FROST & SULLIVAN

Asia: Preferred Destination for Clinical Trials 2020

A Frost & Sullivan Whitepaper

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Introduction

Overview and Key Findings

Asia-Pacific is forecast to record the fastest growth in contract research organisation (CRO) services, at almost 15% annually, and will account for 20% of the global CRO market by 2022.

The estimated number of clinical trial sites set up by biotechnology companies in Asia-Pacific has increased by over 40% each year on average, compared to 11% in the rest of the world, with growth as high as 79% in China between 2016 and 2018.

For Oncology and Immuno-Oncology (IO) studies, trials involving sites in Asia result in a higher recruitment rate and reduced recruitment periods when compared to trials conducted in the United States.

The global biopharmaceutical sector continues its strong growth, largely fuelled by requirements for new innovative medical products, ageing populations, and growth in demand from developing economies.

In 2018, global spending on medicines approached $1.3 trillion[1] and is expected to grow at 5% per annum to reach $1.6 trillion by 2022. Global data, however, masks significant regional variations, with the fastest growth set to occur in "pharmerging" markets, particularly in Asia-Pacific. China is now the world's second-largest medicines market, with spending of $137 billion in 2018, up $40 billion from a decade earlier. Although growth in medicines spending in China has slowed in recent years, it is forecast to increase by about 6% per annum, well ahead of markets in North America and Europe.[2] Significant growth is also projected in markets such as India, Thailand, the Philippines, and Vietnam, indicating the increasing importance of Asian markets in the global biopharma sector.

However, biopharma companies are looking at operational efficiencies amid mounting pressure from payers on product prices. A key cost-cutting strategy is more outsourcing in areas such as manufacturing and clinical research using contract manufacturing organisations (CMOs) and CROs.

Globally, expenditure on CRO services, estimated at $49.7 billion in 2019, is forecast to reach $71.7 billion by 2024 at a CAGR of 8% between 2019 and 2024. Several biopharma companies are even adopting a fully "virtual" model of drug development, by outsourcing to CROs all services from early discovery to the commercial application of the drug. While many biopharma companies continue to engage CROs to provide support on discrete projects, the trend in recent years has been to establish long-term relationships with CROs through partnerships.

As at 2018, global R&D expenditure by the biopharma industry is estimated at $167 billion,[3] however, only 27% of this spending is currently devoted to CROs, suggesting significant opportunity for the growth of CRO services. Mirroring the increasing importance of Asia in the medicines market, the fastest growth in CRO services is projected to be in Asia-Pacific, which is forecast to see a rise of almost 15% annually, accounting for 20% of the global CRO market by 2022, from 15% in 2017.[4]

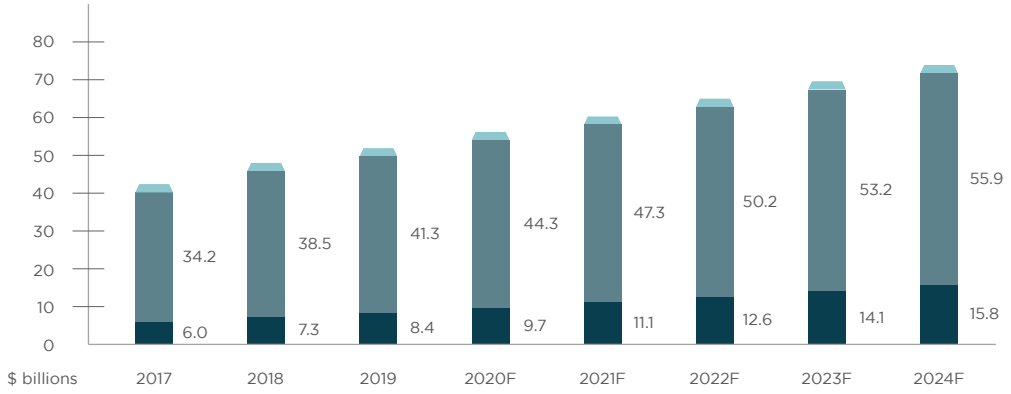
[1]All data is in US dollars ($), unless otherwise mentioned

[2]IQVIA Institute, The Global Use of Medicine in 2019 and Outlook to 2023

[3]Frost & Sullivan estimate

[4]Frost & Sullivan Global CRO Report, 2019; Frost & Sullivan APAC CRO Market Report, 2019

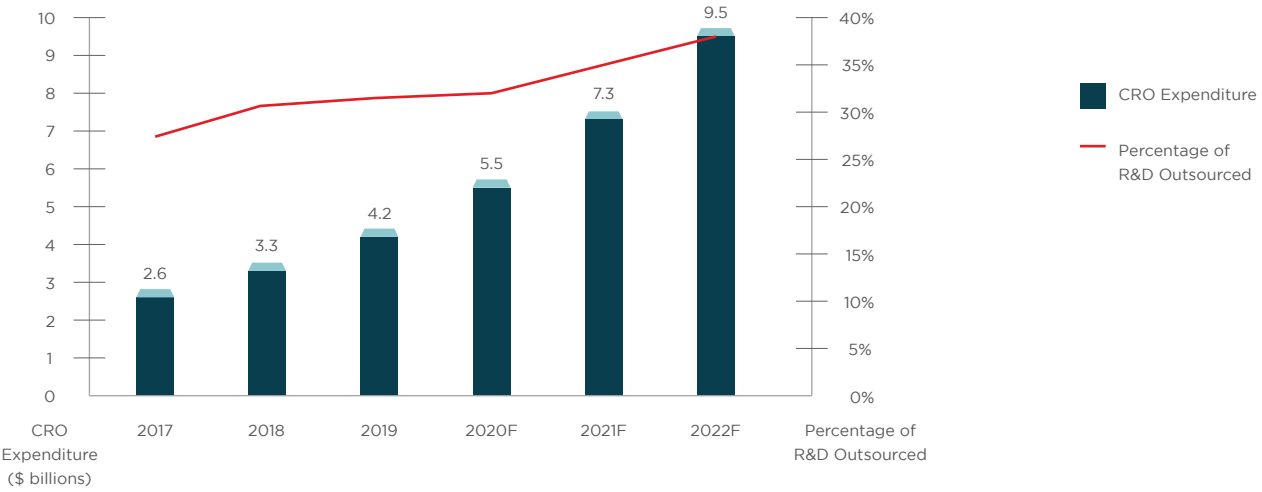
Figure 1: CRO Market, Asia-Pacific and ROW, 2017–2024F



Source: Frost & Sullivan Global CRO Report, 2019; Frost & Sullivan APAC CRO Market Report, 2019

In China alone, CRO expenditure is forecast to record a CAGR of almost 30% between 2015 and 2020, driven by investments in biotech bringing new therapies into research, combined with the financial benefits of outsourcing R&D activities.

