FROST & SULLIVAN

The Changing Face of Global Clinical Trials: Asia-Pacific as an Ideal Destination for Specialty Biopharma

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Executive Summary

INTRODUCTION

The contract research organization (CRO) market in the Asia-Pacific (APAC) region is the fastest-growing in the world, with revenue expected to increase at a 20% compound annual growth rate (CAGR) from 2016 to 2021 compared with the rest of the world's 11.4% CAGR.

The intense pressure on pharmaceutical product pricing and regulations in the United States, the failure of the blockbuster model, and the introduction of new product types (such as biologics, regenerative medicines, and orphan drugs) are driving innovations in the biopharmaceutical industry. Challenges related to rapidly recruiting the right patients; working with the most-pursued investigators; and navigating federal, state, and institutional policies are putting immense pressure on small and midsize biopharma companies in the United States and Europe to look for better and faster ways to commercialize their products.

Ongoing US healthcare reforms under the Trump administration are sending waves of uncertainty around the world. In an attempt to accelerate the path to market, the industry is seeing a shift to Asian countries for their clinical trials. The contract research organization (CRO) market in the Asia-Pacific (APAC) region is the fastest-growing in the world, with revenue expected to increase at a 20% compound annual growth rate (CAGR) from 2016 to 2021 compared with the rest of the world's 11.4% CAGR.

WHY APAC

APAC is fast emerging as the go-to destination as it offers several benefits to US pharmaceutical companies outsourcing clinical trials:

A fast-growing pharmaceutical market:
APAC's pharma market is the fastest growing, at a 7.7% CAGR versus the United States' 4.6% from 2015 to 2020, and is expected to capture a 30% revenue share by 2020, driven by friendly market reforms, fast-growing middle-class and aging populations, and greater market access.

Access to a large, treatment-naïve patient pool:
Disease incidences that are similar to or higher than of Western countries are creating large patient pools. The high incidence rate of stroke, hepatitis, and lung cancer make APAC the only destination to conduct clinical trials. Clinical trial penetration in the region is low compared with the United States, which could simplify recruiting. Limited government or insurance reimbursements make clinical trials a great way for patients to gain access to novel therapies that they otherwise could not avail.

Favorable and harmonized regulatory environment:
The rise of multi-regional clinical trials (MRCTs) has led to several harmonization initiatives between ICH (International Conference on Harmonization) member countries and non-ICH member countries to streamline the trial process.

ICH E17, ASEAN Free Trade Area (AFTA) between ASEAN countries and fast-track regulations in several countries are facilitating faster commercialization for multinational companies. Japan is fast becoming the destination of choice to launch new drugs, and several countries offer conducive environments for specialized therapeutic areas (TAs) such as rare diseases and regenerative medicine.

Strong intellectual property (IP) and legal infrastructure:
IP protections in Singapore and Japan are the strongest globally, while legal hassles in recruiting patients for clinical trials are minimal.

Availability of skilled talent:
APAC boasts skilled workers who have studied and worked in the United States and Europe have experience with global regulations, and understand their home country's culture. Japan is one of the top 10 countries on the h-index, indicating a very high scientific literature ranking. APAC is home to large-scale, advanced clinical trial centers and specialized diseases centers with strong TA expertise.

PARTNER

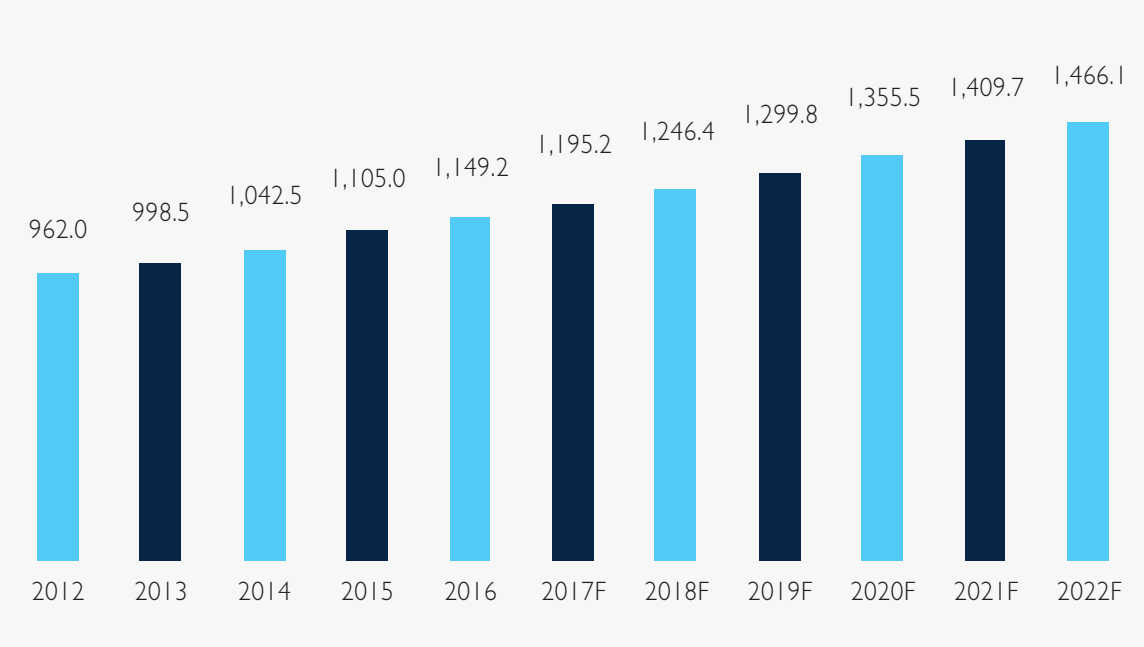
CROs that have deep local insights and are globally scaled offer efficient and effective outcomes to clinical trial studies. Working in APAC requires cooperation among sponsors, CROs, regulators, and investigators across countries, oceans, time zones, and cultures. Sponsors considering the region need a development partner that is not only deeply rooted in the culture, but adept at regulatory nuances. CMIC, the first and largest CRO in Japan, offers a compelling value proposition:

- It has a presence in major Asian countries, with headquarters in Japan, a Southeast Asia headquarters in Singapore, and a presence in the United States.
- It is networked with regulatory authorities and investigators in Japan and other Asian countries to offer consulting and timely support in the critical drug development process.
- It is experienced across TAs, with a major focus on rare diseases, regenerative medicine, and oncology to align with the goals of specialty pharmaceuticals.
- It has a talented team of clinical research associates (some dedicated to specific TAs), medical reps, medical science liaisons, regulatory consultants, and language experts.
- It is a full-range partner throughout the development-commercialization life cycle, supporting the CRO business with in-house sample manufacturing and sourcing and a sales unit for after-launch services.

Transformation Underway in the Biopharma Industry

The pharmaceutical industry is undergoing several shifts that are affecting its growth on a global scale. In the past three decades, drug development has evolved from a national or regionally centered activity to a more globalized phenomenon[1]. Business models have had to evolve as well in an attempt to survive in an intensely regulated and competitive market.

