



**Considerations
for Cell & Gene
Therapy Companies
Contemplating
Foreign Direct
Investment in Japan**

The cell and gene therapy (CGT) field is rapidly developing due to its promise to provide durable, and potentially curative, treatments to people suffering from a wide range of diseases, including rare genetic conditions, acquired diseases, and cancers. As a part of our mission, the Alliance for Regenerative Medicine (ARM) is committed to serving our membership in enabling the development of, and access to, these advanced therapies. Through ARM’s Managed Growth Working Group, an initiative aimed at identifying how ARM can refine and expand its work to better serve our member organization, ARM is devising a geographic expansion strategy that includes the Asia Pacific (APAC) region.

Based on data presented in ARM’s April 2024 Sector Snapshot, the APAC region is second to North America in the number of CGT developers, clinical trials, and investment¹ (Figure 1), and is growing at twice the rate of North America and Europe². To support the APAC geographic expansion strategy, ARM partnered with JLL to lay out the key considerations for companies that are contemplating Foreign Direct Investment in Japan. We chose to focus on Japan because it is a significant biopharmaceutical manufacturing hub, and is home to life science executives with significant global experience. It serves as an ideal blend of innovation and business prospects, offering a base for ARM to support its members across the APAC region.

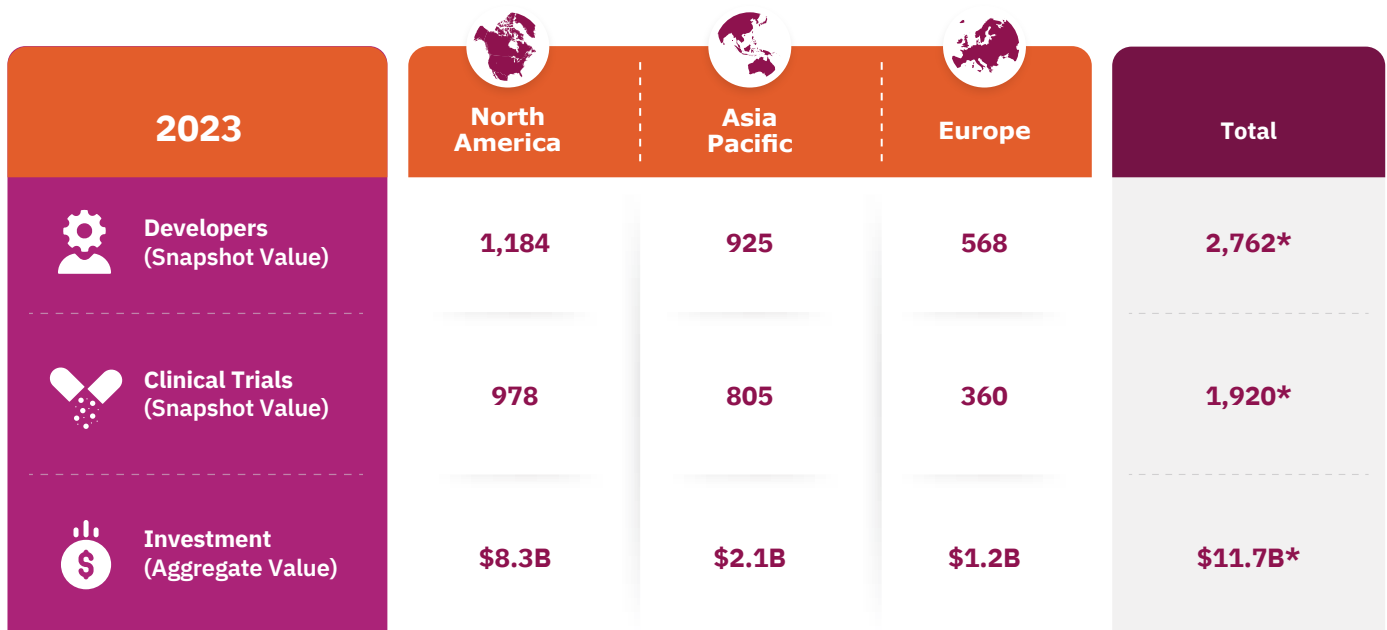


FIGURE 1. Cell and Gene Therapy Sector Data Q4 2023.