Figure 2: CRO Expenditure and Percentage of R&D Outsourced, China, 2015 to 2022F

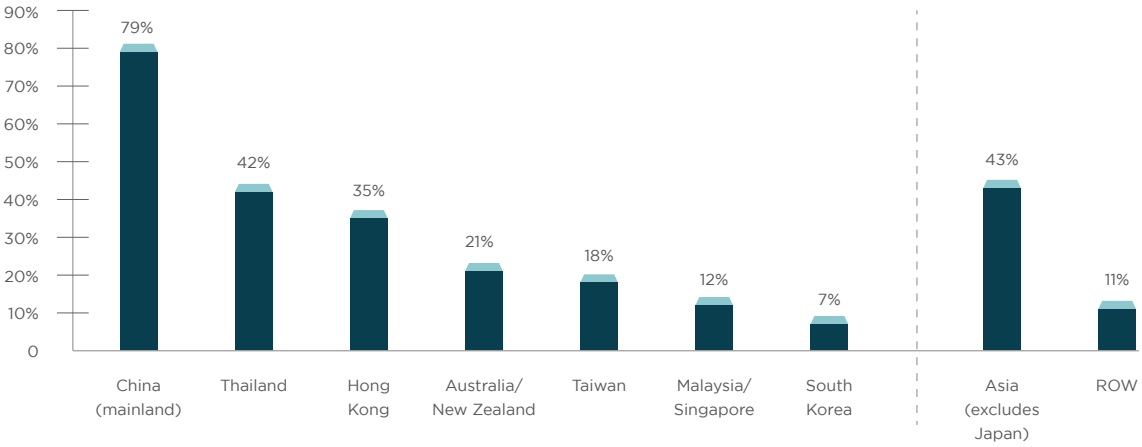


Source: Frost & Sullivan estimates

Asia, accounting for 59% of the global population, is an increasingly attractive location for clinical trials, given its large urban population of over 2.3 billion as at 2019, improving infrastructure, and greater focus by governments in supporting medical research. In addition, investments in new specialised clinical trial centres with state-of-the-art equipment and advanced technology continue to rise in Asia to cater to the growing demands of patients and R&D. Fast-growing Asian economies have leapfrogged the traditional path of enhancing legacy IT systems and are now at the forefront of innovation, with rapid adoption of data management and electronic medical record (EMR) systems.

Over the period 2016 to 2018, for example, the estimated number of clinical trial sites set up by biotech companies in Asia-Pacific exceeded 40% each year on average compared to 11% in the rest of the world, with the Chinese market having more than tripled during the period (+79% each year on average).

Figure 3: Annualised Growth in Clinical Trial Sites Set Up by Biotechnology Companies by Location, Global, 2016–2018



Source: GlobalData, Novotech

Despite the vast opportunities, Asia presents several challenges for clinical trial management. Varying cultural, language, and regulatory requirements in each country can make for a complex operating environment. Biopharma companies are engaging regional CROs with in-country offices and experience to manage these issues.

This report summarises some of the key trends and developments in Asia's CRO landscape and examines the main drivers behind the strong growth in demand for CRO services. Information for this report has been obtained from a review of published literature, as well as interviews with sponsors and investigators undertaking clinical trials in Asia.

Global Clinical Trials Environment

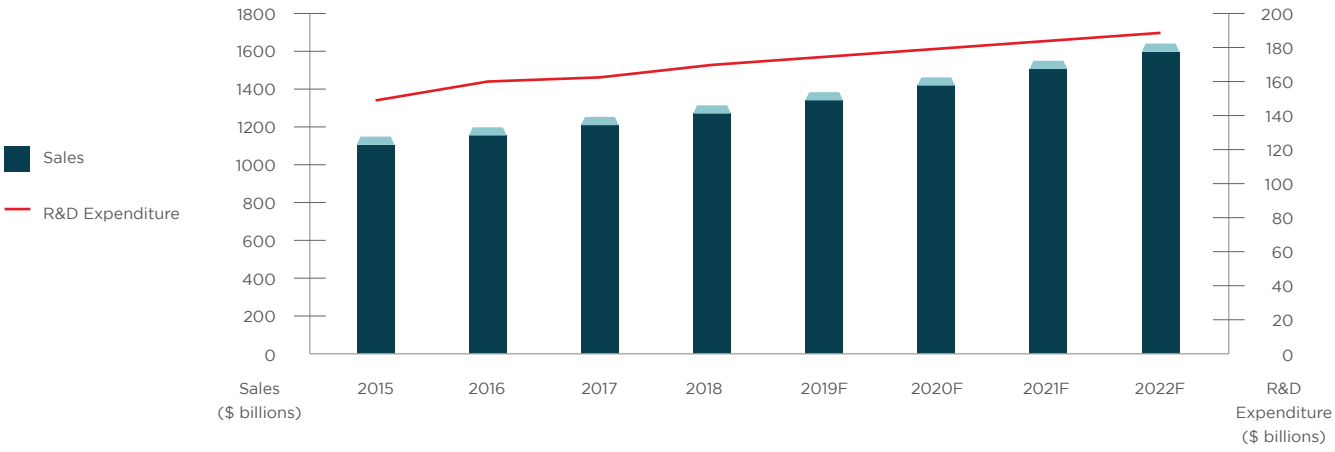
[6]*https://www.abpi.org.uk/facts-and-figures/science-and-innovation/worldwide-pharmaceutical-company-rd-expenditure/*

[7]*EvaluatePharma® World Preview 2017*

Globally, medicine sales are estimated to have reached $1.27 trillion in 2018, and are forecast to grow to $1.6 trillion by 2022 at a CAGR of 5.4% between 2015 and 2022. Although R&D intensity (R&D expenditure as a percentage of sales) is projected to decline slightly during this period, total biopharma R&D expenditure is expected to reach $181 billion by 2022.[6]

With R&D expenditure at 13% of sales in 2018, the biopharma industry has one of the highest levels of R&D intensity of any global industry. Among leading biopharma companies, R&D intensity can be even higher, averaging 20% of prescription medicine sales at the top 20 global biopharma companies in 2016, and forecast to exceed 17% by 2022.[7]

Figure 4: Medicine Sales and Biopharmaceutical R&D Expenditure, Global, 2015–2022F



Source: Frost & Sullivan estimates

[8]*International Agency for Research on Cancer, GLOBOCAN Project, 2008*

[9]*Pharma Intelligence, Annual Pharma R&D Review, 2018*

Factors contributing to the continued growth in medicine sales and associated R&D expenditure include population ageing, rising burden of chronic diseases, innovation and technological advances, healthcare reforms, emerging nation population growth, and greater focus on orphan drug development.

Ageing populations: The proportion of older persons is rising steadily, with the number of people aged 60 years and over projected to double from 11% of the world population in 2009 to 22% by 2050. Ageing populations are expected to have a profound impact on the demand for healthcare services, pharmaceutical products, and medical devices, as the prevalence of chronic diseases and disabilities increases.

Chronic diseases: Chronic diseases such as heart disease, stroke, cancer, chronic respiratory diseases, and diabetes are the leading causes of mortality in the world, representing 63% of all deaths. It is projected that chronic diseases will account for seven out of the top 10 causes of death in the world by 2030. The number of new cancer cases around the world is also expected to increase from 12.7 million in 2008 to 21 million by 2030.[8] Oncology drugs dominate the development pipeline, accounting for 34% of drugs in development in 2018, up from 27% in 2010.[9] As well as cancer, other chronic conditions that account for a significant part of the development pipeline include diabetes, arthritis, and Alzheimer's.

Innovation and technological advances: Technological advances in gene and cell therapies, as well as advanced diagnostics, are transforming the healthcare technology industry. Strong R&D focus and innovation around smarter, faster, and more targeted tools are anticipated to continue driving this sector.

Healthcare reforms: Advanced and emerging economies are undertaking healthcare reforms to improve access to quality healthcare and outcomes, the performance and efficiency of the health system, and control costs.