Figure 1: Pharmaceutical Market: Revenue Forecast, Global, 2012–2022F



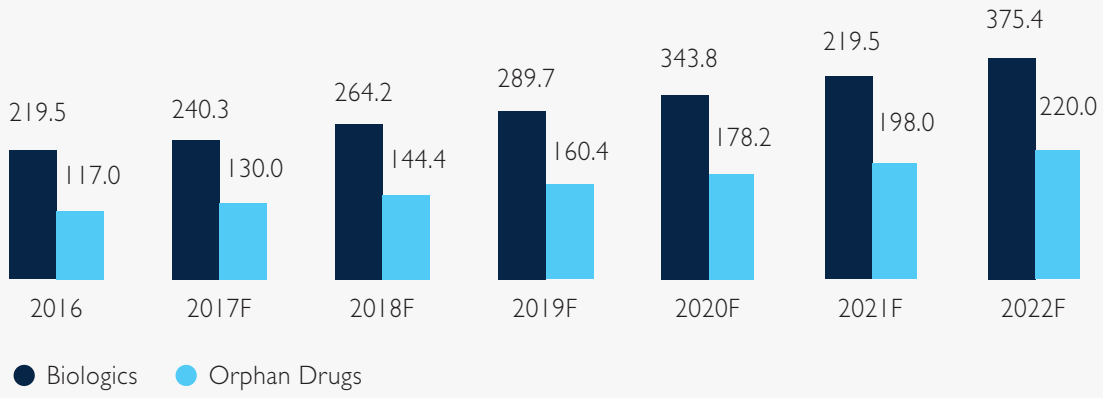
Source: Economist Intelligence Unit (EIU), Business Monitor, Frost & Sullivan

As shown in Figure 1, global pharmaceutical market has been increasing, but growth is expected to slow slightly from 2016 to 2022[2]. Trends that are transforming the industry include the launch of innovative specialty products, regulatory and pricing pressure, and alternative payment models.

The patent cliff for blockbuster drugs and personalized medicine has shifted the research and development (R&D) focus to new products and therapeutic areas (TAs). In the past five years, biologics, orphan drugs, and regenerative medicines have seen increased activity. In 2016, the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research approved 22 novel drugs, of which 15 were biologics and 9 were orphan drugs (2 fell in both categories)[3]. The FDA and European Medicines Agency (EMA) are seeing more new drug applications in these areas, and by 2020, orphan drugs are expected to capture 20% of all prescription drug sales globally[4]. The pipeline of almost every biopharmaceutical company—the majority of which are small or midsize—is focused on biologics and rare diseases. Of the top 20 orphan R&D products based on net present value in 2015, more than 50% are from small to

midsize biotech companies[5]. Besides orphan drugs, oncology and neurology programs have garnered a lot of attention from small biopharma. Since small biopharma tends to look for niche or more difficult areas, new indications have emerged in the R&D pipelines. Figure 2 presents the global revenue forecast for orphan drugs and biologics, and the CAGRs for each segment compared with the small molecules segment.

Figure 2: Biologics and Orphan Drugs Market: Revenue Forecast, Global, 2016–2022F



SEGMENT	CAGR (2016-22)
ORPHAN DRUGS	11.1%
BIOLOGICS	9.4%
SMALL MOLECULE	2.7%

Source: EIU, BMI, Frost & Sullivan, Global Orphan Drug Market, Nov 2016

Technology disruptions have impacted the way clinical trials process is shaped and executed. mHealth, which is delivery of healthcare services through mobile communication devices, is being used not only to communicate and collaborate with care teams and patients, but also to capture clinical data in real-time[6]. Another application of technology in clinical trials is use of predictive analytics to identify candidates using more than their genetic profiles, to include social media and doctor visits data. Finding best sample sizes by using electronic medical records has reduced data errors and improved clinical trial efficiency, thus making trials faster and cheaper[7].

Tighter regulations have also affected the global healthcare industry. The United States has seen annual drug development costs increase by an average of 6% while the number of drug approvals declines. Regulations and pricing policies are expected to further tighten under the Trump administration in 2017 and 2018: The proposed fiscal 2018 budget, announced on 23 May 2017, includes major funding cuts for biomedical research that would severely affect study across chronic and infectious diseases[8]. It would create pricing pressure on products and reduce biopharma companies' ability to invest in R&D, resulting in fewer new therapies. Trump has also proposed eliminating the individual mandate, which requires all US citizens to have an insurance policy, and replace it with tax-deductible health insurance plans, though these proposals have repeatedly failed and has kept the Affordable Care Act's future unclear. Section 340B Drug Pricing, which is to be implemented on 1 October 2017, requires drug manufacturers to provide outpatient drugs at significantly lower prices to qualified organizations[9]. In light of current events, pressure on biopharma companies is likely to continue in the United States.

Alternative payment models have emerged to distribute risk across stakeholders and improve health outcomes. Biopharma companies are expected to take greater responsibility of both cost and quality of their products. These models have worked well in countries with national health systems or stable insurance coverage, but industry experts believe it may be more difficult to implement in the United States, where patients change health plans often. Though the country continues to focus on different financial arrangements, implementation has been postponed by Centers for Medicare & Medicaid Services s till 2018[10].

The influence of such trends is already evident in the industry. The number of clinical trials in United States has been declining gradually since 2014, while developing nations, especially in Asia, have seen an increase in the number of trials[11]. This white paper, based on Frost & Sullivan research, explores the key factors that position APAC as a destination of choice for small and midsize specialty biopharma companies.

Shift to Outsourcing and CROs

Besides the challenges from the industry transformation, US companies also increasingly face challenges in conducting clinical trials at home. The primary barriers include the lengthy regulatory timelines, recruiting sufficient patients, and finding qualified and experienced investigators and key opinion leaders (KOLs)[12], State and local regulations that may differ from federal policies add to the already lengthy trial times. Trial sponsors must abide by all laws as well as the institutional policies of the clinical trial centers that they work with. Hiring qualified KOLs and investigators on trials is becoming increasingly difficult because they tend to focus only on novel compounds.

> *"Developed nations have a lot of regulatory hurdles, which are not from the FDA but institutional policies at research sites that go above and beyond the FDA guidelines.*
>
> *These policies take sites far too long to open a trial."*

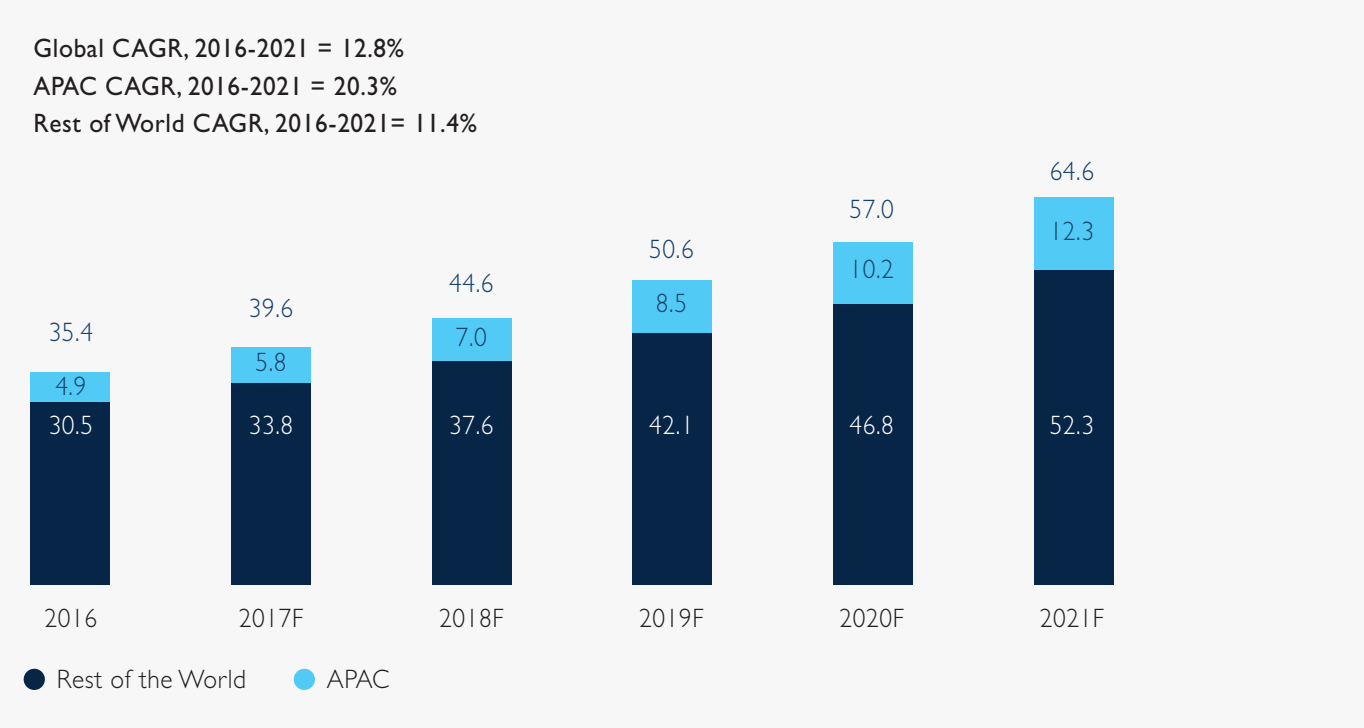
Clinical Research Head, Midsize US Biotechnology Company

