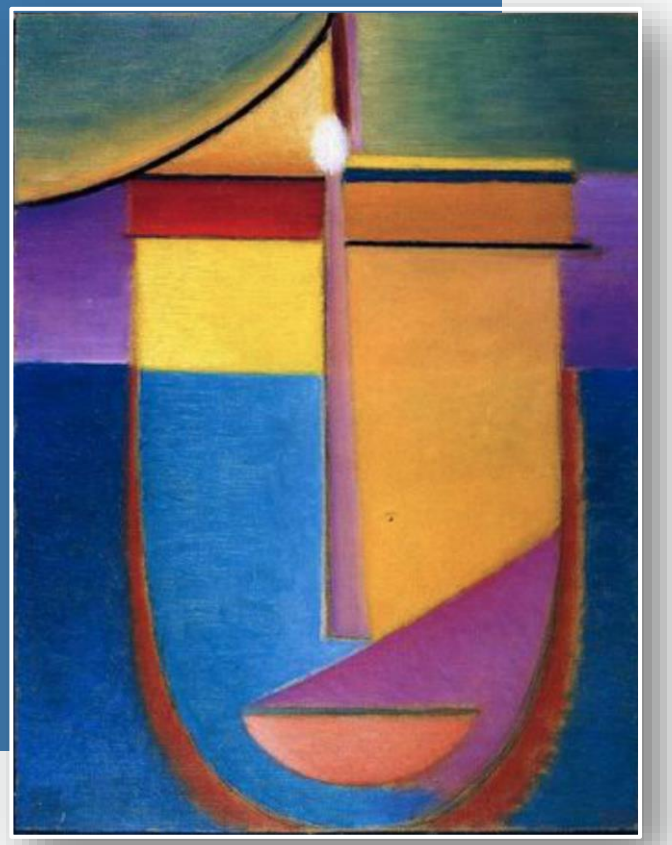

Enhancing the development of the ASEAN markets & accelerating global market expansion for Chinese biopharma companies

December, 2020

研究出版

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Definition of Biomedicines

Biomedicine

The definition of biomedicine is not uniformly defined in the world, and it is explained differently according to different context.
In this report, we follow the definition of biomedicine in the "***China Biomedicine Market Research Report***" **by Frost & Sullivan Consulting**:
"Biomedicine refers to a class of products for prevention, treatment and diagnosis manufactured by comprehensively utilizing scientific principles and methods of microbiology, chemistry, biochemistry, biotechnology, pharmacy, etc.. Common types are monoclonal antibodies, recombinant proteins, vaccines and genes and cell therapy drugs, etc."

Biosimilar Product

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing reference agency-approved **new/innovative product** (reference product).

Country	Name of Regulatory Authority
USA	Food and Drug Administration (FDA)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
Singapore	Health Sciences Authority (HAS)
Canada	Health Canada
Europe	European Medicines Agency (EMEA)
Denmark	Danish Medicines Agency
Switzerland	Swissmedic, Swiss Agency for Therapeutic Products

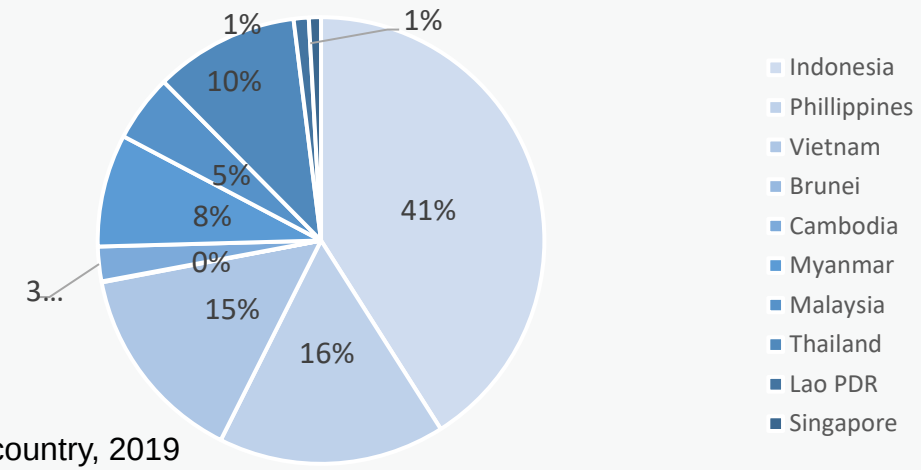
Content

- **Regional Market Landscape**
- **Regulatory and Supportive Environment for Biopharma Companies' Market Expansion in ASEAN Region**
- **Go-to-market Strategy for Chinese biopharma companies and the way forward**

Source: ASK Health Analysis

ASEAN Region: A Diverse Region with Rapid Economic Growth and A Rising Middle Class

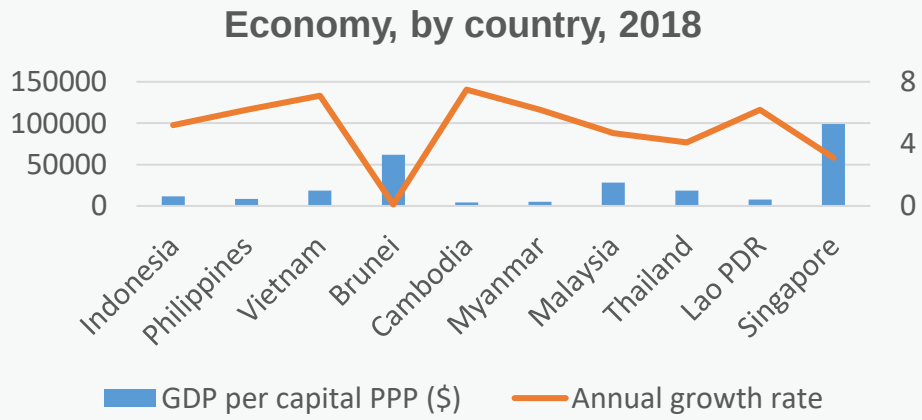
ASEAN is a diverse region with variation across countries in terms of population. **Indonesia** accounts the most of ASEAN population (**41%, 273.5 million),** followed by **Philippines (16%)** and **Vietnam (15%).**



Population, by country, 2019

Rapid economic growth : In the past 20 years, annual Gross Domestic Product (GDP) growth was **5%** on average (Brunei exempted). **Brunei** and **Singapore** are both high-income countries.

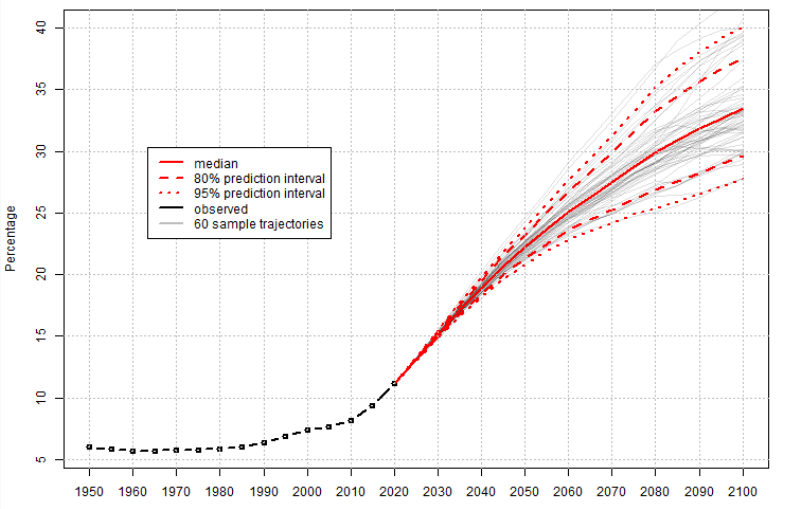
A rising middle class exists: 50 million new consumers will join the ranks of the middle class in **Indonesia**, **Malaysia**, **Thailand** and **Vietnam** by 2022, contributing to the region's $300 billion middle-class disposable income.



Sources: World Bank; WHO, Population Division. World population Prospect, 2019.