*Totals refer to unique quantities and include data from other regions not shown. Figure taken from Alliance for Regenerative Medicine, April 2024 Sector Snapshot: Advances in Engineered Cell Therapy.

¹ Alliance for Regenerative Medicine, April 2024 Sector Snapshot: Advances in Engineered Cell Therapy. <https://alliancerm.org/sector-snapshot-april-2024/>

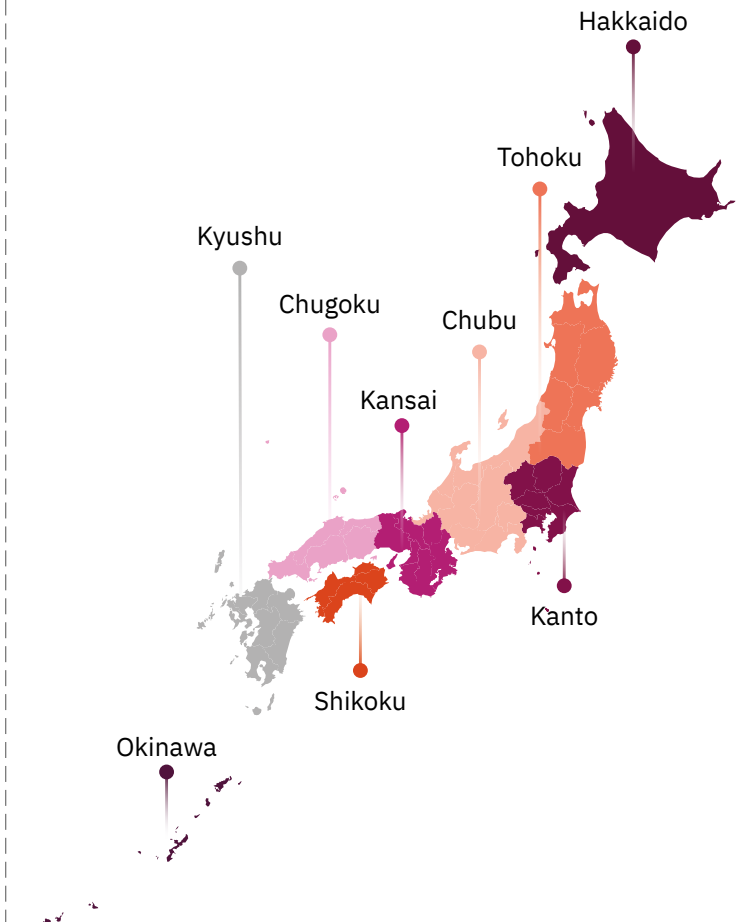
² DHC APAC round table discussion: <https://www.darkhorseconsultinggroup.com/post/dhc-apac-round-table-discussion>

OVERVIEW

Japan is a highly developed country by most key performance indicators. Globally, Japan ranks in the top 15 countries in the world in indicators of market sophistication, business sophistication, infrastructure, knowledge, and technology output according to the 2023 Global Innovation Index³. Japan is the world's fourth largest consumer market and ranks 5th globally on the Global Competitiveness Report.

And with respect to the life sciences, Japan has one of the most developed biotechnology sectors in the world, with elevated expectations in the discipline for regenerative medicine. Regenerative medicine has revived hope in many patients who, until now, lacked viable therapy options. Japan aims to be at the forefront of solutions in this modality of biotechnology.

FIGURE 2. Regions of Japan



MARKET SIZE

Japan's population is aging at a rate unprecedented in other countries. The population includes more than 36 million people over age 65 which represents more than 28% of the population. Japan has what is considered a "super aging society." Japan's National Center for Cancer estimates approximately one million people are diagnosed with cancer each year. The population with cancer is expected to increase and medical expenses are expected to increase every year. At present Japan's prescription drug market is the third largest in the world, sitting behind only the United States and China. As a result, the regenerative medicine industry is evolving quickly to address the needs of the population, it is employing a significant number of people, and also growing quickly. The Ministry of Economy, Trade and Industry expects the domestic regenerative medicine market to grow from JPY 0.95 trillion in 2020 to JPY 2.5 trillion in 2050.

