trials (ISTs), company-sponsored trials (CSTs) or cross-trial health economic modeling.

06

Research Country-Specific Pricing

Pricing in Europe is complex, with country-specific differences depending on pharmacy margins and mandatory discounts. The movement from gross to net price can be significant, with agreed discounts kept confidential, for example, through an agreed patient access scheme, as is common for high-priced drugs in the UK. Tight control of public prices is recommended, as Europe operates a referencing system where certain countries reference other countries and determine their price based on that of other countries. For example, France and Italy are likely to have lower prices than Germany and the UK, which operate free pricing policies at the public price level.

Unlike the US, where it is possible to increase prices on an annual basis, through international price referencing (IRP) and pricing reviews triggered by exceeding revenue caps, European prices move in the opposite direction and fall over time.

When entering Europe, it is important for companies to understand the differences in pricing terminology and how, through pricing and market access mechanisms and further commercial contracting, the net price can end up being a fraction (often ~50% or less) of the public price.

Table 1: An illustration of the various prices, rebates and discounts that can impact the final net price of a drug in Europe

Pricing and Market Access Adjustments	Price (Normalized to 100)
Public price (+/- VAT if applicable)	**100**
Pharmacy or hospital margin	(~15% reduction)
Wholesale margin	(~15% reduction)
Ex-manufacturing price or list price	**70**
Mandatory discounts	(~4% reduction)
Hidden discounts	(~6% reduction)
Innovative contracting discounts	(~3% reduction)
Commercial Contracting Adjustments	
Net ex-manufacturing price	**57**
Channel discounts	(~4% discount)
Invoice discounts	(~2% discount)
Performance rebates	(~3% discount)
Terms and conditions	(~1% discount)
ASP for net ex-manufacturing price	**47** (spread of 44-50)

In the example above, a starting public price of 100 (nominal value) could eventually see a net ex-manufacturing price of ~47 (minimal value) depending on the mix, types and value of margins, discounts and rebates. The extent and level of difference between the public price and eventual net ex-manufacturing average selling price can be significant, meaning companies need to ensure tight pricing governance across Europe (and arguably a tight global pricing corridor if the intention is to launch in other markets). It should be noted that the table above outlines all possible margins, rebates and discounts, but this does not necessarily mean these would be a requirement for all types of medicines. A company with a rare disease drug, for example, may choose a supply chain model for a hospital product that operates a direct-to-pharmacy model from a European central warehouse, cutting out the need for the wholesaler, which would eliminate this cost.

07

Engage Effectively with Payers

Engagement with HCPs and patients to ensure awareness and drive uptake is well understood and transcends all pharmaceutical markets. There are variations in different markets; for example, direct-to-patient promotion is permitted in the US, while contact with patients in Europe should only be allowed as part of a recognized patient support program following the prescribing of the medicine or should be non-promotional, disease-focused and unconnected with a specific approved brand.

Payers should be regarded as the most important stakeholder for the European market to ensure commercial success due to their high influence in determining reimbursement and list prices, as well as eventual net prices, through the agreement of country-specific discounts. No matter how many physicians wish to prescribe a given drug, if the price is suboptimal and the reimbursed countries are fragmented, achieving forecasts – normally communicated to institutional investors long before the first launch – will be difficult to achieve.

Although a European-wide market access strategy with prioritized markets (countries) is needed as part of the overall launch plan, for best outcomes, market access plans to support payer requirements should be prepared at a country-specific level. These plans should be influenced by local access experts who have a history of engaging with agencies, such as *Arzneimittelmarkt-Neuordnungsgesetz* (AMNOG) in Germany, *Agence nationale de sécurité du médicament et des produits de santé* (ANSM) in France, *Agenzia italiana del farmaco* (AIFA) in Italy and the National Institute for Health and Care Excellence (NICE) in the UK. Building a target list of key national and regional payer decision makers is advised, with significant time provided pre launch to ensure they are engaged via well-documented processes for seeking advice.