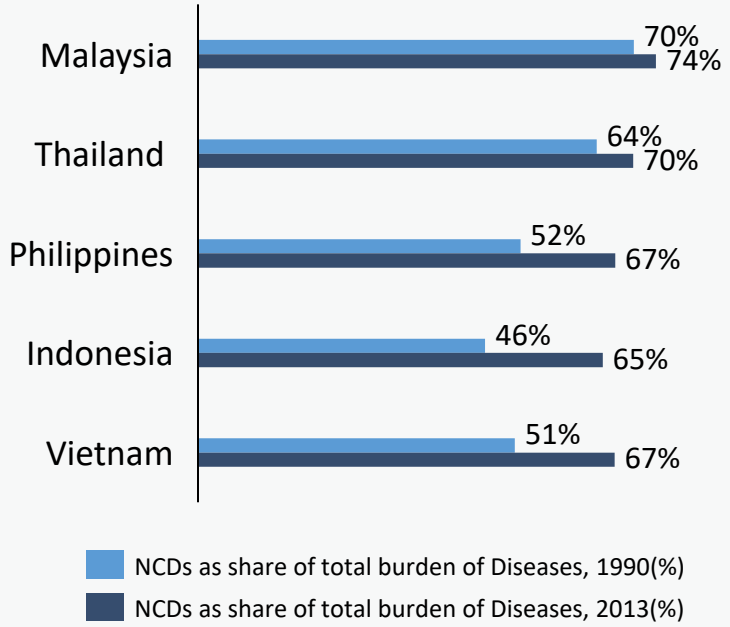
An Aging Population Combined with Epidemiological Shift to NCDs have Contributed to Increase in Health Expenditures

Aging Trend



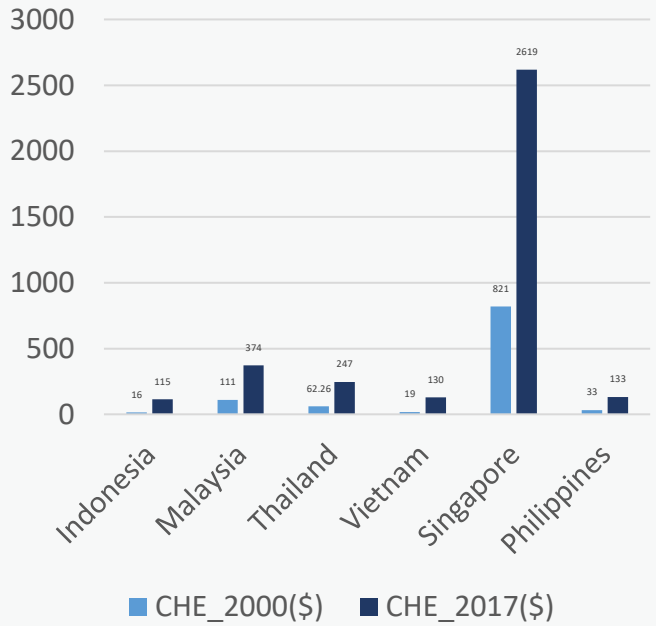
Over 20% of ASEAN population would be 60+ by 2050, compared with just over 10% in 2020

Epidemiological Shift to non-communicable Diseases (NCDs)



Rising burden of non-communicable diseases in ASEAN, 1990 vs 2013

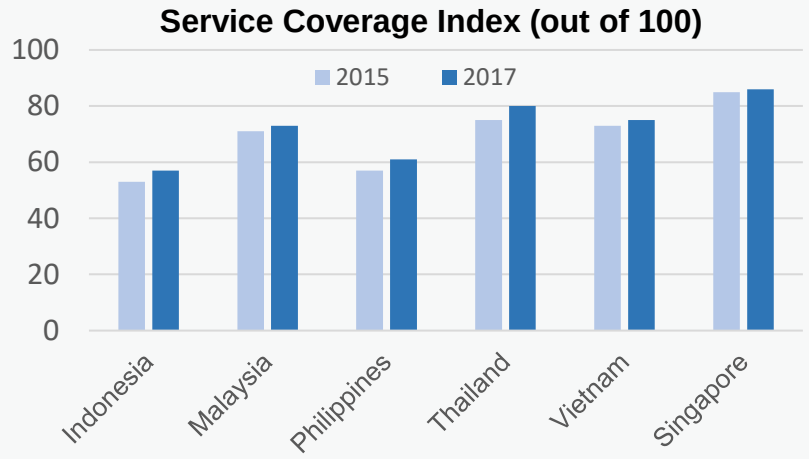
Healthcare Expenditures



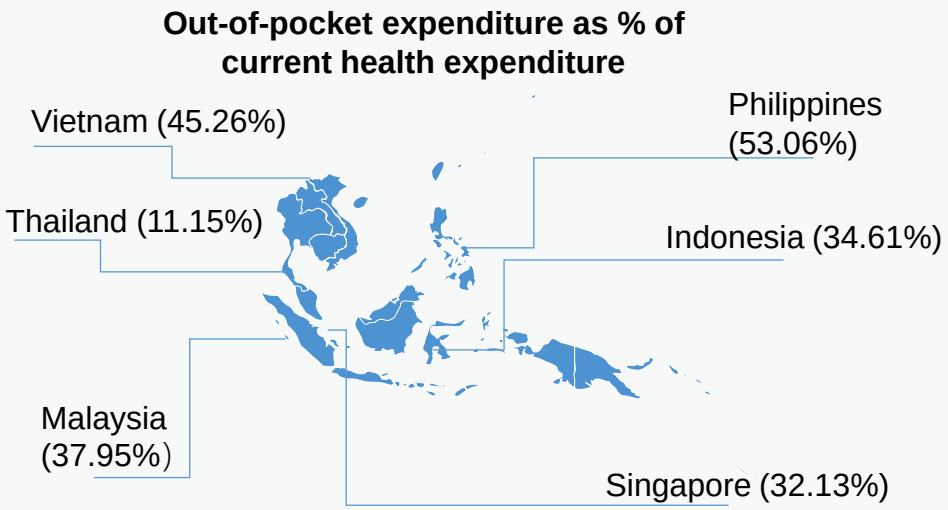
Current public health expenditure (CHE) per capita US$ 2000 vs 2017

Source: 2019 United Nations, DESA, Population Division. World Population Prospects 2019; Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia; World Health Organization

The Universal Health Coverage (UHC) in ASEAN Countries is Improving, with Different Levels of Out-of-Pocket Expenditure



The UHC Service Coverage Index (SCI) measures progress on the UN Sustainable Development Index target 3.8.1, Coverage of Essential Health Services, defined as the average coverage of essential services based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, non-communicable diseases and service capacity and access, among the general and the most disadvantaged population

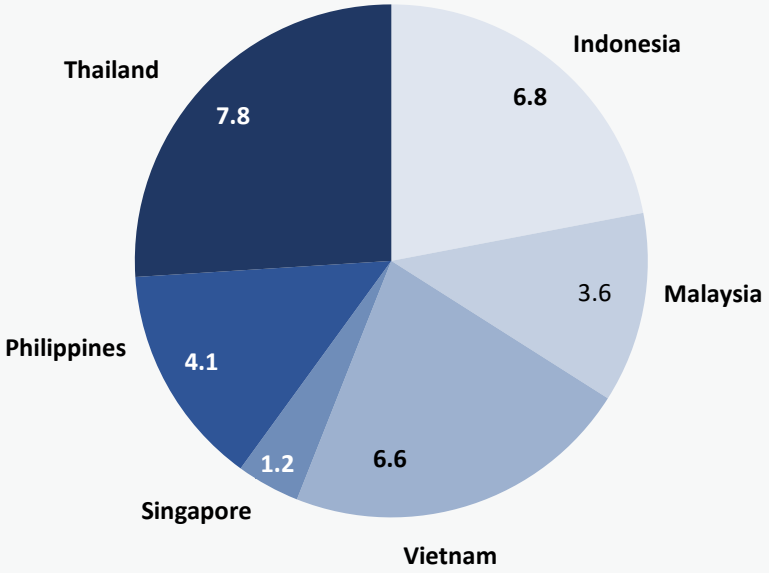


Vietnam	Resolution of the Central Committee of the Communist Party of Vietnam has commitment to move towards UHC. Social health insurance coverage is targeted at 95% by 2025
Thailand	UHC since 2002
Malaysia	UHC using public providers and general government budget since 1980s
Philippines	Expansion of the national health insurance, both in terms of population coverage by the national and local governments and benefits packages by the PhilHealth Insurance Corporation
Indonesia	UHC started since 2014
Singapore	UHC through national Programmes of MediSave, MediShield and MediFund since 1980s.

Sources: Global Health Observatory data repository, WHO; Progressive Realization Towards Universal Health Coverage: ASEAN Member States, a collective contribution under the work of ASEAN Health Cluster 3

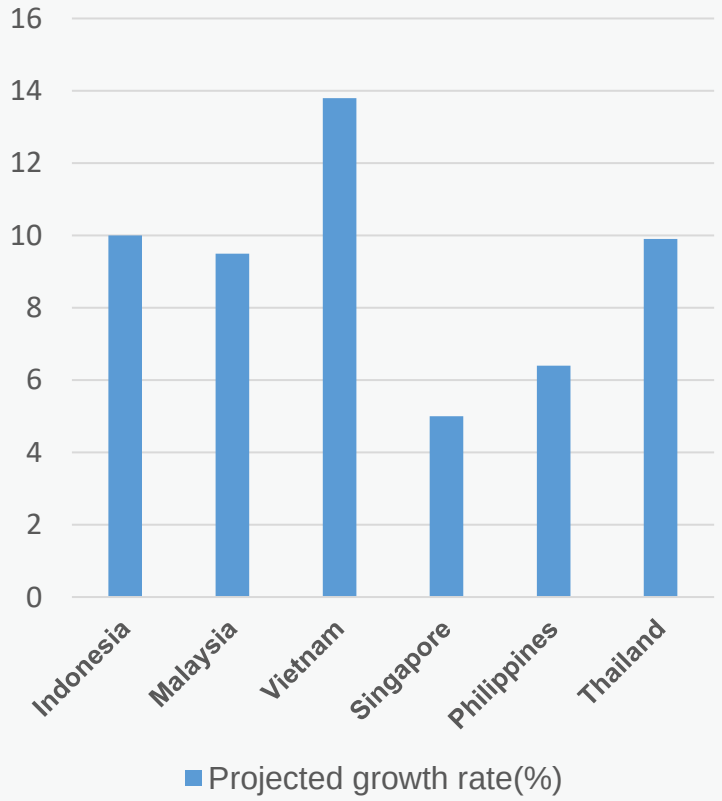
ASEAN Region has a Booming Pharmaceutical Industry with A Significant Amount of Imported Product Consumption