³ Global Innovation Index 2023: Innovation in the face of uncertainty. https://www.wipo.int/global_innovation_index/en/2023/

REGULATION

The Japanese government has declared the regenerative medicine industry a key pillar of its growth strategy. Japan has implemented frameworks to promote the commercialization of regenerative medicine products in efforts to accelerate development and commercialization. Examples from years previous include the Regenerative Medicine Promotion Act in 2013, the Act on the Safety of Regenerative Medicine (“ASRM”) in 2014, the Pharmaceuticals and Medical Devices Act in 2014. Other efforts to support growth of regenerative medicine include the establishment of the Japan Agency for Medical Research and Development which seeks to unify and coordinate research and development efforts across different ministries, and the establishment of industry groups to advance the industry such as the Forum for Innovative Regenerative Medicine (“FIRM”).

EFFORTS TO BRING REGENERATIVE MEDICINE TO JAPAN VIA FOREIGN DIRECT INVESTMENT

Foreign direct investment (FDI) is an investment from a party in one country into a business or corporation in another country with the intent of establishing a lasting interest. A foreign direct investment can be made by expanding a company’s business into a foreign country, such as the establishment and operation of a manufacturing operation.

The Japanese government is highly focused on attracting inward foreign direct investment and foreign capital. To support its efforts, Japan utilizes the resources of two agencies. The largest agency facilitating inward direct investment is the Japan External Trade Organization (“JETRO”). JETRO is tasked with attracting investment from abroad and assists potential investors with information on the investment climate, market opportunities, licensing, and helps with introductions to local governments.

The Ministry of Economy, Trade and Industry (“METI”) is the second agency that assumes an important role in facilitating direct investment into Japan. METI functions as a conduit to foreign investors and provides information on investment opportunities, investment procedure, and provides support programs.

Together, JETRO and METI work closely and collaborate to provide comprehensive support to foreign companies. New investors to Japan will likely receive support from representatives from both organizations when assessing Japan for direct investment.

While Japan is generally open to FDI, historically, inward investment has been low. Japan is now highly focused on changing this and is stepping up its efforts to attract more investment. The current administration has set an aggressive goal of JPY100 trillion of inward FDI by 2030. In 2020 inward FDI was approximately JPY 40 trillion, so the new goal represents an ambitious new target.

JAPAN BIOLOGICS MANUFACTURING LANDSCAPE

Of the 47 prefectures in Japan (the first level of administrative division, like a State in the US), the prefectures with the largest biotechnology and regenerative medicine platforms are Tokyo and Kanagawa (and in particular, the City of Yokohama) located in the Kanto region, and in the Kansai region, the prefectures of Osaka, Kyoto, and Kobe. The size, maturity and density of development in these regions, however, can make site selection very difficult as larger sites and facilities that align with the needs of manufacturing operations are not readily available and/or need significant long lead time improvements.

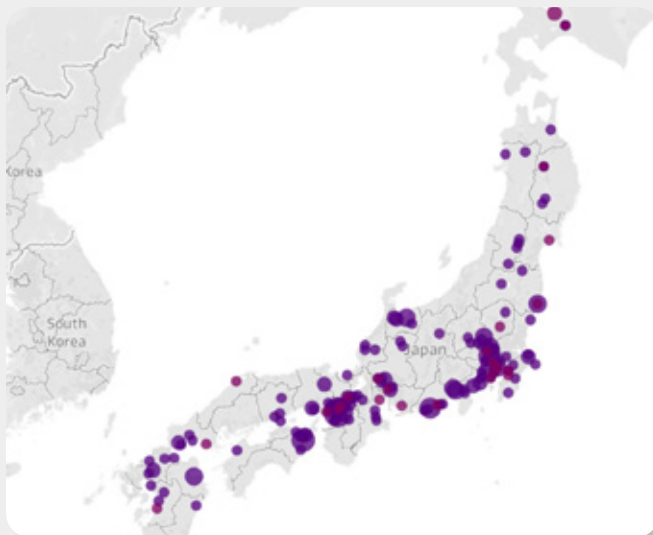


Figure 3. Japan biologics manufacturing landscape.










Dots represent the location and number of companies engaged in biologics manufacturing.

Source: GlobalData.