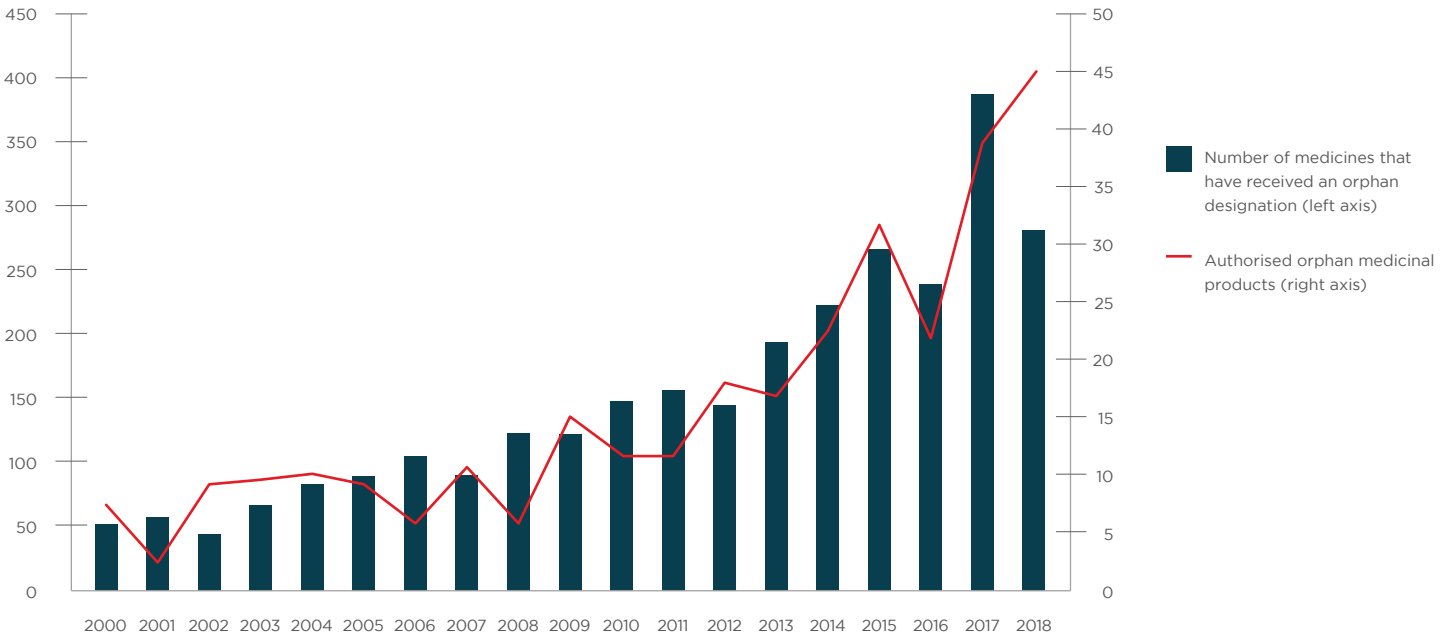
Orphan drug development: There are an estimated 7,000 rare diseases affecting between 6% and 8% of the worldwide population in total. About 350 million to 400 million people worldwide have a rare disease,[10] with 25 million to 30 million affected people in the US,[11] while over 45 million people may be suffering from a rare condition in Asia, with 20 million in China alone.[12] As biological patents worth $67 billion are due to expire by 2020, and many blolckbuster drugs lose patent protection, big pharma companies are gravitating towards specialty drugs and orphan drugs. In fact, most drugs approved by the US Federal Drug Administration (FDA) and European Medicines Agency (EMA) in 2018 were orphan medicines.

[10] *https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA_Rare_Diseases_Brochure_28Feb2017_FINAL.pdf*

[11] *https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases*

[12] *https://www.scmp.com/lifestyle/health-wellness/article/3003866/rare-diseases-china-and-people-raising-awareness*

Figure 5: FDA Orphan Designations and Approved Orphan Products, 2000–2018

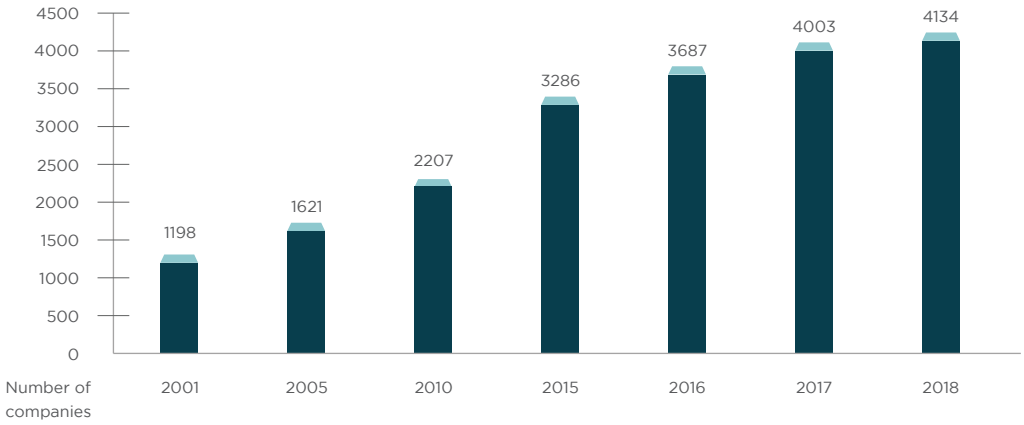


Source: FDA

The factors mentioned above are driving R&D activity, including among smaller biotech companies. Growth in biopharma R&D has been robust, with a 350% rise in companies undertaking research between 2001 and 2018 (from 1,198 to 4,134 companies). Smaller biotechs, those with one or two drugs in their pipelines, have seen significant growth in their share of R&D in recent years, from 15% to 20% of the total drug pipeline between 2011 and 2018.[13]

[13] *Pharma Intelligence, Annual Pharma R&D Review, 2018*

Figure 6: Number of Companies Involved in Pharma R&D, Global, 2001–2018

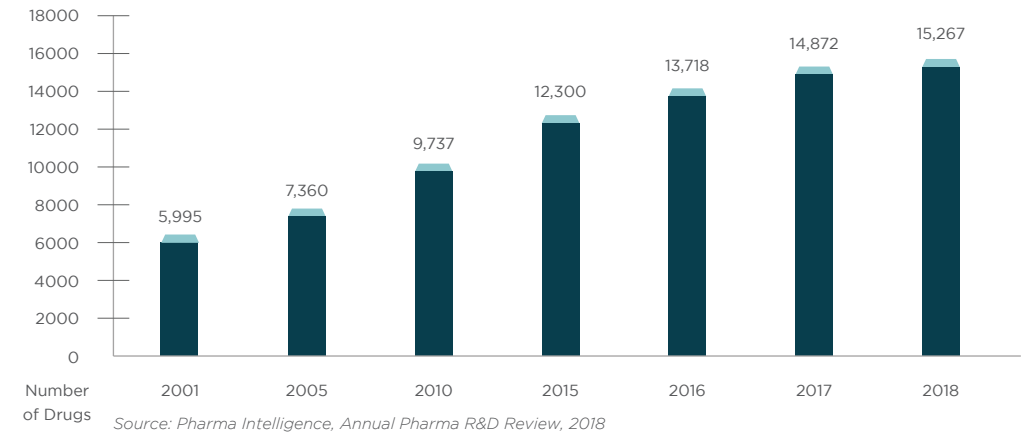


Source: Pharma Intelligence, Annual Pharma R&D Review, 2018

The increase in companies undertaking R&D is matched by an overall growth in the pipeline of drugs under development, from fewer than 6,000 drugs in 2001 to over 15,000 in 2018.[14]

[14] *Pharma Intelligence, Annual Pharma R&D Review, 2018*

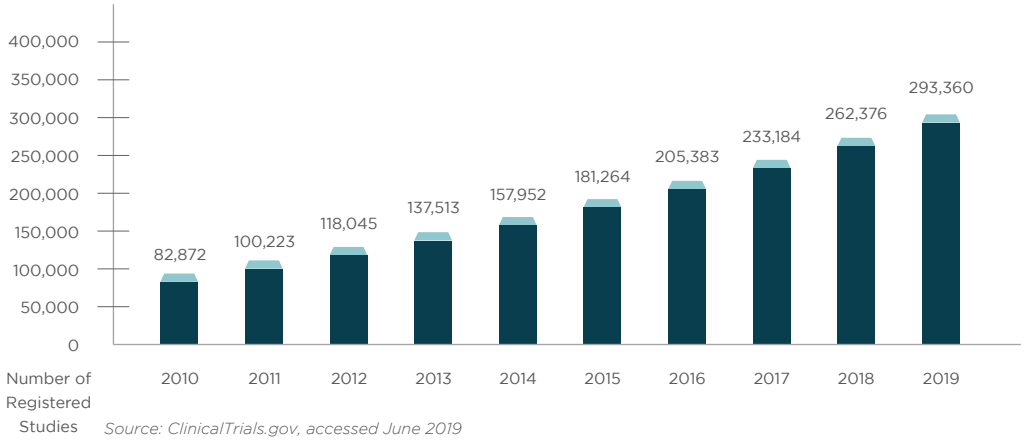
Figure 7: Number of Drugs in the Development Pipeline, Global, 2001–2018



Source: Pharma Intelligence, Annual Pharma R&D Review, 2018

The expansion of clinical pipelines is prompting strong growth in clinical trial activity, with a 350% increase in clinical trial registrations between 2010 and 2019.