2019 Pharmaceutical Industry Market Size ($, Billion)

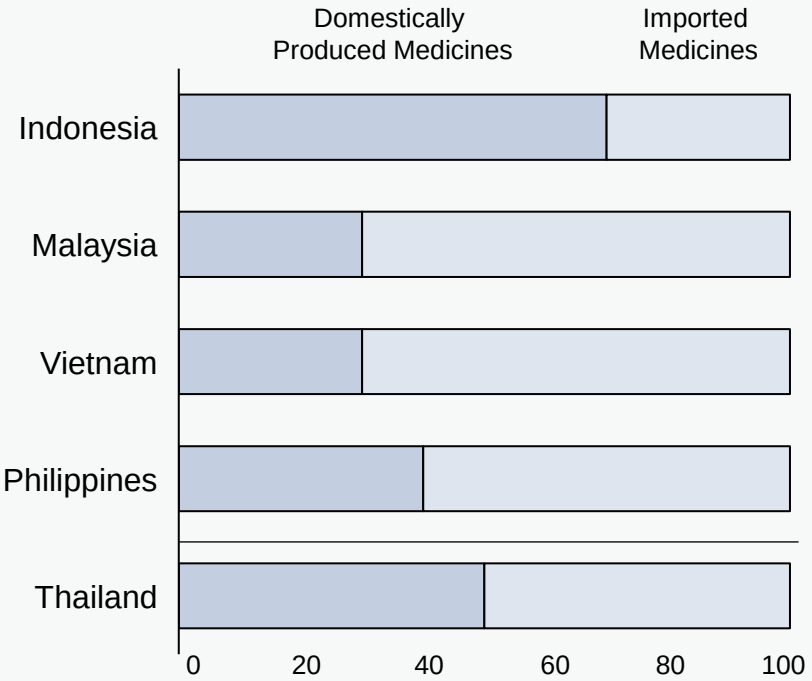


The total Pharmaceutical market size of the 6 ASEAN countries is **$30.1 billion** in 2019

Projected Growth Rate from 2019 to 2020 (%)



Pharma Consumption Domestic v.s. Imported Medicines (value wise) %



Source: Pacific Bridge Medical. Target Asian Market; Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia, World Bank Group

Landscape of ASEAN's Biopharma Market

MNC Pharmaceutical companies' presence in ASEAN

- Of the world's **100** largest pharmaceutical companies, **79** have established presence in ASEAN. Many of them have invested in the development of **innovative biological drugs**
- 8 out of 10 Global Top pharmaceutical and biotech companies are in ASEAN

	In ASEAN
Sanofi SA	✓
Johson & Johnson	✓
Roche Holding AG	✓
Pfizer	✓
Bayer	✓
Novartis AG	✓
GlaxoSmithKline PLC	✓
Merck & Co.	✓
Cardinal Health	×
Sinopharm Group	×

Biosimilars are gaining momentum in ASEAN

MNC pharmaceutical companies with biosimilars approved in Malaysia

ASEAN pharmaceutical companies with biosimilars approved in Malaysia

Source: ASEAN Investment Report 2019, FDI in Services: Focus on Health Care, mapped with Statista's "2019 ranking of the global top 10 pharmaceutical and biotech companies based on revenue"; List of Approved Biosimilars in Malaysia (as of 09 July 2020)

ASEAN: Overall A Promising Market with High Competition and Moderate Affordability

A booming market for the pharmaceutical sector	• A rapid economic growth, an aging population accompanied by an increase in the prevalence of non-communicable diseases, combined with a gradual increase in UHC, have led to a significant increase in healthcare expenditure in the region. • Growing healthcare expenditures, together with a heavy reliance on foreign medicines, bring opportunities for foreign pharmaceutical companies already established the ASEAN market, as well as for new comers.
A competitive market for innovative drugs and less so for biosimilars	• The majority of world's leading MNC pharmaceutical companies have already established presence in the ASEAN region, with 80% of global top pharmaceutical and biotech companies have entered the ASEAN market • The ASEAN biosimilar industry is gaining momentum with limited number of players consisted of both MNCs and local pharmaceutical companies.
Diverse levels of affordability can be potential barrier	• Despite a gradual increase in UHC, significant differences exist in the levels of health coverage and out-of-pocket expenditure as a % of healthcare expenditures, affecting the affordability of expensive medicines, such as innovative medicines and treatments.

Content

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Standard Drug Regulatory Framework

and how ASEAN countries fit into it

** Normally GMP inspection is conducted before review of drug registration in ASEAN countries*

SAFETY, EFFICACY, QUALITY

Comply with ASEAN COMMON TECHNICAL DOSSIER

Guidelines	Singapore	Malaysia	Indonesia	Thailand	Vietnam	Philippines
GLP	OECD-MAD full adherent since 2010	OECD-MAD full adherent since 2013	N/A	OECD-MAD provisional adherent since 2010	N/A	N/A
GCP	ICH-GCP Regional Harmonization Initiative: ASEAN					
GMP	PIC/S Member since 2000	PIC/S Member since 2002	PIC/S Members since 2012	PIC/S Members since 2016	completing the process of applying	completing the process of applying

Source: 1) The Organisation for Economic Co-operation and Development (OECD), National GLP Compliance Monitoring Programmes which participate in MAD,; 2) The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Members & Observers; 3) The Pharmaceutical Inspection Co-operation Scheme (PIC/S), Members,;

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Stage 1: Drug Research and Discovery (R&D)

Use Singapore and Thailand as case studies, as their R&D landscapes are more mature among ASEAN countries

Drug research/ discovery → Preclinical/non-clinical development → Clinical trials Phases I, II, III → Manufacturing Incl. APIS, QC Laboratories → Marketing Authorization*

Infrastructure

Singapore

- **Biopharma MNCs established local labs:** More than 65 different companies are actively conducting biomedical R&D. Among them, leading pharmaceutical and biotech companies have teams with an international representation in their Singapore corporate labs.
- **Local small and medium enterprises (SMEs) sustaining R&D activities:** Cell Research Corporation; Nuance Biotech's partnership with Sphaera Pharma.
- **Various research institutions fostered by Agency for Science, Technology and Research (A*STAR)**: Biopolis, Tuas Biomedical park, Science Park.
- **Growing base of supporting services:** a core base of 20 leading contract research organizations and pharmaceutical companies that manage regional clinical trials from Singapore.

Thailand

- R&D in Thailand features in vaccine and natural compound development. Leading institutes include **National Vaccine Institute, MOPH, Government Pharmaceutical Organization (GPO); Chula Drug Discovery and Development Research Center; Excellent center for Drug Discovery, Mahidol University.**

Resources

Singapore

- **Talent Resources**: More than 16,000 people in more than 100 biomedical sciences companies and 30 research/medical institutes.
- Singapore has launched the **A*STAR Investigatorship (A*I) Award,** to attract bright young researchers to carry out independent research in Singapore's public-sector research institutes.
- **Research Platform/Program:** The establishment of the **Experimental Drug Development Centre (EDDC)** and the **Drug Discovery & Development (D3) platform** aimed to cement A*STAR and Singapore's position as one of the leading centers for the discovery and development of therapeutics in Asia. The activities in EDDC and D3 operate in a seamless value chain, advancing promising early discoveries towards proof-of-concept in an effort to generate economic and health outcomes to benefit Singapore at large.

Partnership

Singapore

- **Public sector's openness to partner companies:** Singapore's network of 30 public-sector research institutes, academic medical centers, medical institutes and hospitals are open to partnering companies to develop new therapies and address unmet healthcare needs. Public funds such as **IAF- ICP(Industry Alignment Fund-Industry Collaboration Projects**) under A*STAR are set to encourage more public-private collaborations.

Thailand

- **Public-Private-Partnership:** The government encourage PPP in the life science field. The country's **Excellent Center for Drug Discovery (ECDD),** a joint effort between **Thailand Center of Excellence for Life Sciences (TCELS), Mahidol University, and Ramathibodi Hospital**, is in partnership with bluebird bio, a US-based biotech company. ECDD is also in partnership with a Japanese university with the goal of being the first in southeast Asia to develop a CAR-T cell therapy targeting CD-19 in acute lymphoblastic leukemia.

Favorable Policy

Singapore

- Government research funding via **RIE2020** of S$19 billion, with S$4 billion dedicated to HBMS, focusing on 5 therapeutic areas, including cancer, cardiovascular diseases and diabetes mellitus.

Thailand

- The government sets up **"Thailand Center for Excellence in Life Science (TCELS)"**- agency to drive life sciences including biopharma.
- The Thailand Board of Investment provides incentives to encourage greater foreign investment in the industry's R&D. The Board of Investment's incentive package comprises an 8-year corporate income tax exemption, an additional 50% corporate income tax break for 5 years where facilities are located in science and technology parks, and an exemption of import duty on machinery.