LOCATION AND SITE SELECTION CONSIDERATIONS WHEN CONTEMPLATING DIRECT INVESTMENT

When considering FDI into a foreign country, it is important to develop a framework to help guide the assessment of the investment climate, location and sites. The graphic below provides an overview of the type of considerations that are typically analyzed when seeking to measure the alignment of locations with company investment goals and objectives. Robust analytical models are developed in alignment with the considerations to capture the differences in Non-Financial and Financial factors to guide decision making.

FIGURE 4. Key considerations when contemplating Foreign Direct Investment.

		Non-financial		Financial
Key Considerations	 Revenue	<ul style="list-style-type: none"> • Forecast by product • Forecast by country • Competitive strategy 		<ul style="list-style-type: none"> • Selling price • Margin • Inflation
	 Risk	<ul style="list-style-type: none"> • Political • Economic • Natural disaster • Intellectual property 		<ul style="list-style-type: none"> • Insurance costs • Natural disaster mitigation • Added construction costs
	 Supply Chain & Logistics	<ul style="list-style-type: none"> • Proximity to suppliers • Proximity to market 	<ul style="list-style-type: none"> • Interstate/Highways • Rail • Port • Air cargo 	<ul style="list-style-type: none"> • Inbound transportation costs • Outbound transportation costs • Transportation inflation costs • Duties and fees
	 Labor	<ul style="list-style-type: none"> • Ability to scale • Ability to sustain • Skill and language capability • Regulation • Unionization 		<ul style="list-style-type: none"> • Labor costs • Benefits costs • Months compensation • Language/shift premiums • Labor arbitrage • Inflation • Expatriate costs
	 Incorporation & Taxation	<ul style="list-style-type: none"> • Treaties • Incorporation options • Permitted business structures • Advance rulings 		<ul style="list-style-type: none"> • Direct tax (income) • Indirect tax (VAT, property, others) • Treatment of losses • Tax on gross revenue • Deed tax
	 Real Estate	<ul style="list-style-type: none"> • Site Size • Configuration • Topography • Permitted use and restrictions 	<ul style="list-style-type: none"> • Environmental • Constructability • Title/ownership 	<ul style="list-style-type: none"> • Site purchase costs • Site preparation costs • Leasing costs • Responsibilities
	 Utilities & Infrastructure	<ul style="list-style-type: none"> • Electricity • Natural gas • Water • Wastewater 	<ul style="list-style-type: none"> • Telecom • Reliability • Excess service capacity 	<ul style="list-style-type: none"> • Utility tariffs and costs • Infrastructure extension / upgrade costs • Utility inflation costs • Application of sales tax
	 Capital Investment	<ul style="list-style-type: none"> • Encouraged status • Ability to import used equipment • Local sourcing requirements 		<ul style="list-style-type: none"> • Sourcing restrictions • Depreciation • Taxation considerations • Duties and fees • Impact on margin
	 Support & Incentives	<ul style="list-style-type: none"> • Government and judicial corruption • Contract enforcement • Bureaucracy • Investment support 		<ul style="list-style-type: none"> • Inflation • Currency exchange • One time and recurring financial incentives

WHAT TO EXPECT WHEN SEEKING A LOCATION FOR OPERATIONS IN JAPAN

Given the historically low levels of foreign direct investment into Japan, there is a general lack on knowledge among the business community about what to expect when thinking about investment in the country. Below we have framed out the landscape that a company might expect to encounter when searching for a desirable location, site or facility for advanced manufacturing operations.



Risk

Risk avoidance is typically high on the list of considerations for a company considering the establishment of manufacturing operations in any country. This is particularly true of Japan given some of the inherent risks associated with its location on the Pacific plate. Japan is very active from a seismic perspective and it also subject to notable storm events. Coastal locations can also be exposed to Tsunami events but in reality, many of the leading biotechnology hubs are protected from such events (either naturally, or via man made barriers such as storm walls).

Consideration	Category	Market Conditions	Insights
Natural Disaster Risk	Seismic	High Risk Low Risk	Assuming a project is looking at locations with a life science competency (tend to be less prone to Tsunamis), the most prevalent risks are seismic and windstorm (which are difficult to avoid given Japan's geography)
	Windstorm	High Risk Low Risk	
	River Flood	High Risk Low Risk	



Supply Chain and Logistics

For cell therapy projects, particularly those with autologous approach, the cycle time sensitivity of the inbound movement of the cellular starting materials and outbound movement of the final cell drug product for infusion to the patient, the need for a robust, predictable, diverse, redundant and reliable transportation network is critical to the successful functioning of an operation. Assuming a company identifies candidate sites or facilities in one of the larger and more connected cities, the transportation network should align with requirements.