Figure 8: Number of Registered Studies, Global, 2010–2019



Source: ClinicalTrials.gov, accessed June 2019

Clinical Trial Challenges in Europe and North America

Sponsors in Europe and North America increasingly encounter challenges around participant recruitment and retention, lengthy timeframes, and relatively high costs, adding to the appeal of Asia-Pacific. Together, these factors are resulting in delays in drug development, which can now cost up to $2 billion and take up to 12 years to launch.

Participant recruitment and retention: Failure to recruit participants is the main reason for trials missing timelines. Sanofi estimates that at least 70% of trials are affected by enrolment issues.[15] A key hurdle for recruitment is the relatively advanced healthcare systems in developed markets, which means that participants are less likely to join trials to access novel treatments. The sheer number of clinical trials on at any one time also gives rise to clinical trial competition, posing another major challenge to recruitment and enrolment of patients.

Many studies also have exclusions based on the participant not having received prior treatments, having an advanced stage of disease, or not being newly diagnosed.

A study of 114 trials in the United Kingdom indicated that only 31% met enrolment goals.[16] One study identified that 25% of cancer trials failed to enrol a sufficient number of patients, and 18% of trials closed with less than half of the target number of participants after three or more years.[17]

Long timeframes: Challenges meeting complex and changing regulatory requirements can impact timelines. For instance, in the US, sponsors must not only follow federal regulations, but also adhere to state and local policies in multi-site trials. The same challenges apply to EU member country policies.

Relatively high cost: Clinical trials account for up to one-third of drug development costs. Major cost drivers include staff and admin (20%), clinical procedures (20%), site monitoring (14%), and site retention (12%).[18]

Consequently, biopharma companies are looking for options that support participant enrolment and reduce trial timeframes and costs. Conducting clinical trials in Asia is an increasingly viable way to address these challenges.

[15]https://www.bloomberg.com/news/articles/2019-01-25/big-pharma-s-drug-studies-are-getting-a-nasa-style-makeover

[16]Bower P., Wallace P., Ward E., Graffy J., Miller J., Delany B., Kinmonth A.L. Improving recruitment to health research in primary care. Fam. Pract. 2009; 26:391–397

[17]Feller S. 2015. One in Four Cancer Trials Fails to Enroll Enough Participants (https://www.upi.com/Health_News/2015/12/30/One-in-four-cancer-trials-fails-to-enroll-enough-participants/2611451485504/)

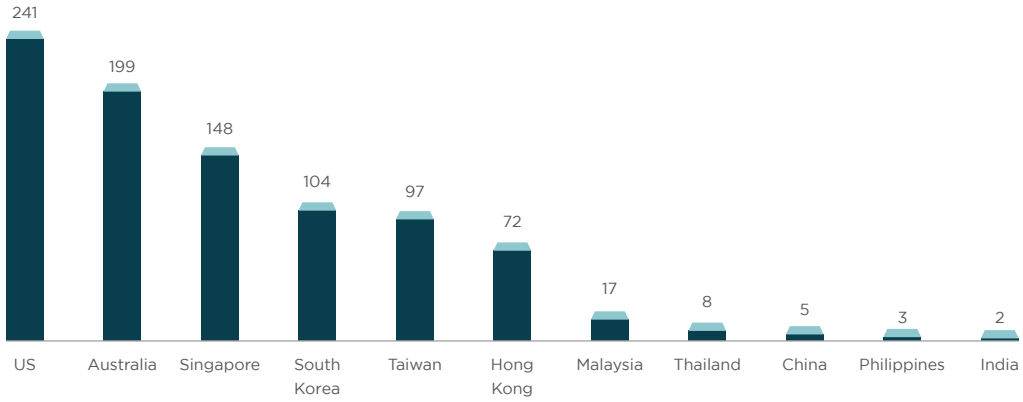
[18]https://www.clinicalresearch.io/sites/blog/clinical-trial-cost-breakdown

Advantages of Asia as a Clinical Trials Destination

Asia has become a key location for clinical trials, owing to its large patient population, scale of medical facilities, government support for clinical trials, the strategic importance of Asian economies as end-consumer markets, lower trial costs, and high-quality standards.

Large potential participant populations: Asia offers access to large numbers of treatment-naïve participants in urban populations who are willing to participate in trials. The clinical trial density is still significantly lower in Asia than in developed markets such as the US, offering significant opportunities for growth with relatively few patients so far exposed to trials.

Figure 9: Clinical Trials Density by Location, Selected Asia-Pacific Countries, 2020



Source: Clinicaltrials.gov (accessed January 13, 2020). Clinical trial density is measured as the number of recruiting sites for industry-initiated trials divided by the location population in millions.

Asia is home to 54% of the world's urban population, totalling over 2 billion people.[19] However, with per capita healthcare spending generally significantly lower in Asia than in developed markets, and medicine reimbursement by governments at much lower rates, Asian populations are more likely to be interested in gaining access to innovative new therapies through clinical trials.

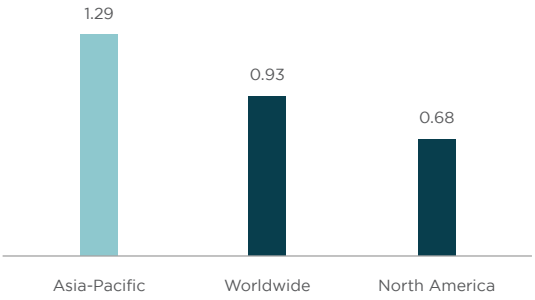
Some Asian hospitals offer massive scale for clinical trials, for example, the Chang Gung Memorial Hospital in Taiwan is the world's largest hospital, with 10,000 beds and serves 8.2 million outpatients a year, and the West China Medical Center of Sichuan University has 4,300 beds and attends to approximately 3.5 million people a year. The hospital employs 6,100 permanent staff, including over 550 associate professors and professors.[20]

Greater efficiency of clinical trials: Asia is often a more efficient region to conduct clinical trials, as evidenced by a comparison of recruitment rates and durations for clinical trials in Oncology initiated in 2018 and 2019. Overall, trials involving sites in Asia-Pacific resulted in a higher median recruitment rate and reduced recruitment periods when compared to trials in the US, as well as the worldwide median.

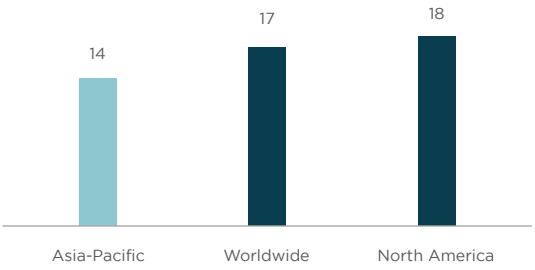
[19] *https://www.un.org/development/desa/publications/2018-revision-of-world-urbanization-prospects.html*

[20] *https://www.worldatlas.com/articles/the-largest-hospitals-in-the-world.html*

Figure 10: Comparison of Clinical Trial Recruitment Rates and Duration by Region, Global, 2018 and 2019



Median enrolment rate (p/s/m) per region for Oncology trials initiated in 2018 and 2019



Median enrolment period (months) per region for Oncology trials initiated in 2018 and 2019