Opportunities

- *R&D in Singapore is keenly focused on high net value research and development into discovery, preclinical, and clinical development of drugs to proof of concept*
- *Thailand is obtaining certain capacity; Other countries are still in initial phases*

*Source: A*STAR, KPMG, ASK Health analysis*

Stage 2&3: Conducting Clinical Trial in ASEAN

Strength of ASEAN as a place to conduct clinical trial

Drug research/ discovery → Preclinical/non-clinical development → **Clinical trials Phases I, II, III** → Manufacturing Incl. APIS, QC Laboratories → Marketing Authorization*

Investigational New Drug Application (IND)

A cost-saving clinical trial market

- Up **to 50% on trial costs** could be saved than that in U.S or European areas.
- Investigator and site fees are 1/2
- Costs for providing trial-related medication, investigations, and hospitalization are 1/3
- Domestic travel costs and support services are also less expensive

Faster patient recruitment, especially for Asian-specific disease

- Higher Incidence of various disease, together with diverse ethnic representation, intensive population migration, and aging trends are creating a large patient pool
- Clinical trial penetration is lower here, which simplifies recruiting
- Limited governmental security or insurance reimbursement stimulates greater motivation to participate

Strong IP protection and legal infrastructure:

- Countries like Singapore presents the strongest IP protection, while legal hassles in recruiting patients for clinical trials are minimal

Availability of skilled talent and reliable data quality

- Many workers in the relevant fields in ASEAN region are well-educated, have studied in U.S. or European areas, thus with global perspective and local cultural understanding
- Validity of results from ASEAN region's clinical trials has been gradually acknowledged by other areas.

Less Time Consuming on IND Approval

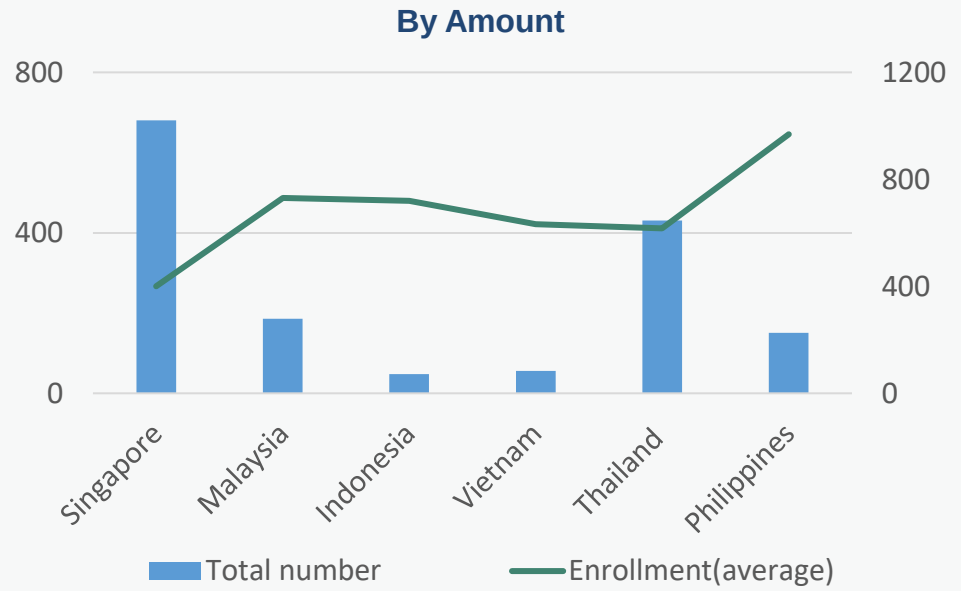
- Comparing with US(30 days) and Australia(30-50 days), ASEAN countries have slightly longer period for IND approval, but significantly shorter than many larger Asian countries, such as China(10-18 months), India(6-8 months), Korea(2-3 months).

Item	Content	Indonesia	Malaysia	Philippines	Singapore	Thailand	Vietnam
IND Application	Timeline	20 working days of evaluation for protocol & amendment of clinical trial after NADFC stated the protocol & amendment complete	45 working days for clinical trial involves biological, cell therapy product.	No specific timelines for trial notification	Clinical Trial Certificate (CTC) and Clinical Trial Authorization (CTA): 30 working days; 60 days for cell and issue products. All Clinical Trails need to be approved by the Health Science Authority (HAS)	IRB: institute EC 2-3 months/ EC-MOPH 6 months	Time required for clinical trial notification: 1 month; Hospital IRB: 1.5-3 months; IND application and MOH IRB permission obtainment: 2-3 months

Source: Frost & Sullivan, APAC Analysis Report ver.2017, ASK Health Analysis

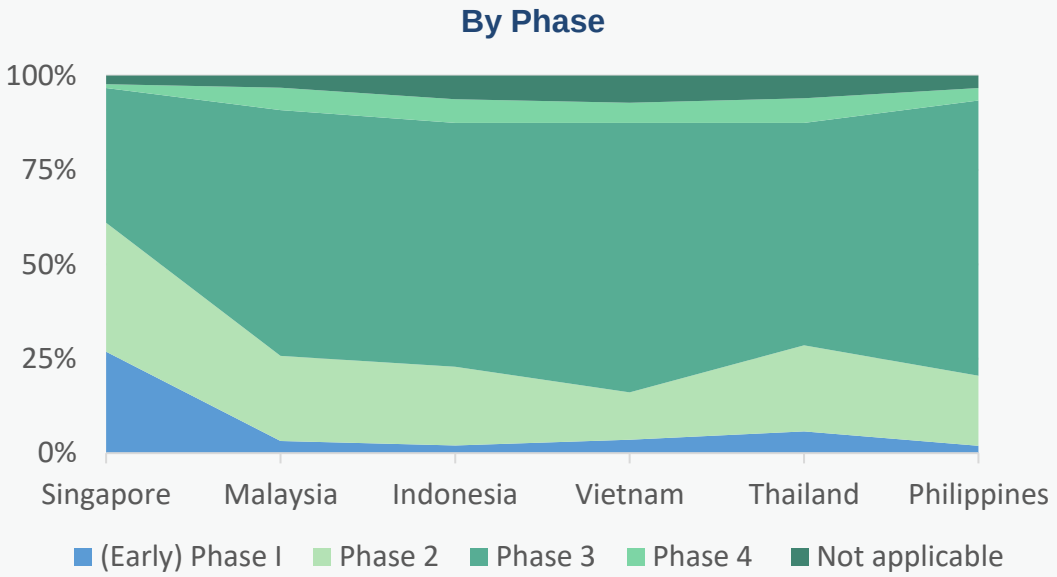
Stage 2&3: Conducting Clinical Trial in ASEAN

Singapore and Thailand are in leading places



Singapore and Thailand are first-considered as clinical trial sites

Most big pharma companies and CROs set their ASEAN bases in Singapore, while Thailand has a well-developed pharmaceutical industry. Thus, they are first to be considered when clinical trials are planned in ASEAN.



Many of the clinical trials in ASEAN were led by U.S. or European organizations, trials being conducted as part of international multi-center Phase III studies (> 70%)

Most early phase trials were conducted in **Singapore**, some in **Thailand**, as these countries have stronger R&D capacity.

Some of the local partners include:
***Singapore**: National University Health System- Investigational Medicine Unit (NUHS-IMU); SingHealth Investigational Medicine Unit, etc.*
***Thailand：** Mahidol University, Naresuan University, National Primate Research Center of Thailand, etc.*

Source: Clinical trial.gov, ASK Health Analysis.

Stage 2&3: Conducting Clinical Trial in ASEAN

Using Singapore as a CASE STUDY

Singapore

Key Strengths

High Compatibility with Global Market Standard

- Advantages for Cross-Region Sample and Data Sharing: Unlike China, Singapore is allowed to transfer sensitive trial sample (cell, blood, etc.) to the US, creating potential pathway for transnational multi-centered clinical trial to avoid ethical risks.
- Governmental Support: Clinical trials are supported by in-house Investigational Medicine Units in public hospitals and the Singapore Clinical Research Institute (SCRI) ; The government also provides subsidies for new drug development.

Strong intellectual property (IP) and legal infrastructure

IP protections in Singapore is among the strongest globally, while legal hassles in recruiting patients for clinical trials are minimal.

Investment in infrastructure to support clinical trials

Particularly in translational research, investment has been made in Phase I/investigational clinical research for novel drugs and diagnostics targeted at Asian diseases, as well as clinician scientists to test insightful clinical hypothesis

One-stop shop access for coordinating regional clinical trial network

The establishment of Singapore Clinical Research Institute creates platform to gather clinical evidence that has not been possible with single sites, assisting in connecting investigators with research interests in the same disease areas, providing opportunity to develop high-impact research questions and acquiring funding.

Other strength: Rapid turnaround, fast patient accrual, and experienced investigators to provide key opinion on the direction of development.

Key Barrier

The cost and speed of setting up clinical trials in Singapore has been constantly pointed out by the industry as a key barrier to conducting more trials locally (Deloitte Survey, 2018).

Source: Deloitte; Frost & Sullivan; Health Science Authority, Singapore, ASK Health Analysis.

Stage 2&3: Conducting Clinical Trial in ASEAN

Opportunities and challenges

Opportunities

- ASEAN has demographic and geographic advantages.
- Many countries, especially Singapore and Thailand, are enhancing their capacities to conduct clinical trials and support new drug development, including priority approval after Phase II trial (e.g. **Named Patient Program*** is approved in Singapore).
- Sensitive human body sample (Blood, etc.) can be legally transferred/shared with sites in other region (Chinese genetic material and data are prohibited for foreign usage according to the National Genetic Law).
- The competition for good clinical trial sites in ASEAN is low, whereas demand for clinical trial sites in the U.S., especially the good clinical trial sites is highly competitive.
- Indonesia and Philippines can be considered as sites of multi-centered transnational clinical trial, as they have largest population groups among ASEAN.
- Overall, consider ASEAN countries as clinical trial sites could potentially improve enrollment rates.

