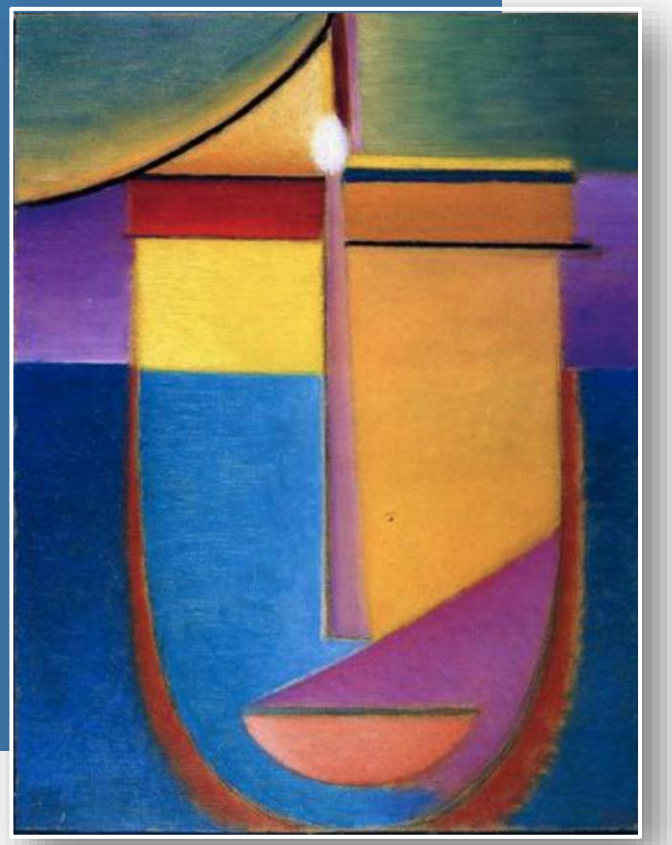

Enhancing the development of the ASEAN markets & accelerating global market expansion for Chinese biopharmaceutical companies

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ASK HEALTH
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List of Abbreviations

Abbreviation	Full name
ACCSQ	ASEAN Consultative Committee for Standards and Quality
ACTD	ASEAN Common Technical Dossier
AFTA	ASEAN Free Trade Area
APEC	Asia Pacific Economic Cooperation
APRF	ASEAN Pharmaceutical Regulatory Framework
APRP	ASEAN Pharmaceutical Regulatory Policy
ASEAN	Association of Southeast Asian Nations
ASK	ASK Health Consulting Co., Ltd.
A*STAR	Agency for Science, Technology and Research
BLA	Biologic License Application
CHE	Current Public Health Expenditure
CoE	Training Centers of Excellence for Regulatory Science
CoRE	Centre of Regulatory Excellence at Duke-NUS Medical School
CPP	Certificates of Pharmaceutical Product
CRO	Contract Research Organization

Abbreviation	Full name
CTA	Clinical Trial Authorization
CTC	Clinical Trial Certificate
CTGTP	Cell, tissue or fund therapy products
CTN	Clinical Trial Notification
DAV	Drug Administration Vietnam
EDB	Economic Development Board
EC-ATMPs	The Excellence Center for Advanced Therapy Medicinal Products
EDDC	Experimental Drug Development Centre
GCP	Good Clinical Practices
GDA	Generic Drug Application
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HSA	Health Sciences Authority (Singapore
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Ethical Review Board
IND	Investigational New Drug Application

Abbreviation	Full name
LSIF	Life Sciences Innovation Forum
MRA	Multi-sector Mutual Recognition Agreement
NADFC	Indonesian National Drug and Food Administration
NCDs	Non- communicable Diseases
NDA	New Drug Application
NPRA	National Pharmaceutical Regulatory Agency
NRCT	National Research Council of Thailand
OECD	Organization for Economic Co-operation and Development
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PPWG	Pharmaceutical Product Working Group
RHSC	Regulatory Harmonization Steering Committee
RMP	Risk Management Plan
SCRI	Singapore Clinical Research Institute
SMEs	Small and medium enterprises
UHC	Universal Health Coverage

Preface: Development of ASEAN* Pharmaceutical Sector from 2020 to 2022

COVID-19 pandemic is accelerating pharmaceutical regulatory harmonization in ASEAN* and stimulating pharmaceutical sector development across the region, creating more opportunities for Chinese biopharmaceutical sector players.