The increasing cost of drug discovery and development, globalization, a lack of extensive in-house R&D talent and infrastructure, and the rise of new revenue market streams have driven biopharma companies to outsource clinical trials to CROs. Outsourcing has been an integral part of the biopharmaceutical industry's value chain, primarily during the early stage, and the globalization trend is further fueling it.

The reasons for outsourcing vary with the size of the company. While large biopharma outsources to have the flexibility of a partner and to reach the market quickly, small and midsize companies' limited funds and resources, specialized pipelines, increasing competition from low-cost nations, and focused local presence drive them to outsource. Their specialized focus in scientific innovation makes them more nimble, but their unfamiliarity with other regions' regulations and cultures makes outsourcing an essential choice. Small biopharma also does not have the luxury to spend the time and money often required for the desired number of patient recruitment in the United States, and recruiting in-demand KOLs and investigators is even more challenging for them.

The global CRO market was valued at US$35.41 billion in 2016 and is expected to reach US$64.58 billion by 2021, growing at a CAGR of 12.8%, as shown in Figure 3. APAC is the fastest-growing CRO market, accounting for 13.8% share in the global market in 2016 and revenue of US$4.89 billion. Revenue is predicted to grow at a CAGR of 20.3% between 2016 and 2021. The CRO market CAGR in Japan, China and South Korea are expected to be 13.0%, 28.3%, and 14.1%, respectively.

Figure 3: CRO Market: Revenue Forecast, APAC and Rest of World, 2016-2021F



Source: Frost & Sullivan Global CRO Report, 2016; Frost & Sullivan APAC CRO Market Report, 2015

A major driver of APAC CRO market attractiveness is the often-mentioned patient availability. The rising middle class and urban population create vast pools of people that are treatment-naïve, driving global companies to expand in this market for revenue. The lower per capita healthcare spending in this region creates attractive clinical trial opportunities. All this, combined with advanced clinical trial centers and experienced investigators, is appealing to multinational companies.

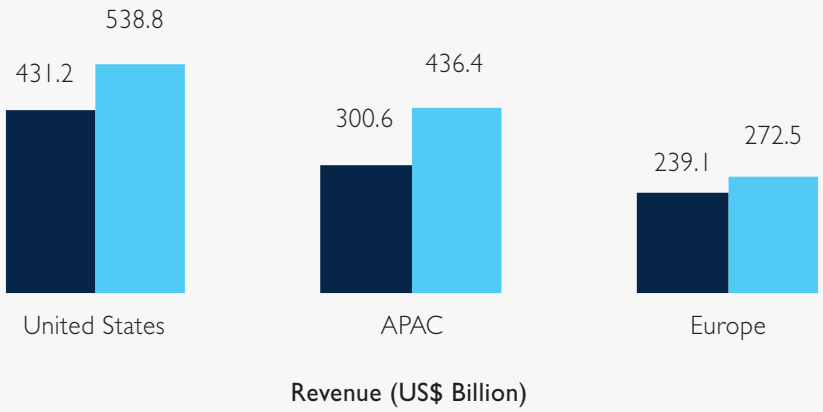
APAC on the Rise

With a fast-growing pharma market, large treatment-naïve population, highly skilled and internationally acclaimed investigators, high-quality data, and harmonized regulations, APAC has become a preferred outsourcing destination for clinical trials.

Fastest-Growing Pharma Market

As one of the largest pharmaceutical markets in the world, APAC's share is growing at a faster pace than the United States and Europe. APAC's pharma market is forecasted to grow at a 7.7% CAGR from 2015 to 2020, compared with 4.6% for the United States and 2.7% for Europe in the same time period, as shown in Figure 3. By 2020, APAC will account for more than 30% of pharmaceutical sales growth worldwide, making it a critical revenue source for biopharma companies[13].

Figure 3: Pharmaceutical Market: Revenue Forecast, US, APAC, and Europe, 2015-2020F



SEGMENT	CAGR (2015-20)
UNITED STATES	4.6%
APAC	7.7%
EUROPE	2.7%

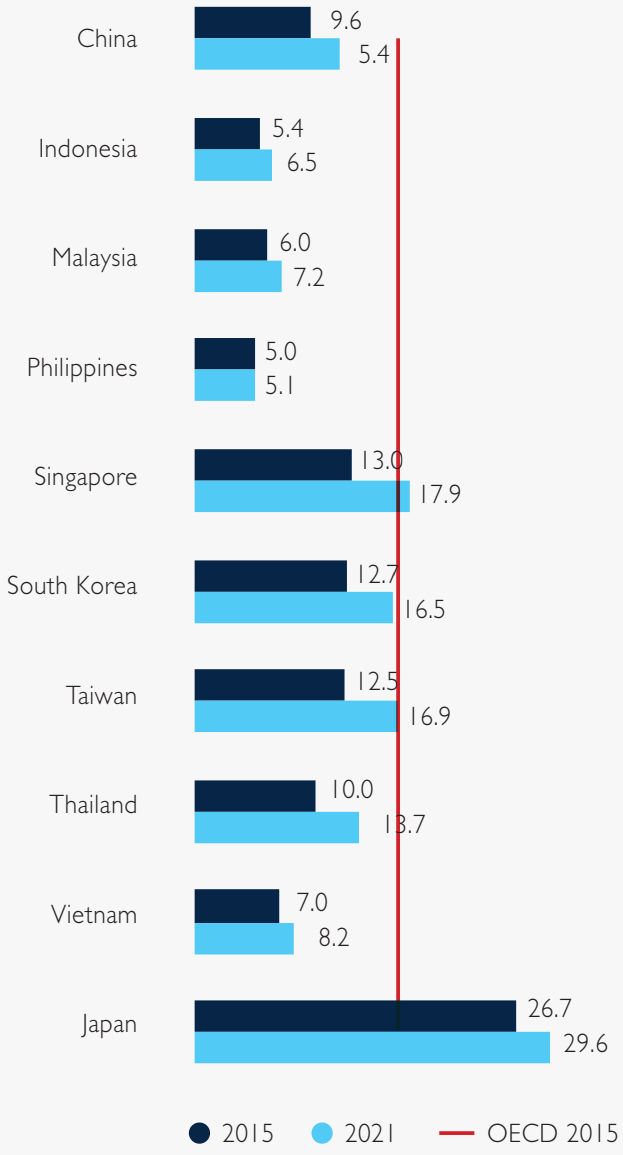
Source: IMSHealth, EIU, EvaluatePharma

APAC pharma market growth is driven mainly by the growth in middle-class and aging populations, expanding market access, and healthcare reforms.