Challenges

- The cost in Singapore are high and the speed of setting up clinical trials is slow.
- Infrastructures, including hospitals where large clinical trials can be hosted, are limited within the region.
- Misalignment of regulations and requirements, as well as different standards of care in each countries forms the main hurdles.
- Other factors to consider:
  - Potential socio-cultural aversion to taking part in trials
  - Staff competency (in some ASEAN countries)

**In Singapore, Named Patient program is approved, which allows biopharma to launch drugs in local market before getting marketing authorization, if it already has FDA or EMA approval (small amount)*

Stage 4: Manufacturing

Drug research/ discovery → Preclinical/non-clinical development → Clinical trials Phases I, II, III → **Manufacturing Incl. APIS, QC Laboratories** → Marketing Authorization*

	Policies/Incentives
Singapore	In recent years, EDB and the industry have been partnering to explore and promote advanced manufacturing technologies and new modalities. A*STAR has also set up biomanufacturing research programme to sustain the Biopharmaceutical Manufacturing industry and enhance productivity through activities such as cell therapy manufacturing R&D programme
Malaysia	Following the crisis of Covid-19, the government looks to support local manufacturers and encourage multinational companies to establish manufacturing plants
Thailand	Joined PIC/S in 2016, the manufacturers are adapted to meet GMP standards
Indonesia	After 11th Stimulus Package in 2016, steps taken by the government, in an effort to develop the local manufacturing capacity for medicines (including raw materials), include a tax holiday, development of a special economic zone as well as building an integrated logistics center (Indonesia Investment.com)
Philippines	Corporate Income Tax and Incentives Rationalization Act (CITIRA): Under CITIRA, up to 100% deduction on research and development expenses; up to 50% deduction for reinvesting profits in the manufacturing industry
Vietnam	The 2017 Law introduces new supports to the investments in drug production, drug materials, and vaccines. The government provides new incentives to R&D in production technology and biotechnology to manufacture new drugs. More specifically, the Law prioritized manufacturing of vaccines, biological products

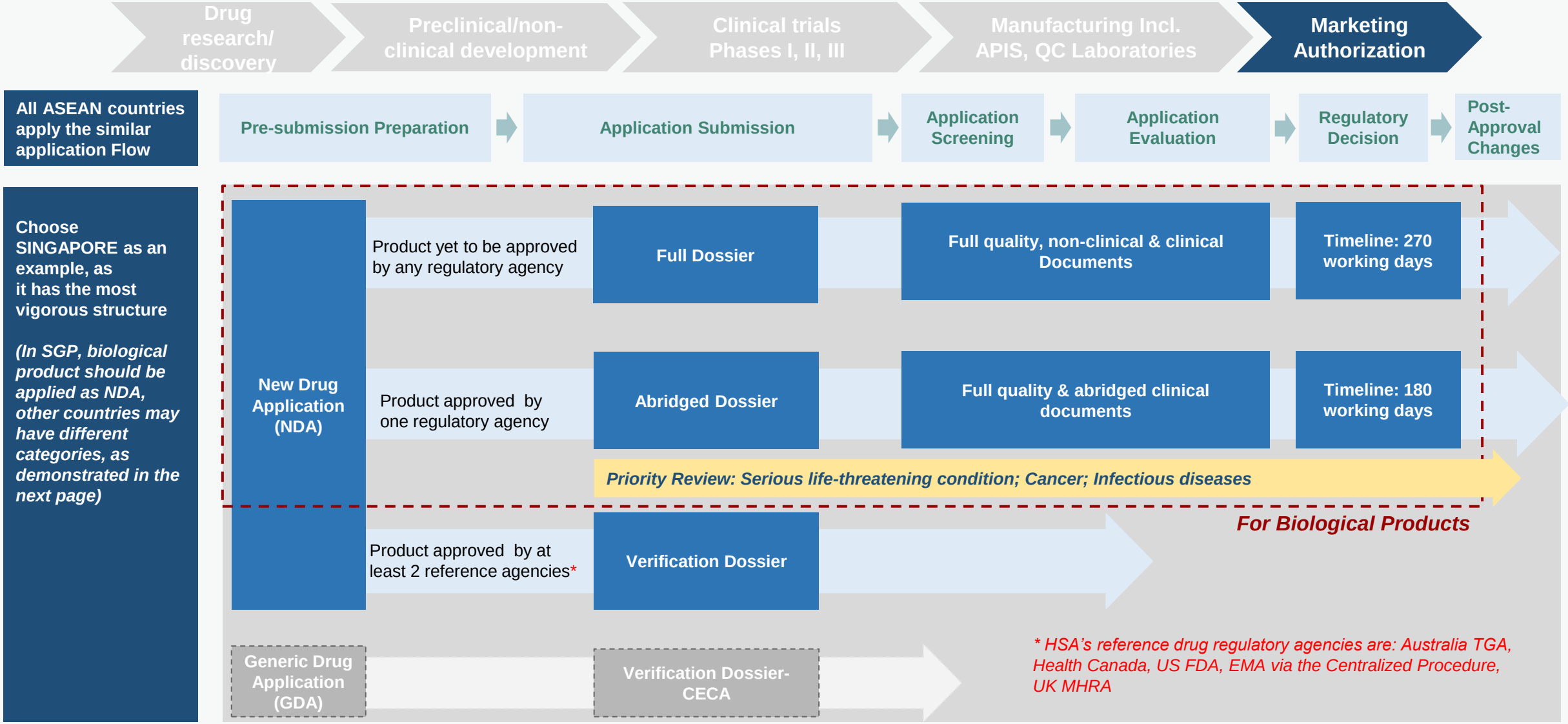
Manufacturing infrastructure
7 leading biopharmaceutical companies have set up their manufacturing operations; 29 commercial plants with a strong base of manufacturing capacity across a diverse range of modalities; The Tuas Biomedical Park also plays an instrumental role in attracting global pharmaceutical companies by providing high standard infrastructure, talents, and third-party services. High quality assurance is accompanied by high cost
Having several manufacturer of biologics drugs such as Alpha Biologics Sdn Bhd, Pharmaniaga, Duopharma, etc. In July 2020, Duopharma signed an agreement with the government investment body VentureTech and Korean firm PanGen to establish the country's first commercial biosimilar production facility
GPO MBP, Thai Red Cross-Vaccines and blood products, Siam Bioscience- biosimilar drugs, Austrianova-cell therapy, TCELS CPU-gene therapy products, etc.
206 pharmaceutical companies in Indonesia, mostly essential drugs; **Kalbe Farma** in 2016 established country's first biotechnology-based drugs facility, includes technology transfer from China and South Korea. Another well known local player is **PT Bio Farma**, a State Owned Enterprise with good capabilities for vaccines/biologics DS and DP
40 out of 61 licensed pharmaceutical manufacturers are GMP certified. Only a handful of companies are engaged in research and production of pharmaceutical raw materials
131 out of 171 pharmaceutical companies have the GMP certificate. 4 of them are manufacturers of vaccines and biologicals

Opportunities: *Thailand, Malaysia, Indonesia have enrolled in PIC/S and established capacity in manufacturing biological products with high quality and low cost; Vietnam and Philippines also have potentials for local production. Singapore offers high quality yet high cost manufacturing ability.*
Challenges: *Lack of structured industry chain may be a hurdle for foreign companies wanting to establish manufacturing facilities in these countries.*

*Source: EDB, A*STAR, ASK Health Analysis.*

Stage 5: Marketing Authorization (Drug Registration)

General process



Source: Health Science Authority, Singapore.

Stage 5: Marketing Authorization

Countries differ in application protocol, timeline, and other detailed requirements