Consideration	Category	Market Conditions	Insights
Supply Chain and Logistics	Ground Transportations Service	Limited Abundant	<ul style="list-style-type: none"> Ground transportation services - moderate to good ability to support patient centers via ground transportation within a reasonable commute Air services tend to be acceptable to very good (very good in the larger Prefectures)
	Air Service Direct Connections	Limited Abundant	
	Air Service Connection Frequency	Limited Abundant	
	Air Service Flight Volumes	Limited Abundant	



Labor

General labor market conditions, measured in terms of labor force size, employment in life sciences, and unemployment are generally favorable from a macro perspective. However, as indicated in the section below, sourcing talent with specific skills comes with more complexity.

Consideration	Category	Market Conditions	Insights
Labor Force Size and Unemployment	Labor Force Size	Very Small Very Large	<ul style="list-style-type: none"> • Prefectures that are likely to be investigated support moderate to very large populations
	Life Science Labor Force	Very Small Very Large	<ul style="list-style-type: none"> • The Life Science labor force is typically moderate to large (larger in the moderate to large Prefectures)
	Level of Unemployment	Very Small Very Large	<ul style="list-style-type: none"> • Unemployment tends to range from 3.5% to 5.5%



Ability to Source Labor

Sourcing appropriate labor is always a critical consideration for technical and highly skilled manufacturing operations. The availability of talent in Japan is highly variable and there are notable differences in the ability to source talent, even among the larger metro areas. The age of the workforce, difficulty in attracting labor away from existing employment, and challenges with employee mobility generally result in the market having more challenging labor conditions. Investors with large operations should budget ample time to source and scale talent and should also consider implementing a robust recruiting strategy to improve the ability to secure the diversity of talent required in advanced manufacturing operations.

Consideration	Category	Market Conditions	Insights
Ability to Source Labor	Management	Impossible ————— Very Easy	As a function of size, the large Prefectures are best able to provide labor. Leading global companies with a desirable brand and HR practices should budget the ability to source 10 to 40 employees in 6 months for Management and Engineering talent, 20 to 60 employees in 6 months for Operations talent, and 40 to 100 in 6 months for QA/QC talent (the market is moderate-to-poor relative to market demand)
	Engineering	Impossible ————— Very Easy	
	Operations	Impossible ————— Very Easy	
	QA/QC	Impossible ————— Very Easy	

Operations: Production Bio Technician
QA/QC: Lab Analyst, Biology, Chemistry, Bio QA/QC, Chem QA/QC



Employee Turnover and Graduate Output

One of the impressive and somewhat unique considerations associated with Japan, is the loyalty and tenure of workers, and commitment to an employer. This translates to very low unforced employee turnover. Graduate output in the engineering and technical disciplines is also generally desirable in the large cities.

Consideration	Category	Market Conditions	Insights
Employee Turnover and Graduate Output	Employee Turnover	Very High Very Low 	<ul style="list-style-type: none"> Employee turnover is typically low (“if you can get them, you will keep them”) Student output is generally moderate to good
	Engineering Graduate Output	Low Output High Output 	
	Technical Graduate Output	Low Output High Output 	



Culture and Living Conditions

One of Japan's strengths from a direct investment perspective, is the desirable quality of life that is offered to expats and management in cities across the country. Services and entertainment are generally available, and crime levels tend to be low. The cost of living outside of primary cities tends to be moderate when measured on a global basis, and unlike many countries, public transit is typically available.

Consideration	Category	Market Conditions	Insights
Culture and Living Conditions	Quality of Life	Low High 	<ul style="list-style-type: none"> Quality of life KPIs are generally favorable, and locations tend to be acceptable-to-desirable for management and expats The cost of living is moderate (compared to the USA) Public transit is important to work force mobility and is somewhat variable among Prefectures
	Cost of Living	Very High Very Low 	
	Availability of Public Transit	Not Available Readily Available 	



Non-Product Regulation

The regulatory environment (non-product regulation) is generally favorable with manageable-to-good labor regulations, generally friendly labor-management relations, and regulations that support business. Japan does have more stringent environmental regulation, and pre-construction permitting timelines can be extensive.