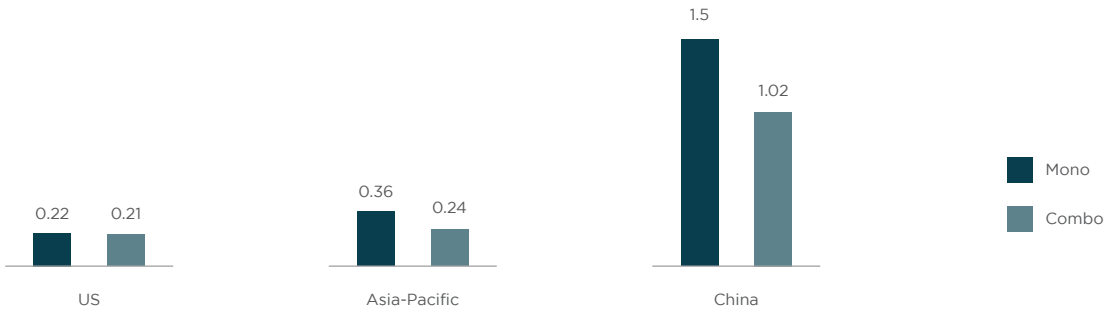
Source: GlobalData

Greater efficiency for complex trials in Immuno-oncology: Most Asian countries lack systematic reimbursement of Immuno-oncology standards of care, which suggests that clinical trials are often the only channel through which patients can access these treatments. This ultimately stimulates recruitment rates and encourages patient adherence to research therapies.

Over 600 sites across Asia-Pacific have been involved in the clinical development of now approved Immuno-oncology drugs, while hundreds more are experienced in managing clinical trials with immunotherapies for both monotherapy and combination therapies. Immuno-oncology drug clinical studies conducted in Asia-Pacific showed a recruitment rate of up to +60% and +15% faster than in the US for mono and combo therapies, respectively.[21]

[21] *https://www.nature.com/articles/d41573-019-00182-w*

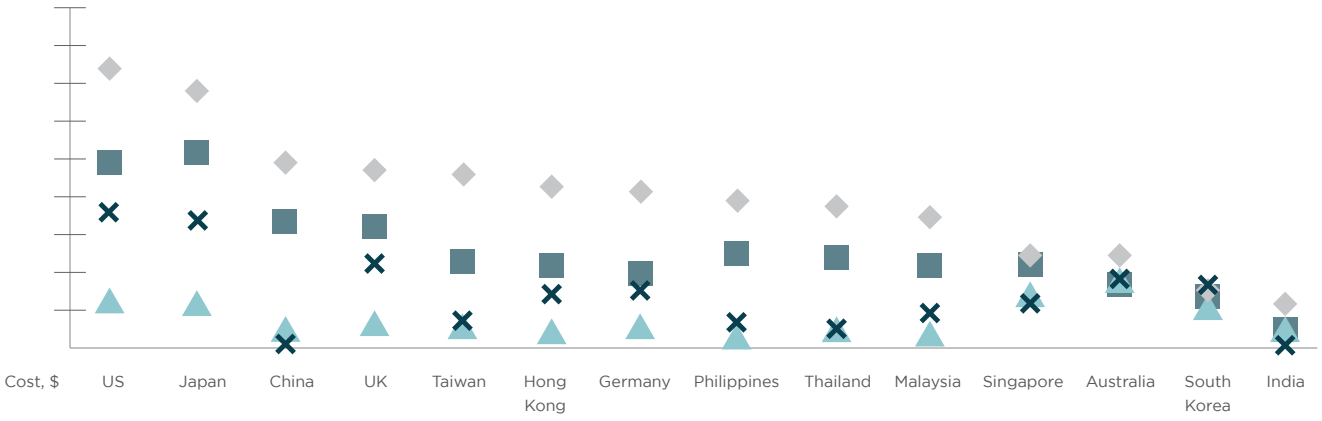
Figure 11: Median Recruitment Rates of Immuno-oncology Clinical Trials, by Region (p/s/m), 2006 Onwards



Source:Nature.com (accessed from https://www.nature.com/articles/d41573-019-00182-w)

Cost efficiencies: Low operational costs position Asia as a highly attractive destination for clinical trials when compared with the US and Western Europe. Data provided by Medidata Grants Manager indicates that doctor visits, medical treatments, and procedures tend to cost less in Asian countries. In addition, rapid start-up and recruitment phases reduce the risk and costs of needing to open new sites or extending studies to meet timelines.

Figure 12: Cost Comparisons of Visits and Tests, Selected Countries, Global, 2016



Cost, $	US	Japan	China	UK	Taiwan	Hong Kong	Germany	Philippines	Thailand	Malaysia	Singapore	Australia	South Korea	India
Initial Visit	$225	$208	$149	$145	$140	$130	$125	$120	$115	$106	$75	$74	$47	$37
Follow-up Visit	$150	$156	$103	$99	$99	$66	$59	$77	$73	$66	$67	$51	$43	$16
Blood Draw	$37	$36	$15	$22	$22	$17	$18	$9	$14	$10	$44	$54	$33	$18
ECG	$110	$104	$4	$69	$69	$21	$47	$21	$14	$29	$34	$54	$50	$5

Source: Medidata Grants Manager, costs comparisons 2016

Diverse ethnicities: With populations of Asian ethnicity (mainly Chinese and Indian) growing significantly in Western countries, clinical trials in Asia are increasingly attractive because regulatory agencies require researchers to recruit subject samples reflective of their communities at large.

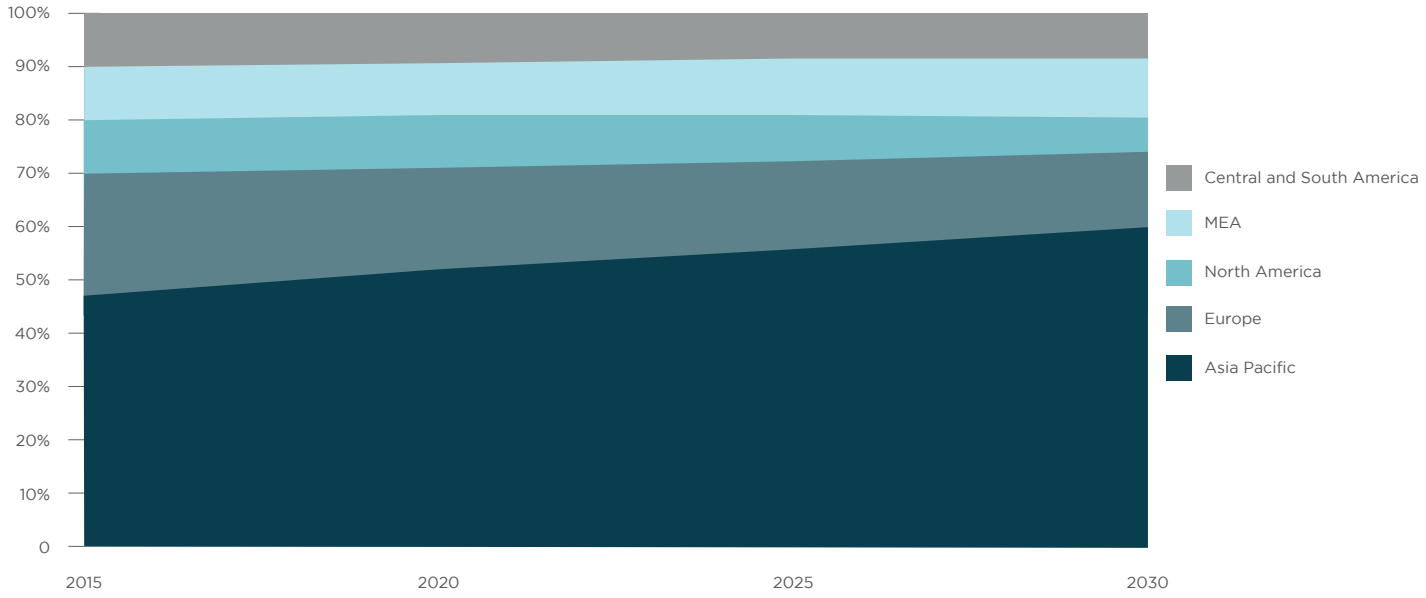
Clinical Operations Director, Biopharmaceutical Company

"We highly recommend going to Asia, as we got reliable results, enthusiastic physicians and patients, and experienced KOLs. For us, a good strategy for US and European companies is clearly to consider Asia for large Phase II and III trials, as it is a very good location to conduct clinical trials."