Item	Content	Indonesia	Malaysia	Philippines	Singapore	Thailand	Vietnam
Regulatory Agency		National Agency of Drug and Food Control	National Pharma Control Bureau	Bureau of Food and Drugs	Health Science Authority (HSA)	Thai FDA	Drug Administration Vietnam(DAV)
IND Application	Timeline	20 working days of evaluation for protocol & amendment of clinical trial after NADFC stated the protocol & amendment complete	45 working days for clinical trial involves biological, cell therapy product.	No specific timelines for trial notification	Clinical Trial Certificate (CTC) and Clinical Trial Authorization (CTA): 30 working days; 60 days for cell and issue products.	IRB: institute EC 2-3 months/ EC-MOPH 6 months	Time required for clinical trial notification: 1 month; Hospital IRB: 1.5-3 months; IND application and MOH IRB permission obtainment: 2-3 months
NDA	Acceptance of CTD format	ACTD format	ACTD format.	ACTD or ICH-CTD	ACTD or ICH-CTD	eCTD format. For other classification, the document has to be in ACTD. The ICH-CTD may be acceptable with mapping to ACTD.	ACTD and ICH-CTD format, or CTD for NCE For NCE: For the rest: only ACTD is accepted.
	Timeline	150 working days after completed documents for a New Drug , Biological Product	Biological products : 254 days	Biological products : 9 months Standard review products : 15 months	Screening: 25 working days Evaluation: Full dossier: 270 working days Abridged: 180 working days Verification: 60 working days	Timeframe for approval, New Biological products – 320 working days Vaccine - 350 working days	24-30 months
	Approval can be obtained by utilizing foreign clinical trial data	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guideline.	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guidance, and accepted by the major reference countries.	Overseas clinical trial data is acceptable.	Overseas clinical trial data is acceptable.	n/a	Global clinical trial data/report.
	Other requirements	Specific country requirement on product labeling on product package	n/a	Reference Standard Sample (at least 300 mg) subject to FDA advise.	n/a	n/a	Sample, Plant master file, Labeling, Package Insert, COA for Drug Substance and Drug Product, Trademark.
	Priority Review System	There is no priority system.	There is no formal priority review system in place. Priority review status will be provided on case to case basis, based on the applicant‘s justification. Timeline for Priority Review: 6-9 months	The priority review system exists. For serious diseases and life-threatening conditions	No separate priority review system or pathway. Only if product is submitted via Abridged Evaluation (with 1 reference country approval); and meets the pre-defined criteria in the guide (unmet medical need, etc).	Priority Review: for product in need e.g. anti-HIV, anticancer or product in need as per endorsed from Thai FDA. Abridged Evaluation: effective from 1 Oct 2015 by referring to the approval & evaluation from one of the reference agencies.	The Drug Administration of Vietnam and the Department of Medical Device and Construction (as regards in-vitro diagnostic biologicals) will consider priority review for: a. orphan drug; b. Drugs for treatments in emergencies, natural disasters, epidemics; c. Local drugs manufactured on modern GMP production lines. d) Vaccines pre-qualified by the WHO.
Clinical trials	Requirement of domestic clinical data for NDA application, if there is foreign data	Not necessary, unless for family planning and public health programs	Not necessary.	Local clinical trial is optional; PSUR submission will be required as part of Post-Marketing Surveillance.	Not necessary.	Not necessary.	Not necessary for certain cases.
	Acceptance of foreign clinical data for NDA	Acceptable if the clinical data following GCP and the result based on evaluation of safety and efficacy is good.	Yes.	Acceptable if the similarity in PK/PD is indicated.	Yes.	Yes.	Yes.
Post-Market Approval	Risk Management Plan (RMP)	Not required	Required for biological products, including biotech products, biosimilars, etc.	Required. No local format	All NDA-1 and biosimilar product must submit RMP	Decided by TFDA	Not mandatory

Source: Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies. APAC Asia,2017

Stage 5: Marketing Authorization

ASEAN countries have more divergence than similarities

Similarities

Application Type

NDA or Biological product, biosimilars are not to be apply as generic drugs

ACTD/CTD Acceptability

ICH guidelines in force are accepted. CTD format is acceptable for innovator, biological and biotechnological products.

Priority Review

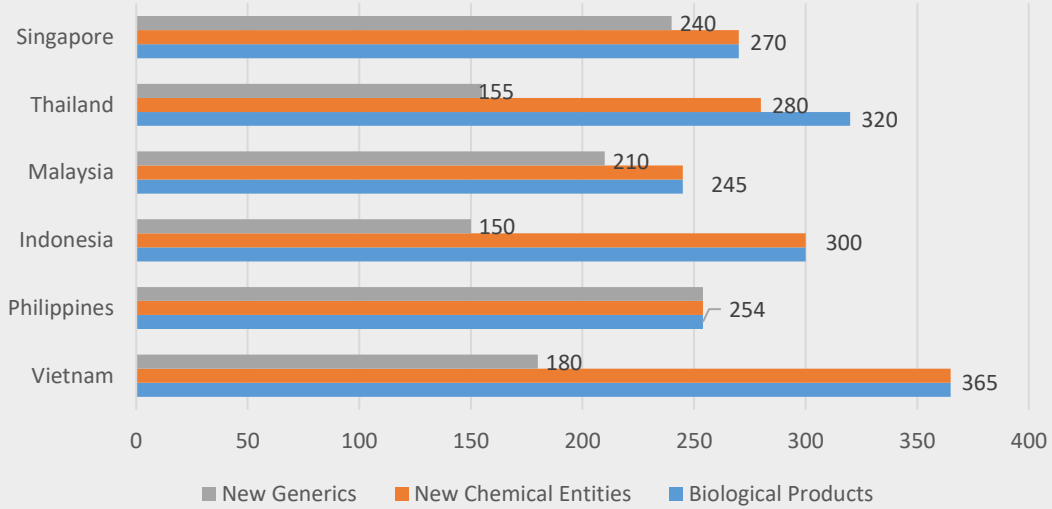
All countries have established formal or informal priority approval systems or abridged evaluation systems, except for Indonesia. Each country differs in detailed qualification requirement for priority approval.

Clinical trial data

For NDA, all countries accept foreign clinical data in the drug registration process; generally speaking, foreign biomedicines are not required to submit local clinical data.

Divergence

Registration Timeline



Product Labelling

Product labels in English are acceptable only in Singapore.

For Philippines, Indonesia and Thailand product labels must be accompanied with their local languages.

In Vietnam and Malaysia, a product label must be in Vietnamese and Malay.

Additional requirements

In addition to ACTD, sample of drug are required in Philippines and Vietnam; not required in Singapore, Malaysia and Indonesia.

Source: The Regulatory Affairs Professionals Society, The Drug Regulatory Landscape in the ASEAN Region (2018)

Regional Harmonization on Pharmaceutical Regulation

Harmonization efforts in the region

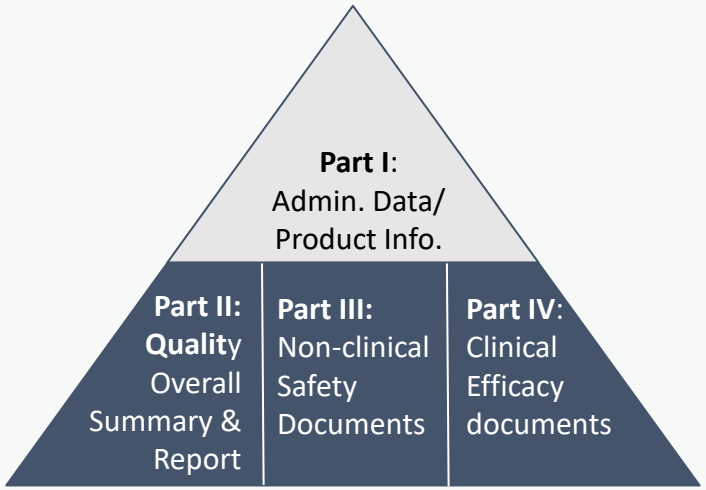
Background

ASEAN Free Trade Area (AFTA)

- A collective effort by ASEAN to reduce/eliminate tariffs in intra-ASEAN trade in the goods sector

ASEAN Consultative Committee for Standards and Quality(ACCSQ)

- As efforts toward ASEAN harmonization, **ASEAN Consultative Committee for Standards and Quality(ACCSQ)** was formed by the ASEAN Economic Ministers in 1992 to facilitate and complement the objectives of the ASEAN Free Trade Area (AFTA).
- 13th ACCSQ Meeting in 1999, it was agreed that a **Product Working Group on Pharmaceuticals (P-PWG)** be set up, comprising of national regulatory and standard bodies, and industry representatives from ASEAN, with Malaysia being designated as the lead country.



The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use- Organization of the Dossier

ASEAN Health Integration under PPWG

- Implement **ASEAN Common Technical Dossier (ACTD)**
- Harmonize labelling standards
- Facilitate approval process after full implementation of the ACTD
- Explore feasibility of adopting a harmonized placement system for pharmaceutical products
- Formalize a post-marketing alert system for defective and unsafe pharmaceutical products

Biologics Technical Working Group (2018)

- Established by the PPWG at the 17th ACCSQ PPWG Meeting TWG with Indonesia and Singapore taking the lead.
- The focus: Harmonization of standards and technical requirements
- Priority Area:
  - Vaccines, biosimilars and blood products
- Action plan:
  - Development of technical guidelines for biologics
  - Modifying ACTD for biologics
  - Guidelines for Vaccines - stability, safety & efficacy, quality
  - Post marketing alert system
  - Capacity building - quality management system, evaluation, training & information sharing

Regional Harmonization on Pharmaceutical Regulation

Regional harmonization programs that have achieved partial results

Project Orbis

An initiative of the FDA Oncology Center of Excellence (OCE), provides a framework for concurrent submission and review of oncology products among international partners.

- Launched 2019, Project Orbis is a collaborative review effort for oncology products that includes **FDA**, **Australia's Therapeutic Goods Administration (TGA), Health Canada**, **Singapore's Health Sciences Authority (HSA)** and **Swissmedic**.
- Collaboration among international regulators may allow patients with cancer to receive earlier access to products in other countries where there may be significant delays in regulatory submissions, regardless of whether the product has received FDA approval.
- The first Project Orbis partnership between FDA, HSA and Swissmedic was made in April 2020. The drug, Seattle Genetics' Tukysa (tucatinib) was approved in combination with chemotherapy drugs trastuzumab and capecitabine to treat adult patients with inoperable or metastasized advanced HER2-positive breast cancer who have received prior treatments

Duke-NUS CoRE: Centre of Regulatory Excellence

CoRE is the first dedicated Asian Centre targeted at the needs of the national health regulators, the biomedical industry and pharmaceutical and medical device companies. Formally inaugurated in November 2014, CoRE offers itself as a neutral platform in the academic setting of Duke-NUS Medical School. Their relevant efforts include:

- promoting convergence and harmonization, as well as competency and capacity building at the Asia Pacific Economic Cooperation (APEC), via its Life Sciences Innovation Forum (LSIF) and Regulatory Harmonization Steering Committee (RHSC);
- training and education have been the key platform to align understanding and implementation of technical requirements and processes, and normalize the baseline competency to facilitate convergence and regulatory cooperation;
- CoRE as a neutral entity has been successful in providing the platform to train regulatory professionals and bringing stakeholders together;
- CoRE is also the entry point for other global stakeholders to reach out to ASEAN regulatory environment e.g DFAT RSP, WHO, DIA.