More than half the world's population lives in APAC[14]; by 2025, the region will be home to 310 of the world's 600 megacities. The fast-growing middle-class in the region with its disposable income will drive the pharma market. The percentage of the population over age 65 is on the rise, most notably in Japan, Singapore, Taiwan and South Korea, as shown in figure 4. In South Korea, 20.5% of the population is expected to be older than 65 years by 2026; Singapore expects that population

group to double by 2030[15]. These countries have a higher rate than the Organisation for Economic Co-operation and Development (OECD) average in 2015[16]. It is estimated that the cumulative cost of elderly healthcare in Asia over the next 15 years will reach US$20 trillion[17], which will increase healthcare consumption and accelerate several therapeutic categories.

Figure 4: Percentage of Population above 65 Years, Selected APAC Countries, 2015 and 2021F



Source: World Bank, OECD, Singapore Department of Statistics, Population.sg, East Asia Forum, Frost & Sullivan

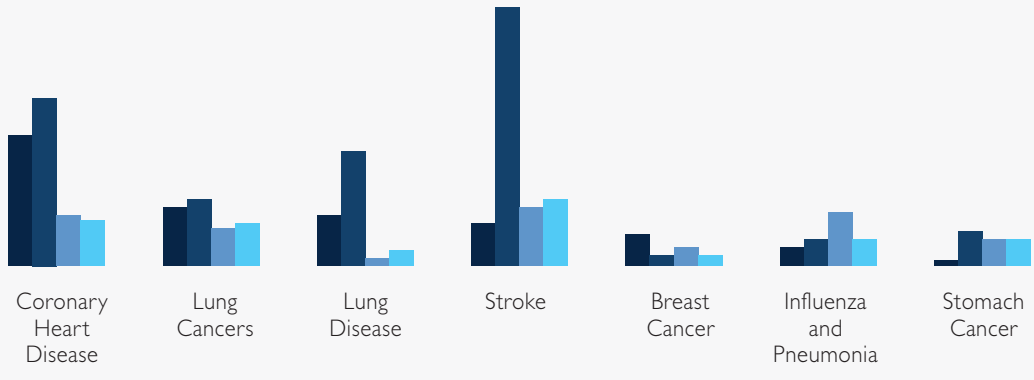
Driven by the rising middle class and disposable income, demand for quality healthcare in Asia is increasing[18]. Governments are making healthcare a priority and taking steps to boost public access to high-quality healthcare services[19]. Several countries have introduced or expanded universal health coverage, including Thailand, Vietnam, China, and Singapore. Private insurance coverage has also increased in the last few years. Singapore's health insurance industry is expected to expand fourfold by 2020 to reach a total value of US$6.8 billion[20]. This will expand market access for biopharma companies and present more opportunities to secure a higher market share[21].

Governments in the region have been streamlining regulations to be friendlier to clinical trials and support R&D innovation. Attractive R&D tax incentives are offered to encourage smaller firms and foreign companies. In China, pharmaceuticals are allowed an extra 50% expense deduction for eligible R&D costs, besides tax cuts and value-added tax exemptions[22].

Large Patient Pool with Attractive Disease Landscape

Asian countries have mirrored incidence rates of Western countries in the past decade. Several diseases have higher incidence rates than the West, such as gastric cancer and lung diseases. According to a 2020 health prediction of World health rankings, certain APAC countries will show spikes in deaths from specific causes, such as influenza and pneumonia in Japan and stroke in China and South Korea. [23]The similar disease landscape provides vast opportunities to recruit patients for global trials.

Figure 5: Mortality Rate of Selected Diseases and Conditions, per 100,000 US vs. APAC Countries, 2020F



	Coronary Heart Disease	Lung Cancers	Lung Disease	Stroke	Breast Cancer	Influenza and Pneumonia	Stomach Cancer
US	78.0	35.0	29.7	25.9	19.4	10.6	2.8
China	99.4	38.8	67.6	153.6	6.1	15.1	21.1
Japan	30.4	21.4	4.3	34.0	10.9	32.1	15.6
South Korea	26.4	25.7	8.7	39.1	6.3	16.3	15.8

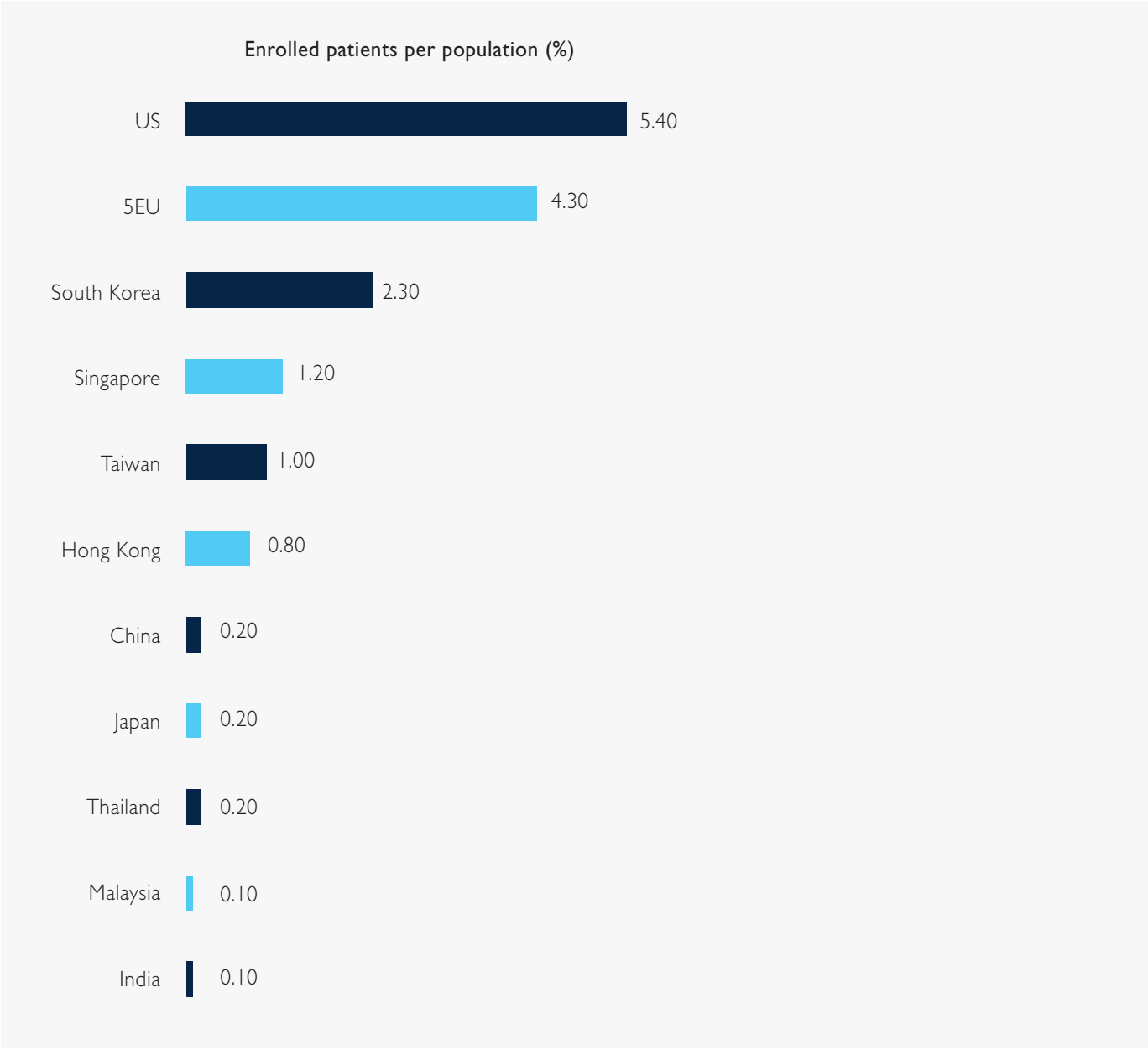
Source: World Health Rankings

Recruitment is often a challenge in conducting trials in the West, because of a smaller patient pool and a higher number of trials. Clinicians often do not refer patients to clinical trials[24]. This impacts enrollment and sometimes results in termination of trials. With a pool of approximately 4 billion people, of which more than 2 billion live in easily accessible urban areas, Asia provides a hub of potential patients[25].