Growing significance of Asia as a medicines market: As wealth in Asia increases, it is becoming important as a medicines market. While Asia accounted for about 45% of global middle-class consumption in 2015, by 2030 it is forecast to reach 60%, with the vast majority – almost 90% – of the next billion entrants into the global middle-class coming from Asia: 380 million Indians, 350 million Chinese, and 210 million other Asians.[22]

[22] *OECD Development Centre, Homi Kharas, The Emerging Middle Class in Developing Countries, 2017*

Figure 13: Middle-Class Consumption Share by Region, Global, 2015–2030F



Source: OECD Development Centre, Homi Kharas, The Emerging Middle Class in Developing Countries 2017

Key opinion leaders' expertise: Asia has knowledgeable key opinion leaders (KOLs) and experts across many therapeutic areas. Many KOLs are global experts in their fields, and their inclusion in trials is extremely beneficial. Many Asian KOLs have been part of the World Health Organization's Technical Advisory Board, and have published papers in reputable medical journals. The number of citable medical journal articles from Asia-Pacific grew by +10% between 2015 and 2018, while numbers from the rest of the world remained relatively flat over the same period (+1%). Locations such as China, Thailand or Malaysia/Singapore demonstrated growth in citable medical documents of +15%, +23%, and +13%, respectively during that period. In 2018, 28% of worldwide medical citable documents came from Asia-Pacific compared with 19% in 2005.[23]

Disease patterns similar to the West: Asian countries show similar or higher incidence rates of major diseases to Western nations, providing a comparable environment to conduct clinical trials. While most disease patterns in Asia increasingly mirror those of Western countries, certain conditions show notable spikes in prevalence.

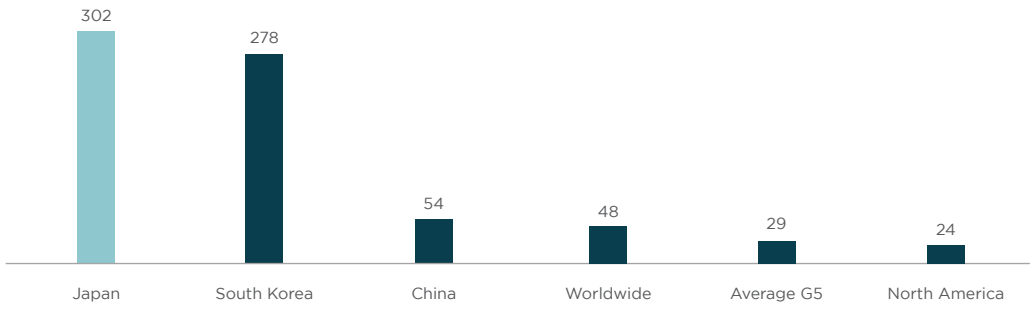
Hepatitis-induced liver diseases, infectious diseases and a range of cancers (such as gastric cancer or hepatocellular carcinoma, NSCLC), are known to be highly prevalent in Asia. For example, the Asia-Pacific region contributes to three-quarters of chronic Hepatitis B virus (HBV) patients worldwide. Specifically, the Western Pacific region comprising countries including China, Japan, South Korea, the Philippines, and Vietnam, accounts for 50% of the world's chronic HBV population.[24]

[23] *Country Rankings Analysis https://www.scimagojr.com/ Accessed January 14, 2020*

[24] *S. K. Sarin, M. Kumar, G. K. Lau; Asia-Pacific Clinical Practice Guidelines on the Management of Hepatitis B: A 2015 Update; Hepatol Int; 2016 Jan; 10(1) - 1-19*

The high incidence and prevalence of certain diseases in Asian countries make the region extremely attractive for conducting clinical trials, given the shortage of patients in the US and Europe for these diseases.

Figure 14: Prevalence of Gastric Cancer Malignancies (per 100,000) by Country, Global, 2018



Source: IPD

Regulatory efficiencies: In Asia, approvals, including Institutional Review Board (IRB), regulatory requirements, import licensing, and contract negotiations can often be undertaken simultaneously. Asian countries have varying requirements for local language translation, import or export licensing, and data on local patients. However, critical changes have occurred in recent years to facilitate clinical trials in the region. The most notable changes have occurred in China, where regulatory timelines have decreased by 16 months since 2016.

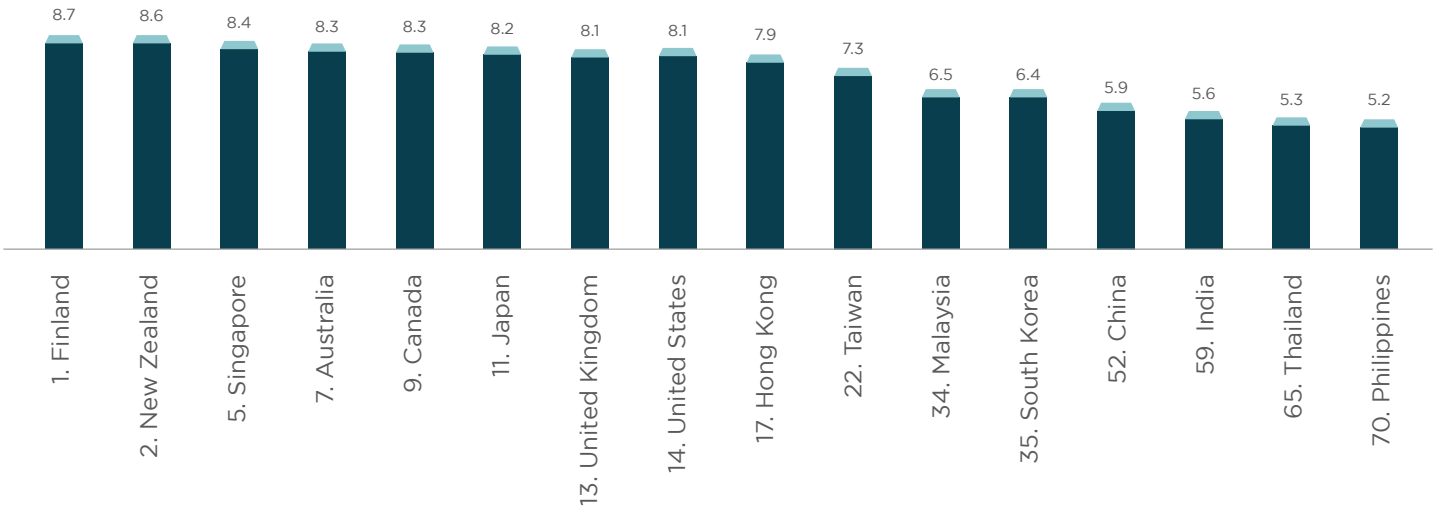
Figure 15: Regulatory Timelines for Clinical Trials by Location, Asia-Pacific, 2020

Source: Novotech

Asia-Pacific countries are also becoming more diligent in developing regulatory regimes that protect intellectual property (IP) rights, a factor previously regarded as a challenge in many Asian markets. The 2018 International Property Rights Index report (a barometer of the state of property rights in all locations of the world) indicated that several Asia-Pacific locations (New Zealand, Australia, Singapore, Hong Kong, and Japan) are in the top 20% of locations globally, while several others (South Korea, Taiwan, and Malaysia) are in the second quintile. China and India have moved to the third quintile, ahead of a number of European countries.[25]

[25] *Property Rights Alliance, 2018 International Property Rights Index*

Figure 16: Property Rights Index by Country, Global, 2018



Source: Property Rights Alliance, 2018 International Property Rights Index

Governments in Asia-Pacific continue to implement measures to improve the regulatory environment for clinical trials in their countries. This has resulted in major advances in markets such as Greater China, South Korea, and Singapore.