08

Optimize Launch Sequencing and Marketing

Launch sequencing is a requirement to protect the value of an asset and prevent price referencing. In price referencing, payers in one country look at the list price of a medicine in another for reference and use this information to price the medicine for their country, which is either the same, lower or higher depending on the economic, social and/or demographic standards. Often, a basket of countries will be referenced rather than just one, taking the average price or the lowest of the basket. While this transparency exists at the list price level, countries are often more concerned with what they pay for each drug at the net price after negotiation of confidential discounts. Although these discounts are not publicized, payers in different countries often have a strong

inclination to approximate what another country will be paying; for example, if a drug is approved by NICE in the UK through a patient access scheme, one can expect the confidential price to be 70-30% of the listed public price.

In many instances, Germany is preferred as the first European launch country due to its population size, transparent healthcare system, review process and, more importantly, the option of approximately one year of free pricing with no initial review period, just a requirement for the drug to be added to the Lauer-Taxe medicinal products database. Provided the company follows up with strong comparator data relevant for German patients, demonstrates a reasonable benefit rating and does not exceed any cost caps, the reduction in price post AMNOG review can be minimized.

This means any country that launches later and references Germany will be referencing a higher price than if the initial launch country were, for example, Italy, where a lower price was agreed following pricing and reimbursement discussions, as no "free pricing" period is available. By choosing a poor order of launch, the overall price corridor ends up being lower and value is "left on the table". That said, launch order is also heavily influenced by pricing and reimbursement timelines, so while one can theoretically launch a drug in Germany on the day of approval, it could take up to 15 months in Italy to deliver the first commercial launch.

09

Establish an Effective Supply Chain

Establishing a European supply chain is harder than doing so in the US, as a product moves across country borders rather than across state borders. This can lead to different licensing, sterilization, packaging, labeling (e.g., multiple languages) and country-specific regulatory requirements. The ownership of the product along the supply chain and the various financial flows, such as order-to-cash processes, can vary, while how and where the product is prescribed can change depending on the healthcare system of the country. A key requirement is that final finished products that enter the European Union require testing and qualified person (QP) release before they can be distributed to pharmacies.

Companies should consider outsourcing to a third-party logistics (3PL) provider and engaging early on to understand and agree upon all necessary country-specific variances. Ideally, these discussions should take place 18 months prior to launch.

10

Think Global – Act Local

Out of the major pharmaceutical markets of the US, Europe and Asia, the need to think globally but act locally is never more applicable than for Europe due to the number of countries and differing healthcare systems, pricing and reimbursement processes, languages and cultures.

So why not just act local without thinking global?

This would be a short-sighted approach and could lead to confusion in the market. For example, building a global brand – with the assumption being that a biopharma company wants to maximize the value of its asset and launch into as many markets as possible – requires the highest degree of standardization possible, which means a single and consistent positioning and brand vision for the product is vital. This succeeds when a brand essentially becomes synonymous with a disease: Viagra® and erectile dysfunction, Humira® and rheumatoid arthritis, Lipitor® and high cholesterol. These examples show a single and consistent positioning in the lead indications, consistent branding (albeit with the need to occasionally have multiple but similarly related brands due to naming constraints in certain markets) and significant disease education.

However, it should be noted that these success stories may never achieve "true standardization" as even products with fewer restrictions, such as fast-moving consumer goods (FMCGs), struggle to fully standardize and need to have the product or brand promise varied to enable acceptance in different markets.

With biopharma products in Europe, "acting locally" is essential, otherwise commercial success is unlikely. Striking a balance between standardization and local adoption will mean a greater acceptance across countries and, ultimately, more revenue through the treatment of more patients. Navigating through the payer differences and securing a value-based price that each country approves while adapting branding and labeling requirements but not eroding the overall value through price disparities across European markets will enable a greater likelihood of success.

Conclusion

This article is designed to educate the reader on 10 key elements that require careful consideration when entering the European market. That said, due to the complexities of Europe and the dichotomy of a single regulatory market, individual country healthcare systems and reimbursement requirements, many more elements will also play a significant role in determining success; for example, the quality of talent recruited, the nature of competition surrounding the therapy area and how the product will affect the existing SoC and address unmet needs in the space. The overarching message for companies is to plan early, seek relevant advice from all stakeholders (regulators, physicians, payers, and patients) at both a European and local country level, and to ensure the chosen market entry strategy is aligned with the company's needs, ambition and vision.