Source: US FDA, Duke-NUS CoRE, Health Science Authority, Singapore.

Stage 5: Marketing Authorization
Opportunities & challenges

Opportunities

- Some ASEAN countries (e.g. Singapore, Thailand, Indonesia) have shortened routes (e.g. abridged, verification routes) that leverage on regulatory marketing approval(s) by major regulatory agencies. A number of countries have plans to provide similar routes based on regulatory reliance.
- The reference agencies differ among the different ASEAN regulators, but largely recognize the US FDA, EMA and TGA.
- Comparing with US (30 days) and Australia (30-50 days), ASEAN countries have slightly longer period for IND approval, but significantly shorter than China (10-18 months).
- All ASEAN countries do not require additional data for foreign NDA application, meaning **clinical trial data requirement is not a major challenge during the drug registration process.**

Challenges

- The implementation of regulatory harmonization is in fact not ideal. Many countries still apply specific requirements, making it a major hurdle for drug registration. *"…the region is not really harmonized in terms of drug registration*", according to several local experts from our interviews.
- Weak enforcement and presence of counterfeits/ unregistered products reduce profits and returns in this region.
- Weak pharmacovigilance and post-market activities in some ASEAN member states (AMS) deter industry's decision to register new and innovative products with implications to the license holder.

Conclusion: Features of the ASEAN Pharmaceutical Regulatory Framework

Overall Opportunities

- Conducting R&D and clinical trial in ASEAN have shown some advantages, especially that Singapore is considered as a competitive global bioscience and technology R&D hub and a strong partner in early phase clinical trial.
- The regulatory framework in ASEAN is deeply impacted by western countries. The reference agencies differ among different ASEAN regulators, but the majority recognize the US FDA, EMA and TGA.
  - Foreign clinical data accepted in all ASEAN countries, meaning no need for additional trial to be conducted locally (Except in certain cases)
  - Achievement has been made on regional harmonization that all countries accept ICH/ACTD
- Several countries are obtaining potential manufacturing capacities: Vietnam, Indonesia, Malaysia, Philippines.

Overall Challenges

- To date, none of the ASEAN member states (AMS) have listed NMPA as a reference agency.
- Although significant efforts have been put into harmonizing the regulatory requirements across ASEAN, country-specific requirements on local administrative data, legal data, country specific stability requirements and product labelling still diverge significantly from one other, adding difficulties to the drug registration process within the region.
- A potential challenge is the lack of capability of the local regulatory and healthcare system to carry out the Risk Management Plans, as the ones made for major reference agencies may not be practically implemented for the local market.
- Language barrier and culture differences may pose potential challenges for foreign companies entering the market.

Things to Consider

- Singapore's role: serves as that first landing point before accessing the rest of the ASEAN market.
  - Strong positioning in R&D and early phase clinical trial, especial in high net value development
  - Sophisticated route for biological product registration
  - Recognized by other ASEAN countries as sound regulatory standards
  - Singapore's movement towards ICH full regulatory member will further accelerate mutual recognition with other ICH members including China

Content

- Regional Market Landscape
- Regulatory and Supportive Environment for Biopharma Companies' Market Expansion in ASEAN Region
- **Go-to-market Strategy for Chinese biopharma companies and the way forward**

ASEAN is an attractive market to be in

Despite the complexity of the ASEAN market, with a large population, a booming economy, a fast growing healthcare sector, and a biomedical sector that is gaining momentum, ASEAN is an attractive location for biomedicines, especially for biosimilar products and me-too drugs.

Several Chinese pharmaceutical companies with biomedical products have made the first move to enter the ASEAN market through:

- Licensing-out products
- Co-developing products with local partners
- Forming JV/ invest in local players
- Establishing local capacity

Our interviews with leaders of Chinese biopharma companies have also unveiled that

- Some has included ASEAN countries as one/more of their multi-center clinical trial sites
- Some are planning to enter ASEAN either through identifying local partners or collaborating with MNC partners with presence in the region.
- A number of Chinese biopharma companies are considering moving some functions to ASEAN, or establishing overseas headquarters in **Singapore**, to take the advantage of the region's interconnectivity with both the eastern and the western markets.
- Several Chinese CRO/ CDMO companies have been/are going to establish manufacturing capacities in ASEAN.

In this section, we will illustrate some of the go-to-market strategies Chinese biopharma companies have taken in ASEAN, and some key considerations from their experience. One of the industry expert we interviewed described ASEAN as the following:

"There is no unified strategy, as each country needs its own strategy …. prior to enter the market, you should have some main focused territories, like Singapore, Malaysia, Thailand, Indonesia and the Philippines, instead of covering all 10 countries."

- A Southeast Asia Region Head of an MNC Biopharma Company

Current Activities of Chinese Biopharma in ASEAN

	Organization	Product(s)	Presence In ASEAN	Activities
Biopharma/ Biotech	Henlius	HLX10, a recombinant, humanised, anti-PD1 monoclonal antibody	ASEAN, especially Indonesia	Licensing-out to an Indonesia Pharma, PT Kalbe Genexine Biologics, to develop and commercialize HLX10 in the ASEAN region
	Everest Medicines	Xerava (Eravacycline) antibiotics	Singapore	Licensed-in Eravacycline to develop and commercialize in Asia including Singapore. It has been approved by HSA to enter Singapore market in April 2020
	Yisheng Bio	YS-ON-001 for treatment of pancreatic and liver cancer	Singapore/Malaysia	Clinical trials/ Manufacturing
CMOs	WuXi Biologics	Manufacturing facilities	Singapore	Plan to build manufacturing facilities in Singapore

Clinical Trials conducted (partially) in ASEAN countries by Chinese biopharma/CROs

	Organization	Biomedicine Product	The ASEAN Country of MRCT
Biopharma/ Biotech	Henlius	HLX02	Philippines
	BeiGene	Pamiparib	Singapore
CROs	Tigermed	EGFR-TKIs	Singapore
	Clin Choice (FMD China)	Ovarian cancer drug	Malaysia

Source: ASK Health Analysis

Go-to-Market Strategy
Licensing-Out

Overview

Currently, most Chinese biopharma companies that seek to expand to the ASEAN market have chosen to license out one of/their pipelines to MNC or local companies in the region

- Total number of cases is limited; licensed pipelines are all oncology drugs
- Most cases are in early stage, either in development phase or waiting for regulatory approval

Case Study: Henlius

Henlius（2696.HK）is a leading biopharmaceutical company in China with the vision to offer high-quality, affordable and innovative biologics for patients worldwide with a focus on oncology and autoimmune diseases. Since its inception in 2010, Henlius has built an integrated and efficient global R&D platform with key facilities in Shanghai, Taipei and California. Starting from biosimilar, Henlius presses forward with novel mAb products and immuno-oncology combination therapies with proprietary anti-PD-1 and PD-L1 mAbs as backbone. Henlius establishes a diversified product pipeline of biosimilars, bio-innovative drugs and combination therapies, and builds an integrated platform covering the whole product lifecycle including R&D, commercial-scale production and commercialization.

Licensing-out to ASEAN local partner

Henlius has entered into an Exclusive License Agreement for HLX10 with **PT Kalbe Genexine Biologics ("KG Bio")**, a holding subsidiary to the Indonesian pharmaceutical company PT Kalbe Farma ("Kalbe Farma"）. HLX10 is a recombinant humanized anti-programmed cell death (PD-1) monoclonal antibody (mAb) injection independently developed by Henlius. With the collaboration, KG Bio will be granted exclusive rights to develop and commercialize HLX10 in relation to (i) the first monotherapy for the treatment of solid tumor (MSI-high) (ii) the two combination therapies and (iii) two new indications. KG Bio may in license in accordance with the Agreement in 10 countries in Southeast Asian Region, including the Philippines, Indonesia, Malaysia, Singapore, Thailand, Laos, Myanmar, Cambodia, Brunei and Vietnam.

*Through the collaboration with **KG Bio**, Henlius will strengthen its market access to Southeast Asia for HLX10 as a part of its international strategy through Kalbe Farma's extensive sales network in the market, with the aim of sharpening its global competitiveness and brand awareness in the field of immuno-oncology. The collaboration also further strengthens the development of its immuno-oncology combination therapy in Southeast Asia, which has a population of 650 million and significant unmet needs.*

Key Considerations of Licensing-out in ASEAN region

- Reliable partner. "Chinses companies usually do not have full access to all the information, since a lot of information do not have public access"
  "A reliable partner could guarantee long-term collaboration and sustainability of the 'Licensing-out' business model"
- Financial regulations: need to consider overseas financial safety, which is affected by political factors, such as local regulation and policies, and prestige of local partners.