In Taiwan, for example, the Taiwan Food & Drug Administration (TFDA) introduced specific enhancement measures for clinical trials protocol review in 2017, including establishing cell therapy/gene therapy clinical trials fast-track review mechanisms, streamlining first in human trials review process, and refining the review process of clinical trial protocol amendments based on the degree of changes.[26]

[26] *https://www.fda.gov.tw/EN/newsContent.aspx?id=22495*

Dr Josh Lin, Director of Phase I Center, Department of Oncology, National Taiwan University Hospital

"Taiwan is a good place to run clinical trials in oncology because we have a large population concentrated in a few cities, which simplifies the patient recruitment process."

Hong Kong offers a fast approval timeframe of between three and six months, and has established the Clinical Research Ethics Committee of the Hong Kong Doctors Union. The Committee is empowered to issue IRB approval for research conducted in private practice. Once IRB approval is obtained, principal investigators can apply for a clinical trials certificate from the Department of Health.[27]

[27] *http://blog.credevo.com/2018/11/15/hong-kong-how-to-utilize-clinical-trial-regulatory-process-effectively/*

Singapore has introduced an Exemption and Expedited review process for studies that involve minimal or less than minimal risks and will be reviewed by the SingHealth Centralised Institutional Review Board (CIRB) within 30 days.[28]

In South Korea, the new Comprehensive Five-year Plan will involve a significant increase in expert staff to support rapid approval processes.

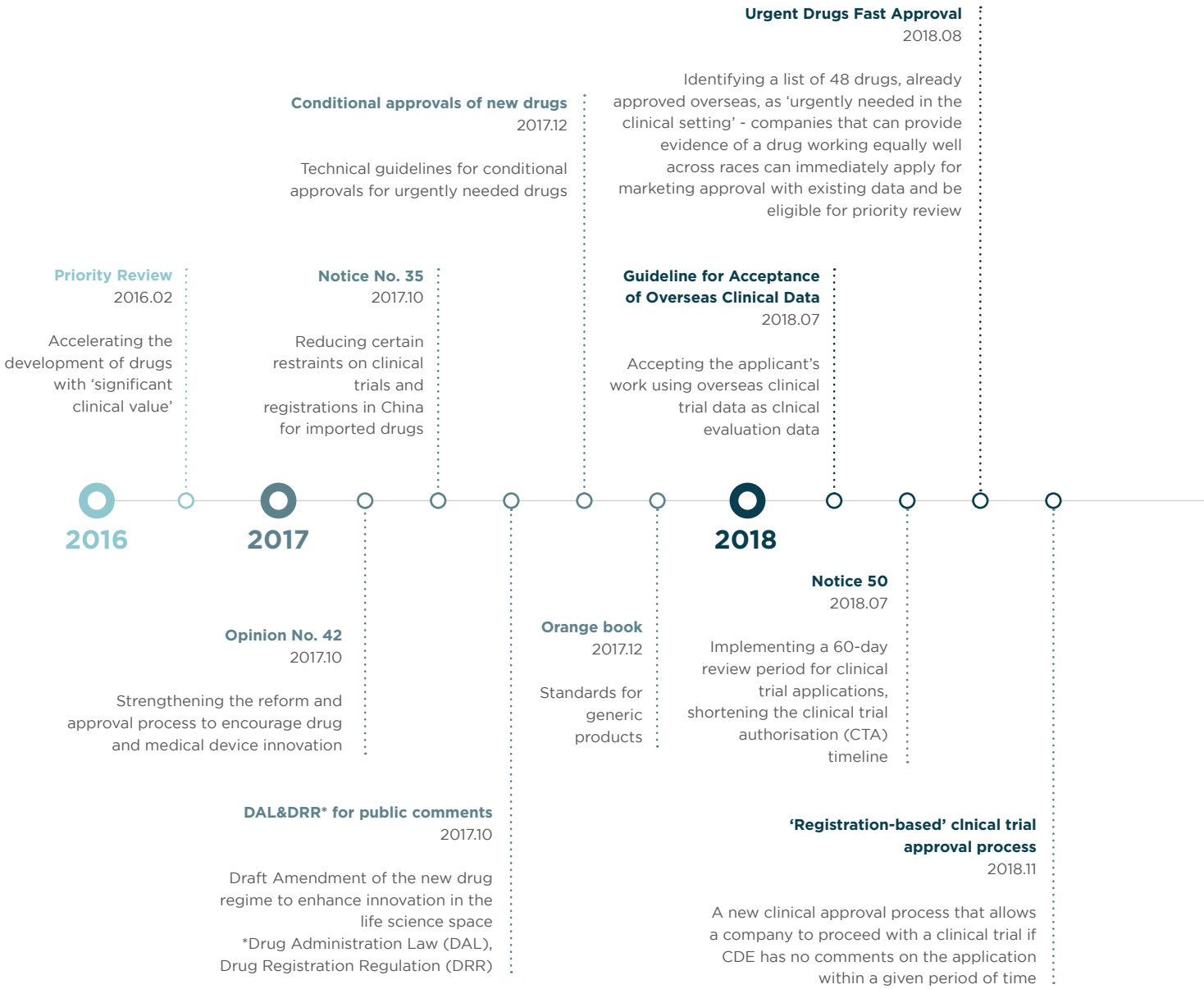
[28] *https://research.singhealth.com.sg/Pages/CentralisedInstitutionalReviewBoard.aspx*

"Asia-Pacific is an attractive region to conduct clinical research. The regulatory activation timelines are similar to other parts of the world, while aspects of study execution and standard of care are consistent. Attention to detail in data entry is apparent along with faster response times for query resolution than other regions. Patient costs also tend to be lower than in the US and EU. Additionally, Asia offers favourable recruitment rates."

Associate Director, Clinical Trial Management at a US Biotechnology Company

In China, the Chinese National Medical Products Administration (NMPA, previously the Chinese FDA) proposes fast-track reviews for breakthrough technologies and clinical priority areas. The NMPA has issued a series of regulatory reforms to address concerns around the promotion of R&D activity in China, especially from foreign companies. The main goals of the new reforms are focused on improving the drug review process, shortening the Investigational New Drug (IND) and New Drug Application (NDA) review timelines, and encouraging new drug innovation.

Figure 17: Recent NMPA Regulatory Reforms to Support Innovative Drugs Development, China, 2016–2018



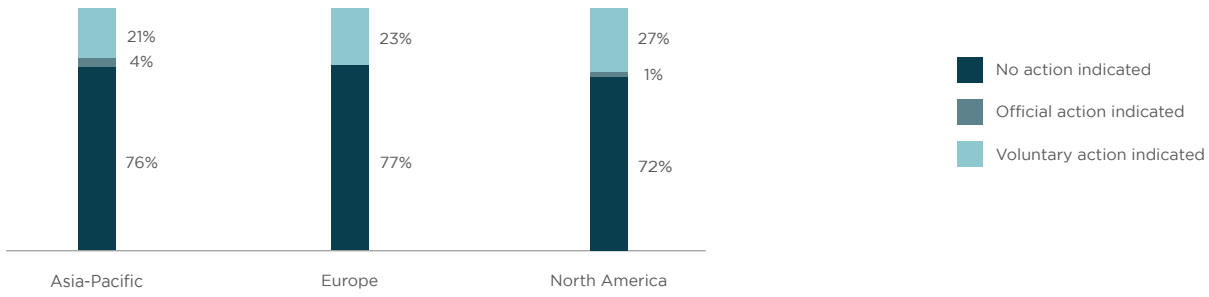
Source: Deloitte (accessed from https://www2.deloitte.com/insights/us/en/industry/life-sciences/innovative-biopharma-china-regulatory-change.html)

[29] *https://www.sciencedirect.com/science/article/pii/S2451865418301315*

Experienced investigators: The global pool of investigators is shifting from the US to other countries, with non-US investigators now approaching parity in numbers with their US counterparts.[29] Asia-Pacific has a growing number of experienced investigators. As at 2019, there are over 43,000 active principal investigators (PIs) across Asia-Pacific markets, which is comparable to North America.