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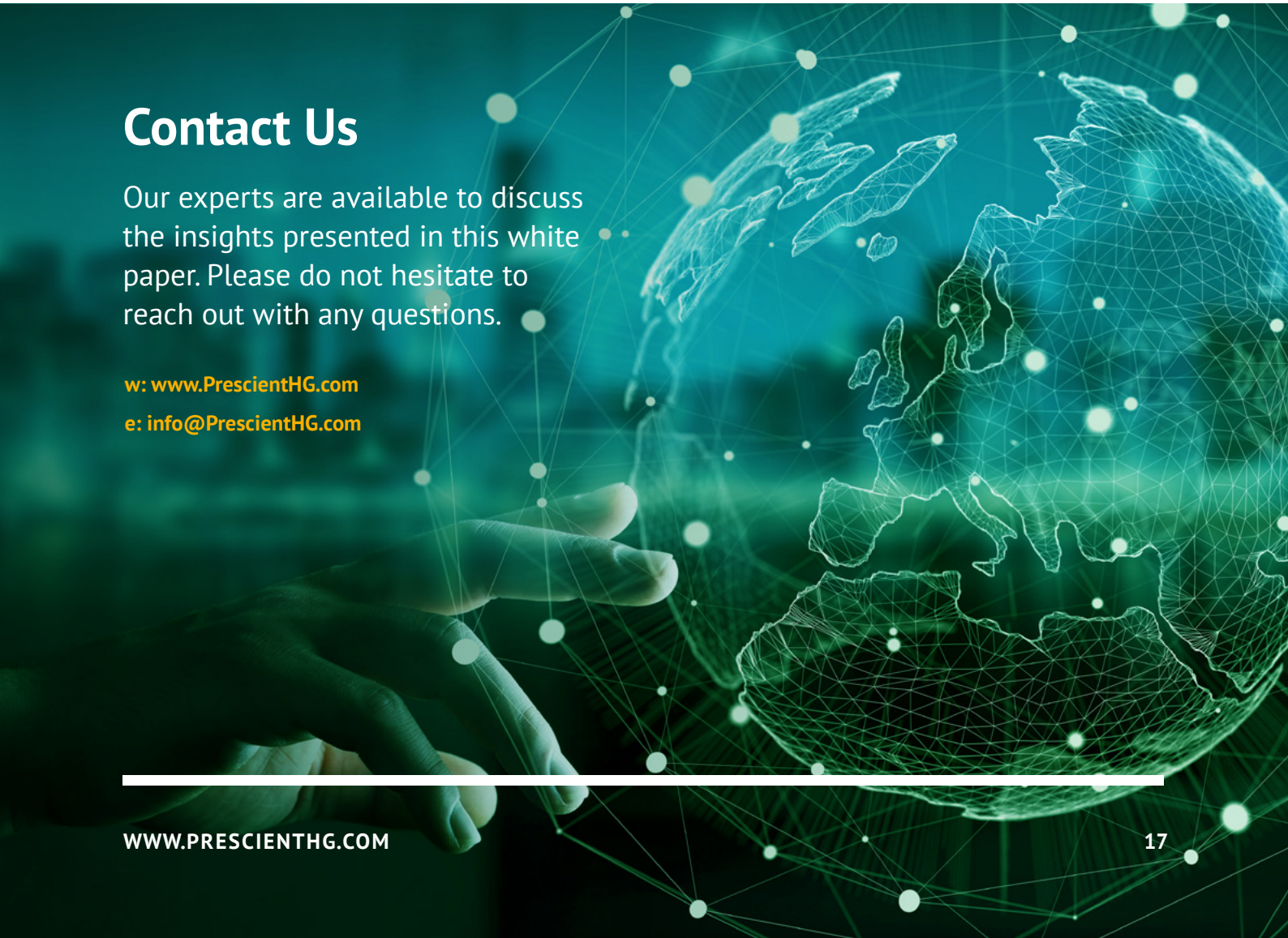

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