Consideration	Category	Market Conditions	Insights
Non-Product Regulation	Labor Regulations	Restrictive Flexible	<ul style="list-style-type: none"> • Labor regulations tend to be manageable • Labor management relations tend to be desirable • Business regulations are manageable • Environmental regulations are not too restrictive • Permitting tends to be long (budget at least 12 months for preconstruction permitting)
	Labor Management Relations	Poor Good	
	Business Regulations	Inflexible Flexible	
	Environmental Regulations & Permitting	Restrictive Flexible	



Real Estate and Project Implementation

Finding suitable sites (new build projects) and facilities (to acquire/lease) to support a proposed investment can be one of the more challenging considerations when entering the Japanese market. Land provided by the government is mostly in rural and less attractive locations for cell and gene therapy. More desirable sites are generally in high demand and come at a cost premium. These sites are also commonly controlled by developers who typically have a preference to lease space. The type of speculative development in the market does not generally align well with the needs of large operations that might require large floor plates, and separation from non-synergistic uses. It is also important for investors to understand that there will likely be a need to budget for a longer project implementation timeline to start of production, and this is difficult to be nimble and move fast through the permitting process.

Consideration	Category	Market Conditions	Insights
Real Estate and Project Implementation	Schedule Confidence	Low High	The availability of suitable real estate options is low, particularly as project size increases. US companies should be prepared to budget much longer project implementation timelines and be prepared to inject notable up-front capital to improve sites/facilities
	Site/Facility Availability	Not suitable Desirable	
	Synergistic Surrounding Uses	Not Suitable Synergistic	



Utilities

Electricity tends to be one of the more critical considerations that needs to be navigated when identifying sites and facilities for a new manufacturing operation. The lead times associated with the upgrades of capacity and extensions of both electricity transmission and distribution lines is long. One of the critical filters that needs to be applied to the identified candidate sites is the availability of excess power to support project requirements.

Consideration	Category	Market Conditions	Insights
Utilities	Electricity	Limited Availability Significant Available Capacity 	Electricity is the most problematic utility that requires significant up front due diligence. Additional capacity can take 3 +/- years to obtain approval.
	Gas	Limited Availability Significant Available Capacity 	
	Water	Limited Availability Significant Available Capacity 	
	Wastewater	Limited Availability Significant Available Capacity 	



Incentives

The incentives landscape in Japan is highly variable. Larger cities/prefectures might not offer any incentives of tangible value to a company seeking to enter the market to manage upfront and/or recurring costs. In comparison, some cities focused on developing the ecosystem of life sciences capabilities might be significantly more interested in using incentives to attract investment. With this context, unlike the US, incentives tend to come in the form of smaller subsidies and/or a reduction in tax. There are also challenges negotiating cash or cash equivalent awards to help manage up front and ongoing costs. This can become a challenge for investors contemplating investments that are very capital investment.

Consideration	Category	Market Conditions	Insights
Incentives	Incentives	Low High 	Generally not compelling



IN SUMMARY

Japan is expected to be a country of interest for global life science companies seeking markets that align with advanced medical technologies. Japan's regenerative medicine market is forecasted to expand in response to the needs of an aging population. Direct investment into Japan is manageable and receives a desirable amount of support from agencies that are focused on helping facilitate FDI activity. Some of the market nuances, however, will dictate the need for advisors to help with FDI initiatives.

About ARM

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. ARM actively engages key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, ARM represents more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

About JLL

JLL is a global real estate services company that was formed in 1999 through a merger of Jones Lang Wootton and LaSalle Partners. JLL provides a wide range of real estate services including investment management, asset management, leasing, property management, and consulting services. JLL has over 106,000 employees in 80 countries around the world and is ranked 190 of the fortunes 500 list.

ABOUT THE AUTHORS

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Matt Jackson and Shannon Curley are leaders of the firm's Global Location Advisory and Execution practice. Based in Washington DC, Matt and Shannon support clients with direct investment projects across the globe, and working in collaboration with local JLL professionals, help facilitate projects from inception to completion. Matt and Shannon specialize in complex manufacturing projects and are members of JLL's Life Science Advisory Committee.



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