In December 2020, Singapore EDB (Economic Development Board) and ASK Health jointly launched the first version of this whitepaper: *Enhancing the development of the ASEAN markets & accelerating global market expansion for Chinese biopharma companies,* aiming at helping Chinese biopharmaceutical sector players to understand ASEAN's regulatory landscape and to capture the market opportunities.

In the past two years, the global economy and health system have undergone a once-in-a-generation shock since the outbreak of the COVID-19 pandemic. The ASEAN countries are no exceptions, given their deep involvement in global trade. More specifically, the pharmaceutical supply chain in this region has been disrupted due to various pandemic-related reasons.

In response to the pandemic, the ASEAN governments have enhanced pharmaceutical regulatory development and cooperation to accelerate access to innovative pharmaceutical products, including biologics. Actions taken ranging from the authorization of emergency use of vaccines to the enhancement of national priority review mechanisms for pandemic related pharmaceutical products. These activities have stimulated new drug development and registration.

Moreover, the pandemic has brought increased attention to the importance of regional pharmaceutical regulatory harmonization. Progress made include the successful conclusion of deliberations on the ASEAN Pharmaceutical Regulatory Policy (APRP) and the development of the ASEAN Pharmaceutical Regulatory Framework (APRF), which is expected to lead to a legally binding APRF Agreement across ASEAN countries.

Chinese pharmaceutical companies have accelerated pace of expansion in ASEAN during the past two years. From the early phase of drug research and development to new drug registration and commercialization, Chinese companies have made different points of entry into the ASEAN market according to their strategic plans.

The whitepaper has been updated with updated new data on ASEAN's economy and health system. It also includes recent regulatory developments in the biopharmaceutical sector across ASEAN, including advanced cell and gene therapies. Since Chinese pharmaceutical companies continue to make new progress in their internationalization efforts, we have also updated the cases studies on Chinese players' activities in ASEAN. We hope this updated whitepaper will inspire new strategic thinking and actions among the pharmaceutical sector players in China.

**ASEAN: ASEAN is an intergovernmental organization of ten Southeast Asian countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam.*
Source: Association of Southeast Asian Nations: Investing in ASEAN 2021I2022; Asia Partnership Conference of Pharmaceutical Association (APAC): Pharmaceutical Market Regulatory Environment in Asia 2021 (APAC PMRE)

Introduction of The Authors

Introduction of the Singapore Economic Development Board

The Singapore Economic Development Board (EDB), a government agency under the Ministry of Trade and Industry, is responsible for strategies that enhance Singapore's position as a global center for business, innovation, and talent.

EDB undertakes investment promotion and industry development in the manufacturing and internationally tradable services sectors, and industries within our purview account for more than a third of Singapore's annual GDP.

One of EDB's priorities is developing the biopharmaceutical industry, a core component within Singapore's manufacturing sector. The local biopharma industry has grown three-folds in the past two decades, and recorded an impressive 11.1% growth in biopharma manufacturing in 2021. Today, Singapore is home to many best-in-class biopharma manufacturing facilities such as Lonza, GenScript, Amgen, Novartis and Abbvie, who manufacture biologics, drug substances and products for the global market.

Despite the challenges posed by the pandemic, EDB continued to facilitate investments from global heavyweights such as Sanofi and BioNTech, who announced plans for greenfield investments in Singapore. Beyond investments, EDB helps companies forge partnerships with key opinion leaders, research institutes, emerging biotech sectors as well as contact clinical research organizations to rapidly advance pipeline assets.