> *"It is becoming more and more challenging to recruit patients in the United States, which is a highly competitive market. Almost all the biopharma companies wish to work with the same key opinion leaders who will preferentially work with only the most novel and exciting compounds, so it becomes even more difficult to gain their participation. Even if they participate, their enrollment may be minimal. This is one of the reasons we decided to move our clinical trials out of the US—first to Europe, then to Central and Eastern Europe, and then Asia-Pacific was the next logical choice."*
>
> Associate Director of Clinical Operations, US Biopharma Company

The penetration of trials in APAC is also less, offering a more treatment-naïve population. Figure 6 shows the percentage of a population enrolled in trials in 2016. India has the lowest rate; other Asian countries also have significantly lower rates than the United States and the combined population of five European Union countries[26]. A lower density in APAC provides an additional advantage in patient recruitment.

Figure 6: Clinical Trial Penetration, Selected Countries, 2016

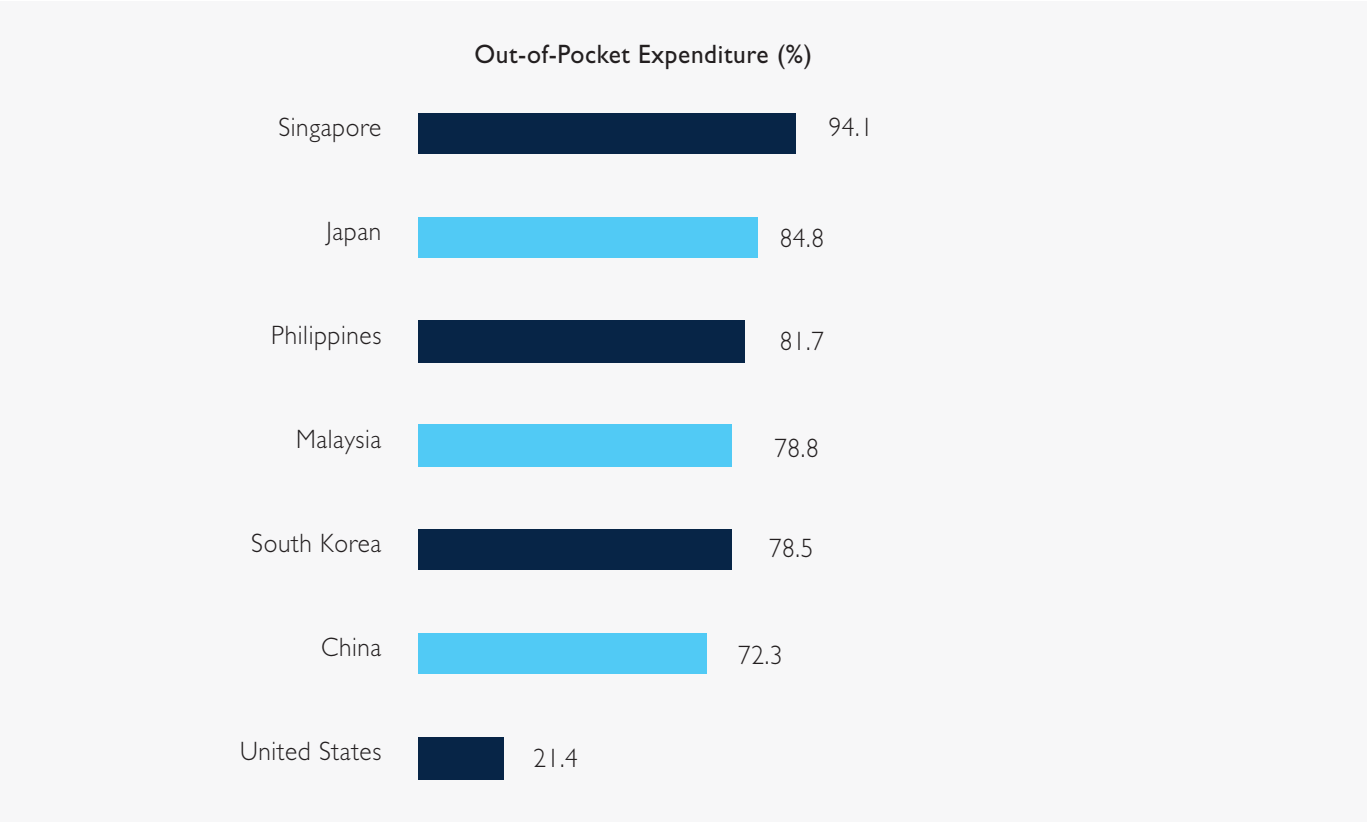


Source: Clinicaltrials.gov (accessed 5 June 2017), http://www.worldometers.info
Methodology: Clinical trial penetration is calculated by dividing the number of enrolled patients in clinical trials in 2016 by the population.
Note: 5EU includes United Kingdom, Germany, France, Spain, and Italy.

Unlike in the US, the reimbursement landscape is not mature in several Asian countries; patients have to pay out of pocket for novel therapies or depend on local charities to fund them[27]. Figure 7 shows the out-of-pocket health expenditure comparing the United States with selected APAC countries.

Out-of-pocket expenditure in APAC is significantly higher, which makes clinical trials a great opportunity to access novel therapies and treatment options otherwise unavailable in the current treatment regime[28].

Figure 7: Out-of-Pocket Expenditure as a Percentage of Private Expenditure on Healthcare, Selected Countries, 2014



Source: World Health Organization Global Health Expenditure database

Favorable Regulatory Regime

Japan, South Korea, Australia, and Singapore adhere to a well-developed ethical and regulatory framework. They follow standard international codes of conduct adopted from the ICH, International Organization for Standardization (ISO) and even European Union guidelines, allowing for easier integration and acceptance by institutions globally.

With the increasing globalization of drug development and shift to APAC, MRCTs have seen a substantial growth for regulatory submissions. The ICH drafted a guideline in May 2016 known as E17 to support the increasing use of MRCTs. The guideline defines the factors that must be considered in planning, designing, and executing MRCTs[29]. Different national health authorities are also supporting guidance for MRCTs.

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has made concerted effort for standardization so that more and more MRCTs are conducted in the country and drug lag is reduced. The Chinese FDA also issued guidance on MRCTs of drugs in early 2015, to see more trials happening in the country[30].

Several harmonization initiatives exist between Asian countries to support easy data acceptability and reduce drug approval timelines in the region. ASEAN countries' harmonization initiative—AFTA—has standardized the drug approval process with common documentations, ASEAN Common Technical Documents (ACTD) and ASEAN Common Technical Requirements (ACTR). ACTD gives information on the format and structure of the dossier to be used for applications in the ASEAN region, while ACTR is a set of written material intended to guide applicants to prepare an application that is consistent with the expectations of all ASEAN drug regulatory authorities. ASEAN AFTA members include Brunei, Indonesia, Malaysia, Philippines, Singapore, Thailand, Vietnam, Laos, Myanmar, and Cambodia[31].

Other collaborations exist among APAC countries. China, Japan, and South Korea's Tripartite Cooperation on Clinical Research aims to improve the landscape of clinical trials among the three countries because they are believed to have similar genetic homogeneity and disease patterns. Trial data generated in South Korea and China have frequently been accepted for drug registration in Japan. Harmonization agreements also are in place between Taiwan and Japan; and between Taiwan and APEC (Asia-Pacific Economic Cooperation) organization to support clinical trials and easier goods exchange.