Source: Helius website

Go-to-Market Strategy
Co-development

Apart from licensing-out, some Chinese biopharmas have also established or are planning to establish partnerships with local pharmaceutical companies in ASEAN during the drug discovery phase. Others are considering the JV or direct investment models

Co-Development

Case Study (Information collected from an anonymous interviewee):

A Chinese biopharma is developing a biological product for an infectious disease and is in the process of identifying local partners in the ASEAN region for co-development. The potential local partners they are discussing with are specific to individual ASEAN country. Each partner will champion local clinical trial, registration and distribution in their own country. Their ideal local partners are the ones with good government relations. Co-developing and distributing the biological product can potentially further enhance their relationships with national governments.

JV & Direct investment

Under discussion (Information collected through interviews)

Some Chinese biopharma companies we have spoken to are also considering setting up JVs with local pharma in ASEAN, or making direct investment into local companies. Such approaches can result in a tighter relationship with the ASEAN partner compared with the licensing-out model.

Key Considerations for Co-development in ASEAN region

- Consider Singapore and Thailand as first-choice places to conduct early phase development, as they have stronger R&D capacity and abundant resources (talents, infrastructures, etc.); Singapore is strong in translational research, often conducting FIH Trials and Phase II trials for US, Europe, and Chinese pharma companies
- Support on new drug development, including priority approval after Phase II trial (e.g. Named Patient Program)
- In ASEAN, sensitive human body sample (Blood, etc.) can be legally transferred/shared with sites in other regions; where as in China, genetic material and data is prohibited by law for foreign usage.

Indonesia and Philippines can be considered as centers for multi-centered transnational clinical trials, as these countries have larger population size, providing more patient resources and faster enrollment.

Key Considerations for JV & Direct Investment

- Similar to the licensing-out model, finding reliable and resourceful partners/ investment targets are one of the key considerations for forming JV and making investment.
- Government to government relationships between China and the specific ASEAN country, where the JV/ investment target locate in, also need to be taken into consideration before establishing the JV and/or making investment.

Source: ASK Health Analysis

Go-to-Market Strategy
Establishing local capacity

As ASEAN provides a diversified base to support companies' different manufacturing capacity and technology platforms, more mature Chinese companies can also consider building solid business in ASEAN through investing in establishing self-owned businesses in this region. In this aspect, Chinese CROs/ CDMO are the front runners.

Case Study: (Information collected from an anonymous interviewee):

A leading global open-access technology platform company offering end-to-end solutions to empower organizations to discover, develop, and manufacture biologics from concept to commercial manufacturing.

Establishing local capacity

In May 2018, this company announced its interests in establishing a biologics manufacturing facility in Singapore, leveling up the Chinese biomedicine companies' global presence. Choosing Singapore as its drug substance manufacturing facility outside of China is of strategic significance to this company. It allows access to local talents and emerging biotech companies that need to use their platform.

This company is actively expanding its global footprint. Just three weeks before announcing the Singapore facility, the company announced the plan for building first global site in Dundalk, Ireland, which will be the world's largest facility using single-use bioreactors. During the same period, the company had also announced establishing an integrated biologics development, clinical and commercial manufacturing center in the city of Shijiazhuang in northern China. As an important part of their global strategy, "the new site (in Singapore) plays a key role in the company's global biomanufacturing network to ensure that biologics are manufactured... to benefit patients worldwide," said the CEO of this company.

Key Considerations for Establishing local capacity

- The current trend of de-globalization increases the need to build local manufacturing sites in each of the market a business operates in
- Singapore government is supportive and keep updating relevant policies; businesses established in Singapore can potentially raise capital from both US and China with favorable tax policies

Source: ASK Health Analysis

The Way Forward

ASEAN market opportunities and potentials for Chinese Biopharma

Macro Trends

Political Factors

“Belt & Road” (B&R) Initiatives（“一带一路”）

Initiated in 2013, the “Belt & Road” policy by Chinese government has promoted more regional collaborations in pharmaceuticals export and local manufacturing:

- The China Development Bank, Silk Road Fund, SinoSure and other governmental financial initiatives continue to support biopharma industrial distribution and promote enterprises with independent IP rights and international competitiveness, to expand to internationally and develop international cooperation.
- The continual diplomatic activities between China and ASEAN will bring more mutual agreements on regulations and requirements.
- Under B&R, Chinese government has invested in infrastructure building in developing countries, laying solid foundation for local manufacturing and distribution.

Therefore, It is expected that B&R will create more opportunities for regional collaboration in the biopharmaceutical industry through investment and local infrastructure development, etc.

Mutual Recognition

China and Singapore have both been accepted as ICH Regulatory Members

- As China and Singapore have both become official ICH regulatory member in 2017, Chinese NMPA and Singapore HSA are in the process to meet the global standards and ICH requirements.
- It is expected that once both countries' regulatory frameworks are updated according to ICH’s standards, mutual recognition will be achieved as a result.

Changes made by Covid-19

Increased awareness of the drug approval process

- The trials can improve much faster than they used to be. Some of the countries that used to take months to go through the regulatory review of the clinical trial now probably can do it in weeks.

The digitalization of clinical trials

- The physical limitations have stimulated new methods of conducting multi-centered clinical trial. Digitalization has been one of the major trend.
- The next step forward then is the use of available data to generate evidence for the drug registration rather than depending all on novel clinical trials.

The Way Forward

ASEAN market opportunities and potentials for Chinese Biopharma

Near-term opportunities for Chinese Biopharma

Product specific opportunities

- **Biosimilar:** Bigger opportunities lie in biosimilar products, which have fewer competitors in ASEAN and are more affordable compared with innovative drugs.

- **Me-too drugs:** Chinese biopharma's strong capability in incremental innovation and fast iteration can significantly reduce the price of biomedicines, making them more affordability to ASEAN patients compared with the First in Class drugs of MNCs.

Setting up manufacturing facilities

As discussed in Section 2, AMS including Singapore, Malaysia, Thailand and Indonesia have been developing biomanufacturing capacities, with different levels of maturity. Chinese biopharmas can consider moving certain part of manufacturing capacity to ASEAN, or increasing their manufacturing capacity through invest in new facilities in ASEAN, to support their ASEAN expansion.

Supporting the development of ASEAN's local biotech industry

- **Technology transfer:** Since the biomedical industry in many ASEAN countries are still in their infancy, Chinese biopharma can co-develop this industry together with local players via technology-transfer.

- **Investment:** More mature Chinese biopharma, CRO/CDMOs and their investors are looking for new investment opportunities; ASEAN markets can be good candidates given its market size, growth trend, geopolitical status, etc.

Long-term opportunities for Chinese Biopharma

Innovative biomedicines

As ASEAN is experiencing a rapid economic growth, which has resulted in a rising middle class, it is expected that the affordability of innovative drugs will increase in the next decade. Therefore, it is expected that demand for more expansive breakthrough therapies, such as innovative biomedicines, will also increase long term speaking. Some Chinese biopharmas have made the first move to capture such opportunities.

The Way Forward
Overcoming challenges

Work together to overcome challenges

Apart from the challenge of regulatory divergence on drug registration among AMS, which has been elaborated in Section 2 of this report, the following challenges have also been frequently mentioned by the Chinese biopharma companies interviewed for this report:

Lack of cross-regional mutual recognition
In earlier part of the report, we have identified the macro trends of moving towards mutual recognition between China NMPA and Singapore HSA. For other ASEAN countries, mutual recognition with NMPA remains a major challenge. In fact, the majority of Chinese biopharma companies interviewed, have identified lack of mutual recognition between the drug registration regulatory bodies of ASEAN countries and NMPA as a major barrier for NMPA approved biomedicines to entry ASEAN. Therefore. more efforts need to be put into promoting mutual recognition between NMPA and relevant regulatory bodies of other ASEAN countries.

Difficulties in local partnership building
Interviews with Chinese biopharma have revealed the challenge of identifying suitable local partners to support their ASEAN expansion, especially when they need partners specific to each ASEAN country. Support on understanding major players per AMS, and establishing platforms to enable easier access to country specific partners can potentially help Chinese biopharma to overcome this challenge.

Points to consider for identifying reliable partners in ASEAN

- Perform market research to decide on which ASEAN country/countries to focus on, based on local demand for your product, existence of competing products, local reimbursement policy, process of drug registration, etc.
- Consider which approach to use for entering the AMS: licensing out, co-development or JV.
- Conduct research on the local pharmaceutical companies and make a short list of potential local partners. Their areas of focus, past sales performance, strength of their networks, experiences in drug registration and past experience in international collaboration can be effective indicators of their suitability.
- Chinese biopharma companies without ASEAN experience and network may also consider enlisting experienced consultants with on-the-ground teams, country specific experience and network; working with local organizations/ government bodies in specific AMS, which are tasked with supporting foreign businesses; multi-national CRO/CDMOs that have established presence in ASEAN; prestigious local investors if also coming from an investment angle.

Contact us

Mr Andy Chua

Regional Director, Greater China,
International Operations

Singapore Economic Development Board

Phone：+86（21）6385 2626

Email: andy_chua@edb.gov.sg

Dr Siah Sin Cheng

Director (Investment),

EDBI

Phone：+65 6972 0257

Email: siah_sin_cheng@edbi.com

Dr Chang Liu

Regional Director, Greater China and
South East Asia

ASK Health

Phone：+86（21）6505 3S88

chang.liu@accessh.org