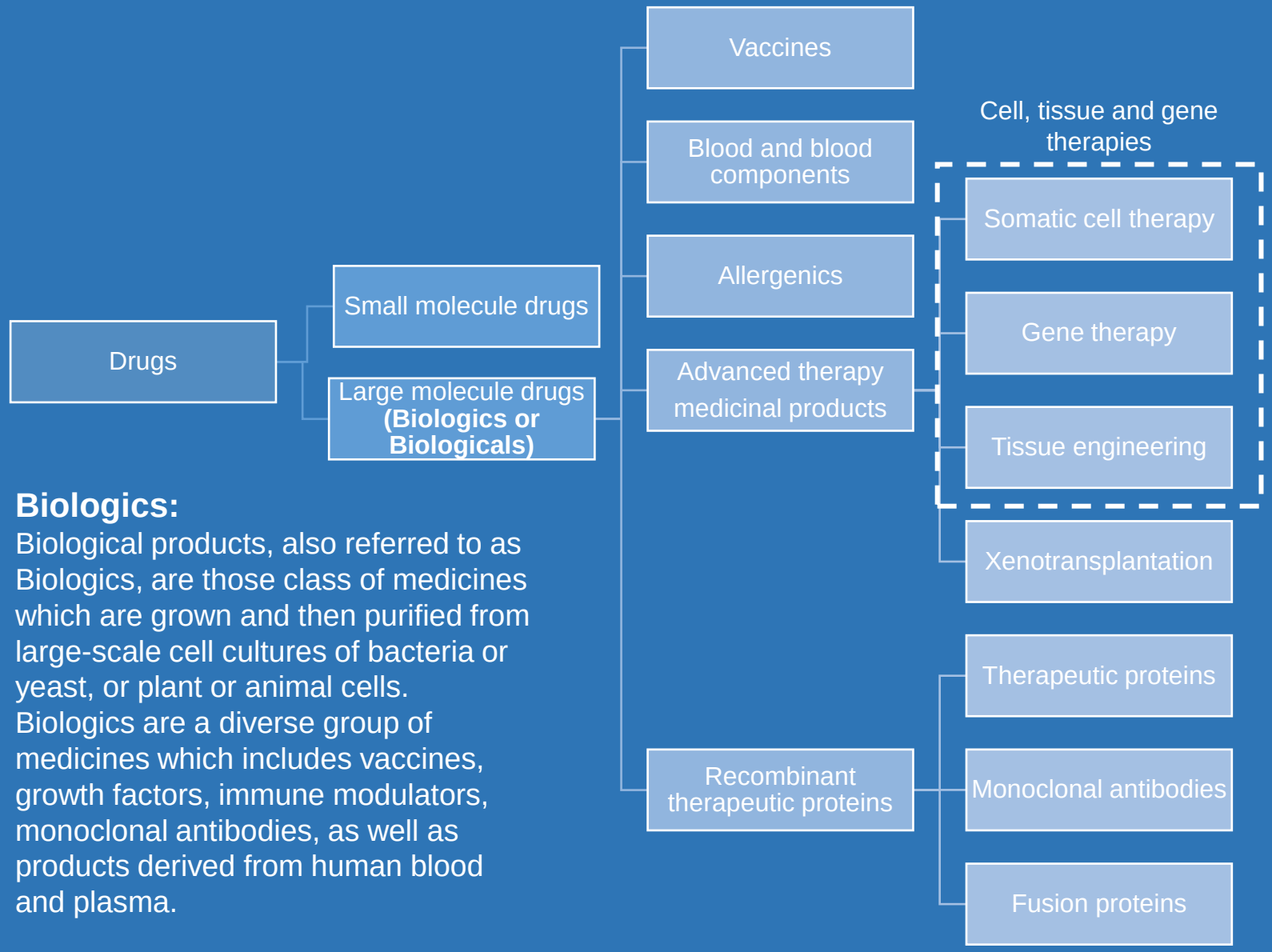
Introduction of ASK Health

ASK Health Consulting Co., Ltd. (ASK) is an international thank-tank, advisory company and implementation partner. Started in China in 2015, We are committed to playing a significant catalytic role in promoting healthcare and aging sector innovations to meet the needs of the people in China. ASK Health is working toward its long-term goal by working in three key areas to foster health innovations: establishing and growing innovation platforms; conducting research and analysis; providing consulting services to public partners, private partners, and nongovernmental organizations.

Our work empowers partners to discover and to develop innovative healthcare models in the country and region. Our partners include leading enterprises, growing startups, governmental organizations, think tanks, and academic institutes. Our team works closely with partners to encourage cross industry, cross border, and interdisciplinary collaboration.

Our collaboration with EDB on the biopharmaceutical industry started in 2020, from the research on ASEAN's biopharmaceutical regulatory landscape and market opportunities. Since then, ASK has been supporting Chinese companies exploring the ASEAN market and understanding Singapore's role as the gateway to ASEAN, through research, event organization and provision of one-on-one assistance. This updated whitepaper is our continuous efforts in supporting Chinese biopharmaceutical sector's ASEAN expansion.