Fast-track processes also exist to allow faster drug availability by either creating priority reviews for certain rare or life-threatening disorders or for world-first drug approvals. South Korea introduced a new Clinical Trial Authorization (CTA) process in 2002 for improving its regulatory environment. The procedure allows for applications to be submitted in parallel to institutional review boards/ethics committees and South Korea's regulatory body, Ministry of Food And Drug Safety. This has greatly reduced approval time to between 4 and 8 weeks[32]. Japan's Sakigake route introduced in late 2015 also provides priority review to such drugs and aims to review within 6 months[33].

The region is becoming a go-to location for conducting clinical proof-of-concept studies to use Asian data in the US for supporting the product profile and reducing lag time between US approval and other destinations. The US FDA accepts foreign data for early studies and does not require Investigation new drug (IND) application approval[34].

Several Asian countries offer a conducive regulatory environment for rare diseases and regenerative medicine. Japan, China, Singapore, and South Korea are front-runners in stem cell therapy due to market-friendly government regulations and significant funding. Japan has a conditional marketing approval option for regenerative medicines, which allows companies to sell the drug earlier in the clinical research, expanding their revenue cycle. Japan already approved a drug on conditional and time-limited authorization of 5 years marketing in September 2015 for heart failure due to ischemic heart disease[35]. China has 30 regenerative medicine centers and has spent 0.53 billion USD on the research. Both these countries are leaders in publishing scientific papers, just behind the United States[36]. Even for rare diseases, Asian countries have established systemic regulatory and economic incentives. To promote research on rare diseases and orphan drugs, Japan, China, and Taiwan provide government grants, creating growth opportunities and placing Asia on the world's clinical trials map[37]. Table 1 compares the regulatory environment of selected Asian countries with the United States.

Table 1: Comparison of Rare Disease and Orphan Drugs Regulations of Selected Countries[35,38]

CRITERIA	US	JAPAN	SOUTH KOREA	TAIWAN
Legal Framework	Orphan Drug Act (1983), Rare Diseases Act of 2002	Revised orphan drug regulations (1993)	Orphan Drugs Guideline (2003)	Rare Disease Control and Orphan Drug Act (2000)
Subsidies	Government grants for clinical research	Government grants for clinical & non-clinical research	-	Government grants and awards from the central competent authority
Market Exclusivity	7	10	6	10
Tax Credits	Up to 50% for clinical expenses	Waived consultation fee, up to 50% development cost, 15% tax credits, up to 14% corporate tax reduction	50% subsidized application fee	Not disclosed
Fast-Track Approval	Yes	Yes	No	Yes
Pharma pricing	Market-driven	Price negotiations	-	-

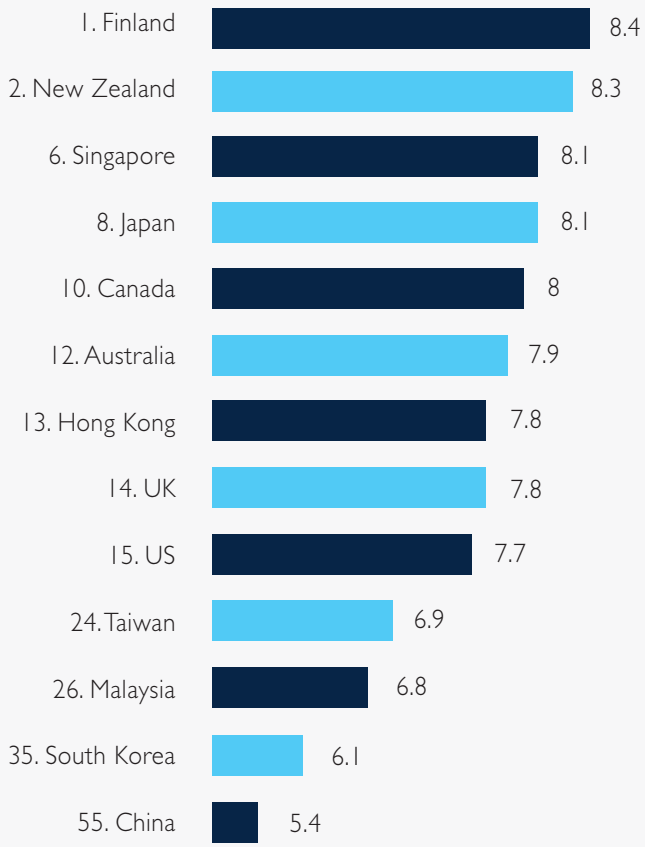
Data output quality from studies conducted in Asian countries can be used to support international regulatory applications, including to the US FDA and EMA, and is regarded of high quality. The adverse findings rate is lower in APAC during data inspections by the US FDA and EMA than in Western countries. For example, the percentage of critical EMA Good Clinical Practice (GCP) inspections in APAC was reported to be roughly 5%, compared with 16% in North America, between 2000 and 2012[39], indicating high compliance to standards.

> *"Work carried out in Asia is usually of a high quality. Both the trials and data quality is quite high in Hong Kong, Singapore, South Korea, and Japan."*
>
> Associate Director of Global Clinical Operations, US Biopharma Company

Strong IP Rights Protection and Legal Environment

IP rights in Singapore and Japan are consistently ranked among the 10 most secure out of 128 countries. The United Kingdom and United States are 14th and 15th, respectively, alongside some European countries. Figure 8 shows the IP Rights index of selected countries[40].

Figure 8: IP Rights Index, Global, 2016*



**The IP Rights Index comprises protection of IP rights, patents, and copyrights. It compares 128 countries.*
Source: The International Property Rights Index 2016.

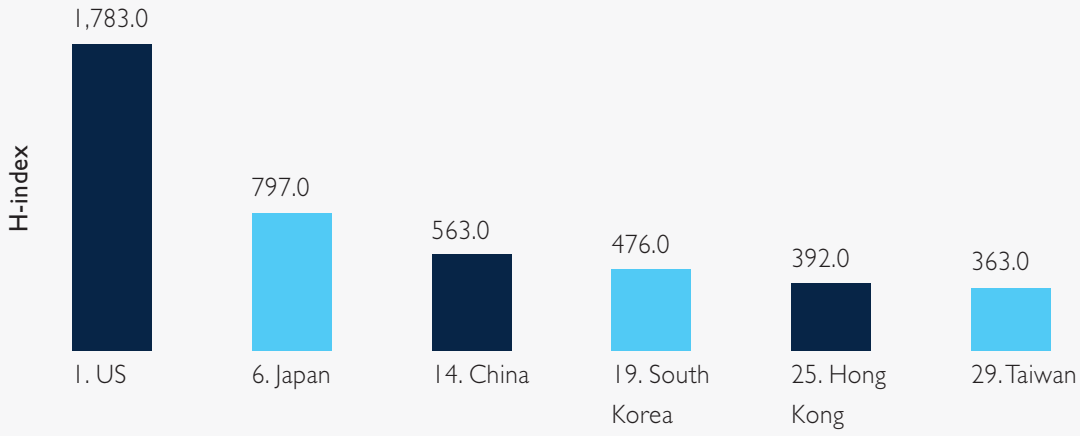
Legal liabilities associated with referring or enrolling patients in clinical trials in APAC countries are relatively lower than in the United States. The potential for a lawsuit targeting healthcare providers and referring physicians is quite high in the United States, making the recruitment process risky and difficult; such hurdles are negligible in APAC.