Equivalent quality standards: Asian countries are rapidly becoming more competitive by building appropriate site experience, technological expertise, infrastructure, and scale to manage large clinical trials. Asia-Pacific clinical trials demonstrate compliance levels equivalent to Europe and North America, as indicated by analysis of the outcomes of US FDA inspections by region.

Figure 18: US FDA Inspections by Outcome and Region, Global, 2016–2018



Source: FDA, accessed from https://www.accessdata.fda.gov/scripts/inspsearch/index.cfm

A summary of the key characteristics of individual markets in Asia-Pacific as clinical trials locations is given below.

Figure 19: Characteristics of Key Clinical Trial Markets, Asia-Pacific, 2020

China
- Very large, homogeneous population
- Strong focus of NMPA (previously CFDA) on shortening regulatory timelines
- Largest clinicial trial hub in Asia, with over 17,000 active investigators

India
- Large treatment-naive population
- High disease population load
- The clinical activity grew by over 40% in 2018 on the back of regulatory pathway improvements
- About 1,800 investigators have participated in a minimum of 5 studies

Thailand
- Large homogeneous population
- High prevalence of communicable diseases
- Efficient regulatory system
- Low operational cost

Malaysia
- Multiethnic Asian population
- Streamlined regulatory system and strong government support
- Quick start-up timelines
- Low patient costs and IRB fees

Singapore
- Multiethnic Asian population
- Regional clinical research hub
- Efficient regulatory process and good infrastructure

South Korea
- Homogeneous and concentrated population
- High quality medical services and excellent infrastruture
- The most active Asian country in clinical research after China, with over 400 sites opened by biopharmas companies in 2018

Taiwan
- Multiethnic Chinese population
- The 3rd largest pool of clinical activity in Asia after mainland China and South Korea

Philippines
- Large treatment-naive population
- Low costs
- Overall good level of English

Hong Kong
- Officially recognised by the NMPA for conducting clinical trials for mainland China
- Global KOLs in various specialities

Australia/New Zealand
- High quality research, facilities and equipment
- Fast set-up and approval times
- Sponsor can claim R&D case refund

Source Novotech

Case Studies

Phase 1 for the study of an orphan metabolic disease

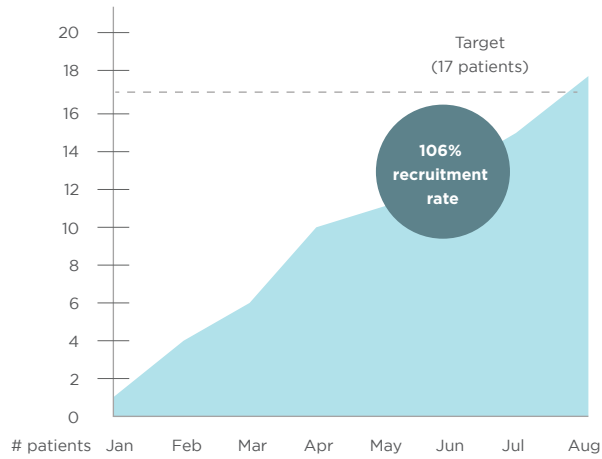
Western sponsor looking to accelerate their clinical development in an orphan indication.

Multiple sites in China, Malaysia, and Thailand

Project timelines:
14 months from study start to last patient enrolled

6 months	Start-up	Study Start	*May*
		Initial HA Submission Actual	*Jul*
		Initial EC/IRB Appr Actual	*Sep*
8 months	Recruitment	Initial HA Approval Actual	*Nov*
		Firsr SIV Actual	*Dec*
		First Subject Enrolled Actual	*Jan*
		Last Subject Enrolled Actual	*Aug*

Cumulative patient recruitment over time



Managing complex global trials

Phase III study for the treatment of breast cancer

43 sites located in Taiwan, Australia, Hong Kong, Singapore, and South Korea

Publicly-listed US biotechnology company with over 150 employees

Contracted Novotech due to poor performance of previous global CRO

Involving an APAC specialist led to successful recruitment of high performing sites in the region

Ability to undertake rescue studies

- Novotech was engaged to manage Asia-Pacific following performance issues of global CROs
- Difficult to recruit patients, complex protocol design and inclusion/exclusion criteria
- Multiple vendor - Global CROs responsible for managing study in Europe and US
- Large number of sites selected by previous CRO
- Any delays due to changeover of CRO were deemed unacceptable by sponsor

Recruitment performance

- 43 sites were involved across Taiwan, Australia, Hong Kong, Singapore and South Korea
- About one-third of global recruitment from APAC countries
- Taiwan had the highest performing sites across study
- 104% recruitment rate across APAC sites

104% recruitment rate

Target: 169 patients

Actual: 176 patients

Need for Specialised Support in Asian Clinical Trials

While Asia has become a key location for clinical research, the region also presents challenges that drive the need for specialised CRO support in clinical trials.

Regulatory complexities: Regulatory regimes are heterogeneous across the region, and significant change is underway in the regulatory frameworks that govern clinical trials in each country. The IRB approval, regulatory, import licensing, and contract negotiation processes can be undertaken simultaneously in some countries, while in others, they are sequential. There are also varying requirements for local language translation, import or export licensing, and data on local patients. Material Transfer Agreements (MTAs) may also be required for the export of biological samples.

Language and cultural differences: North America, Australia, New Zealand, and Western Europe have a high level of English fluency; however, this is not the case in Asia, which has a broader variety of languages spoken. This necessitates translation of material into the local languages, increasing the complexity of conducting a trial. Social status and the importance of "face" are also crucial cultural issues in Asian societies.

For example, it is usual for senior staff members to communicate non-compliance to principal investigators, and junior employees to submit improvement ideas via process-based templates to avoid uncomfortable hierarchical conflicts between junior and senior staff. There can also be issues in the collection of informed consent from participants, with one study in India indicating that community leaders can play a role in influencing the decision of local residents to give consent for clinical trials.[30]

The characteristics mentioned above signal the need to partner with a CRO that fully understands the clinical trials environment in Asia, allowing the sponsor to benefit from the advantages the region offers as a clinical trials location. Key factors that should be considered in choosing an appropriate CRO partner are listed below.

[30]Ali et al, Challenges of conducting clinical trials in Asia, Int J Clin Trials. 2018 Nov; 5(4): 194-199

Table 1: Factors to Consider in Choosing a Clinical Trials CRO Partner in Asia

Factor	Discussion
 **Capabilities**	How capable is the partner's operations team? What is their experience in running clinical trials in the relevant clinical area? Do they have appropriate language skills and cultural awareness?
	Does the partner have staff on the ground that can maintain the day-to-day site, KOL, PI, and regulatory relationships?
	Does the partner fully understand the regulatory requirements and have a robust plan to address all regulatory hurdles?
	Does the partner have expertise in FDA and EMA submissions?
	Does the partner use appropriate technology, such as clinical trial management systems, electronic data capturing systems, trial master files, and market intelligence systems?
	Does the partner offer a fully-integrated, end-to-end solution for delivering the trial?
 **Network & Partnerships**	Is the partner able to manage trials in multiple countries simultaneously with local teams in each country?
	Does the partner have demonstarted relationships with local KOLs in the relevant therapeutic area?
	Does the partner have a successful track record in participant recruitment?
	Is the partner able to work successfully with other parties where appropriate and required?

Source: Frost & Sullivan

Overall, Asia offers an increasingly attractive and important location for clinical trials. However, cultural, infrastructural, and regulatory issues drive a need for sponsors to collaborate with a CRO partner that can bring the right capabilities and network to the relationship.

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