Resource Availability

A major attraction that compels foreign companies to conduct clinical trials in APAC is the availability of skilled resources. Asia not only boasts of strong TA expertise but also of talented investigators and doctors that have returned home after studying or working in the West. In an attempt to encourage repatriation, the Chinese government created initiatives such as the Thousand Talents Program, which provides professional and financial incentives to attract Asian talent working overseas and persuade Chinese scientists to return[41]. Japan, South Korea, Philippines and Vietnam are also seeing return of expatriates and skilled workers[42]. Singapore's Ministry of Health pays for the final year of studies for Singaporean medical graduates who are studying medicine abroad if they return home to work[43]. Asians who return from their overseas stints have an edge due to their global mindset and an in-depth understanding of the home culture, which foreign experts' lack[44]. This creates a world-class talent pool capable of supporting large clinical trials.

The quality of clinical data in Asia is comparable to world standards; several countries' scientific literature is ranked high in journals and citations. Figure 9 shows the h-index of several countries in 2015, with Japan among the top 10 countries globally.

Figure 9: H-index for Selected Countries, 2015*



Source: Scimago Journal and Country rank

**Note: H-index is an author-level metric that measures both the productivity and citation impact of the publications of a scientist or scholar. The index is based on the country's total set of the scientist's most-cited papers and the number of citations that they have received in other publications*

Another significant driver is the availability of strong TA expertise and specialized disease centers. In South Korea, Woodirul Spine Hospital is one of the top global spinal treatment hubs, with more than 1,130 neurospinal specialists and state-of-the-art technology[45]. Singapore's Gleneagles Hospital is the leading center for cardiac care, and its Asian Center for Liver Diseases and Transplantation is the first private facility for liver diseases, with a worldwide consensus honor from the Joint Commission International for quality patient care. In stem cell therapy, Asian countries are front-runners globally, due to market friendly regulations in Japan, China, Singapore, and South Korea. APAC is currently home to large and advanced clinical trial centers. The largest hospital in Asia boasts more than 9,000 beds, while the largest US hospital has roughly 2,400 beds. National governments are also committed to investing in technology and building advanced centers. For instance, South Korea stands as a top 10 location worldwide in the number of studies conducted annually. It has embraced technology for faster clinical trial registration and data capturing[46]. The Chinese government increased drug innovation funding with about US$16 billion from the central government and US$49 million from local governments[47]. South Korea's National Enterprise for Clinical Trials (KoNECT), focuses on talent and technology innovation in research and trials[48].

> *"In Asia-Pacific, we started doing clinical trials in Australia and New Zealand first. However, later on, we realized that other Asia-Pacific countries should also be considered, as there is access to a higher number of patients and the bigger universities have wide experience in doing research. The quality of data has proven to be consistently high. In addition to this, the principal investigator (PI) and staff are usually very compliant to protocols and regulatory standards, which unfortunately is not always the case in the US and Europe"*

Associate Director of Clinical Operations, US Biopharma Company

Despite the vast opportunities, US companies are hesitant about running trials in APAC because of the unfamiliarity with the region, regulatory heterogeneity, and cultural and language differences in each country[48].

To fully leverage the opportunities that APAC offers, sponsors can turn to CROs that are truly both global and local.

Working with the Right Development Partner: CMIC

There is no dearth of CROs that can manage clinical trials in APAC, be it the large global players or small, regional, niche vendors. But the questions that most biopharmaceutical companies ask before outsourcing are: How reliable is this partner? Will they treat our project with same passion and deliver?[48] **Quality**, **reliability**, **flexibility**, and **innovation are important evaluation factors** when selecting a CRO partner, besides affordability[49]. Outsourcing clinical trials to the right CRO partner that understands the term "globalization" is critical for biopharma companies because their brand reputation is associated with the quality of work. But unlike large biopharma companies, small and midsize biopharma look for a development partner that understands their specific needs and is not transactional[50].

Global trials involve multiple regulatory frameworks and research cultures, but must apply the same clinical data. To that end, it is critical that biopharmas leverage CRO partners that have global capability support and can scale up easily, but also a strong localized presence and expertise in the targeted regions. CROs that possess dedicated teams in APAC markets are better able to use strategic planning to address various global trial challenges, particularly those related to regulatory and oversight requirements. Maintaining working relationships and fluent communication with regulatory agencies is also crucial for a partner. Discussing protocol reviews directly with regulators can ensure ongoing compliance and aid in the development of the regulatory plan during study start-up.

> *"For a biopharma like us, we need a CRO that can act as a partner in development and not just in a transactional nature. We don't want vendors that just help us file documents with local health agencies. The CRO relationships that have successfully worked with us are the ones that can provide very helpful local strategic advice. For example, in Japan, you need a CRO who has relationship with PMDA, and when we are stuck with some regulatory issue, they understand how to navigate through. They can talk to local agencies and find a solution. Also, having good awareness of drug development in that country, as well as globally, is really important."*
>
> Vice President of Regulatory Affairs, US Biopharma Company

"One of the factors we consider when choosing a CRO to outsource clinical trials in Asia is the availability of an experienced local project manager. It is crucial that the manager is an effective communicator and is able to manage different functional experts, the regulatory team, medical affairs team, and drug safety team. The CRO must have the right and ample pool of resources to upscale the project anytime. We have had troubles in the past working with CROs who didn't have the team to expand at the right time for other projects, so we had to hire another CRO at the last minute."

Associate Director of Clinical Operations, US Biopharma Company

CMIC is well positioned and experienced in the Asian market to support end-to-end CRO needs of small and midsize biopharma. Celebrating its 25th anniversary in 2017, it is the first and largest CRO in Japan with a full range of services and monitoring experience across TAs, and specialized focus on rare diseases and oncology. Headquartered in Japan with a Southeast Asia center in Singapore and presence across major Asian countries,

CMIC creates an unparalleled team of experts who can proactively navigate through all drug development elements from early-phase research to product commercialization in a wide range of subjects for both drugs and medical devices. CMIC's unique pharmaceutical value creator model supports a full range of discovery, development, manufacturing, sales and marketing, site management, consulting, price negotiation, and post-marketing feedback services.

Figure 10: CMIC's Value Preposition

1. Significant presence in the fast-growing Asian pharma market

In order to tap into the fastest-growing pharmaceutical market, CMIC has strategically positioned itself across major Asian countries through its 16 affiliates to have access to the growing local population and understand the cultural intricacies of each country. The regional headquarters in Singapore helps CMIC manage regional operations and local teams.

2. Strong regulatory track record

The team has been involved in more than 80% of new drug approvals in Japan. Its experienced consulting team has relationships with the PMDA and the Ministry of Health, Labour and Welfare to gain maximum benefits for clients in Japan. CMIC's consultation offering not only helps in documentation but also advises on the best commercialization approach by utilizing fast-tracks and priority reviews and establishing operational structures.

CMIC has a deep understanding and track record for cross-border pre-clinical and clinical bioanalysis between the US FDA, EMA, and Japanese/APAC authorities, with experience in inspections with FDA, EMEA and PMDA. It has conducted about 300 post-marketing surveillance protocols in Japan and 30 in South Korea. A robust team of more than 60 medical writers provides high-quality deliverables in English, Japanese, and other languages.

3. Deep TA expertise with focus on rare diseases, regenerative medicine, and biologics

CMIC has experience across TAs with special teams that focus on areas aligned with the small and midsize biopharma pipeline. A dedicated subsidiary, OrphanPacific, focuses on rare diseases, while CMIC's regenerative medicine group has taken about 50 projects from more than 20 companies for the last two years.

CMIC also has a focus on biologics through CMIC's joint venture with JSR Biologics. This division provides contract services for manufacturing and development of next-generation antibody products. CMIC and JSR Group also own a biopharmaceutical contract development and manufacturing organization (CDMO), KBI Biopharma Inc., which operates 4 facilities in the United States and has served more than 250 clients globally during the last 20 years.

> *"Our company focuses on rare diseases. CMIC has demonstrated their experience in conducting clinical trials for rare diseases and we have worked with them on trials across multiple phases of development. The interactions between CMIC and the global team are of a high quality. They have all the necessary expertise and experience to help companies conduct clinical trials in Japan. CMIC is well-known in Japan for being a top-tier CRO."*
>
> Associate Director of Global Clinical Operations, US Biopharma Company

4. Experienced team with local knowledge and international exposure

CMIC group has about 6,000 global employees, 1000 clinical research associates, (some dedicated to specific TAs), and 600 medical reps in Japan, along with several contract medical science liaisons. CMIC's regulatory consultation team of more than 50 consultants—most of whom have 25 or more years of industry experience in Japan—has excellent relationships with local regulatory authorities and KOLs.

With these experiences, the team provides one-stop consultation services from early-phase research to product commercialization for drugs in all TAs and medical devices. CMIC also has significant experience working with international biopharmaceutical companies. For example, for its Japanese CRO division, more than 70% of orders during the 2017 fiscal year are from international companies—including all the top 10 global biopharmaceutical companies through either client's global headquarters or their local affiliates in Japan.

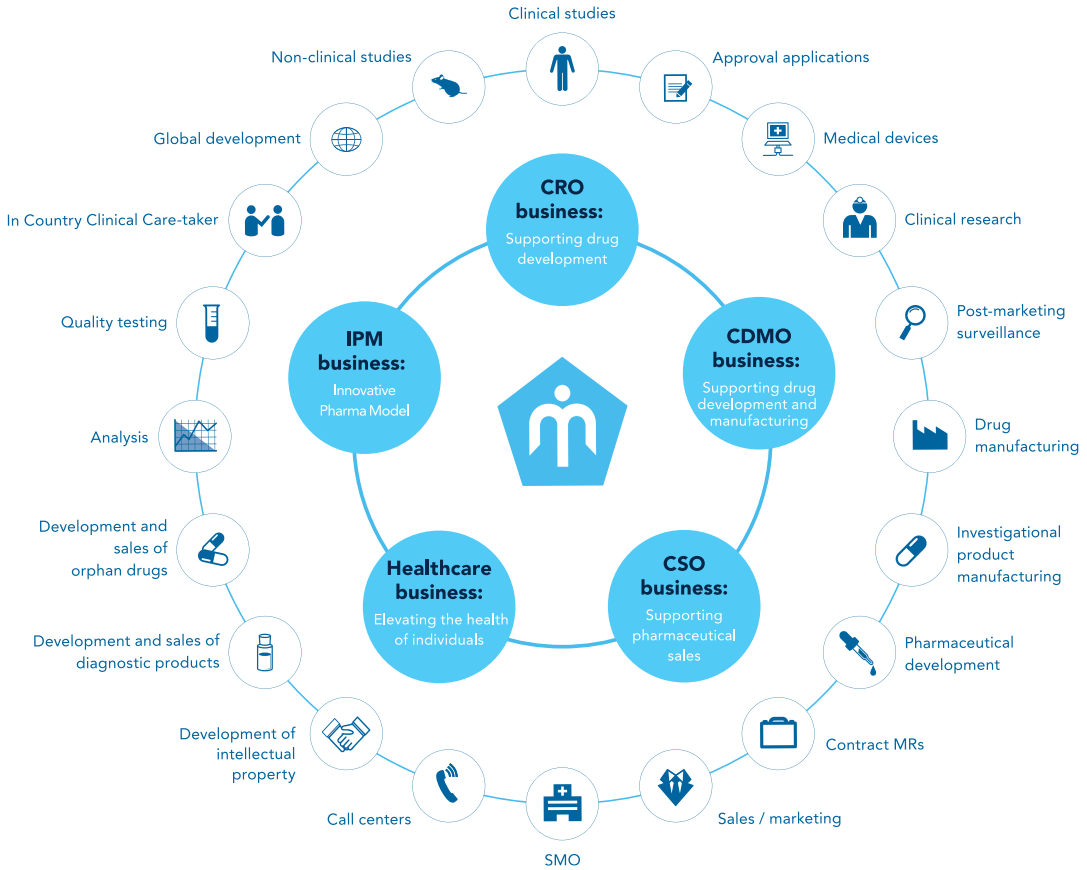
5. Integrated services for a full-range service partner

CMIC's unique amalgamation of several functions has established it as a one-stop provider from research through commercialization. CMIC's competitive advantage is the CDMO business that seamlessly supports the CRO unit in drug development and investigational new drug manufacturing services at its GMP and GCP-compliant facilities in conjunction with analysis and measuring work during non-clinical and clinical trials which reduce overall costs and eliminate sponsor sourcing hassles. Just in fiscal year 2017, CMIC has provided 47 investigational new drug services, 23 commercial production services, and 21 formulation development services. It has 3 CDMO sites in Japan, including an under-construction building for injectable. Its New Jersey-based US subsidiary, CMIC CMO USA Corporation, is the first Japanese CDMO to join the Pharma and Biopharma Outsourcing Association.

CMIC's site management organization unit provides clinical trial support to medical institutions and patients. It has worked with more than 2,000 sites in Japan, which provides a significant advantage to recruit patients. Its contract sales organization (CSO), CMIC Ashfield, provides support on drug sales and marketing as one of the top 5 players in Japan. CMIC also has a Chicago-based bioanalysis division for biomarker and pharmacodynamics work and seamless bioanalysis operation between Japan and the United States.

With such a wide range of services across the value chain, CMIC enjoys a unique competitive position that helps clients achieve the maximum benefits in becoming truly global.

Figure 11: CMIC's pharmaceutical value creator model



"We chose CMIC as it is very well-known in Japan and is highly experienced. We had a great experience working with them. We are very impressed with their commitment, communication, and collaboration skills."

Associate Director of Clinical Operations, US Biopharma Company

"CMIC provided us very good advice, as well as helped us with PMDA in different research initiatives. They helped us conceptualize things, both for PMDA and also for our partners. Their team members really cared about the outcome of our trials and compound development as much as we did. That's important to a company like us that the group is as passionate about the drugs as you are. They have been really good partners."

Vice President of Regulatory Affairs, US Biopharma Company

The Last Word

The fast and ever-changing pharmaceutical industry has put APAC on the world map as a destination that is difficult to ignore. APAC is increasingly being seen as an integral element of global clinical trial success. Facilitated by a fast-growing pharmaceutical market, vast availability of treatment-naïve population, highly skilled and internationally acclaimed investigators and KOLs, high-quality data, and harmonized regulations, APAC presents itself as a holy grail for commercialization and clinical trials.

Standing at an exciting turn of the clinical development journey, APAC is an unavoidable venue, with Japan often proving to be the first place to launch innovative drugs. Japan's largest and first CRO is a compelling development partner with its unique, end-to-end service offerings including CDMO, CSO, regulatory consulting, and post-marketing surveillance.

CMIC has carried out clinical trials and approvals across Asia by providing targeted regional regulatory expertise and capabilities. Its deep roots in all major Asian countries and its US presence places CMIC in a strategic position to understand both local sensitivity and global consistency to help pharmaceutical partners progress on their drug discovery path. CMIC's rare disease and regenerative medicine focus further enhances its competitive positioning for specialty pharmaceuticals looking to venture into the region.

APAC is expected to continue its acceleration as a clinical trial powerhouse. Working with the right partner in the growing region will create an opportunity to thrive in the region and achieve faster commercialization.

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CONTACT INFORMATION:

Frost & Sullivan
100 Beach Road
#29-01/11, Shaw Tower
Singapore 189 702

Global
877.GoFrost
myfrost@frost.com

APAC
(65) 6890 0999
apacfrost@frost.com