Definition of Biologics and Advanced Therapy



Biologics:
Biological products, also referred to as Biologics, are those class of medicines which are grown and then purified from large-scale cell cultures of bacteria or yeast, or plant or animal cells. Biologics are a diverse group of medicines which includes vaccines, growth factors, immune modulators, monoclonal antibodies, as well as products derived from human blood and plasma.

Advanced Therapy:
"Advanced therapy" refers to a segment of medical products and treatments that use **gene therapy, cell therapy & tissue engineering**.

Advanced Therapy is an emerging class of "large molecules". They are biologics but the mechanism of action of these new classes of therapies is different from what has historically been used.

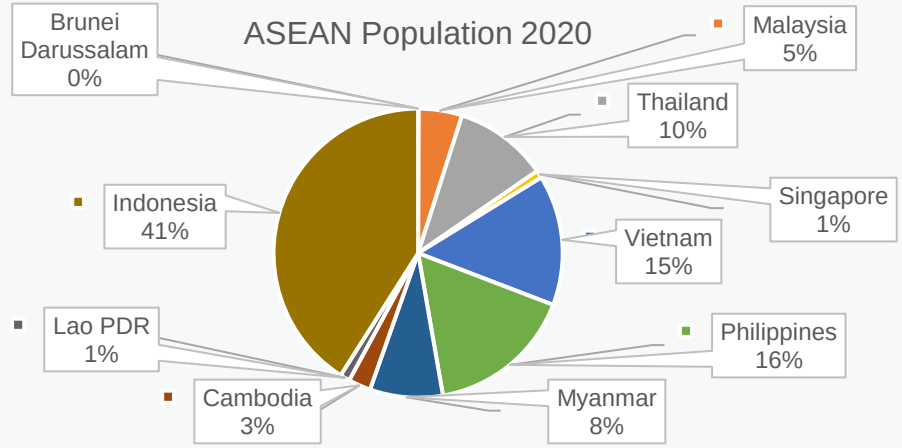
In 6 major ASEAN countries, **Singapore** (HSA, Health Sciences Authority) **and Malaysia** (NPRA, National Pharmaceutical Regulatory Agency) have definitions and specific regulations for Advanced Therapies.

Source: U.S. FDA. What are 'biologics' questions and answers; Kiran Chin, What are Advanced Cell Therapies

Content

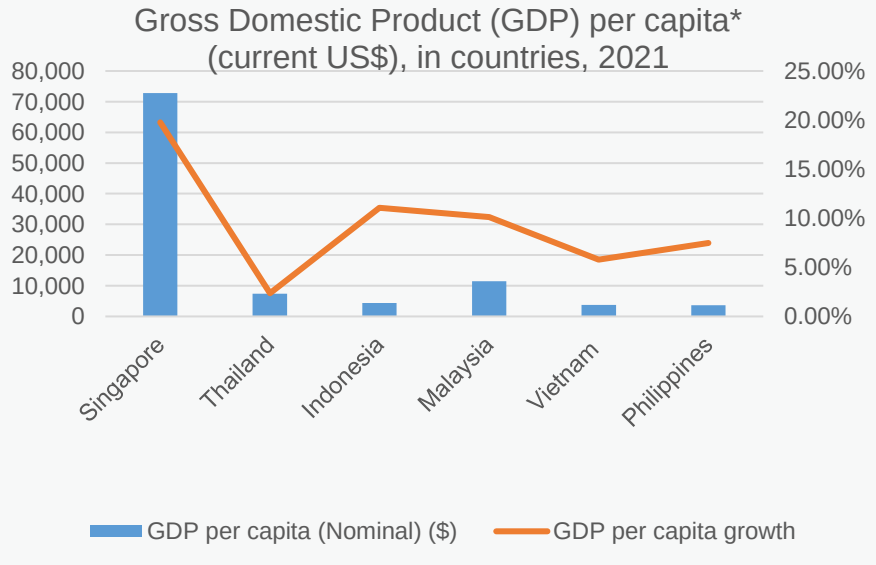
ASEAN Region: A Diverse Region with Rapid Economic Growth and A Rising Middle Class

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



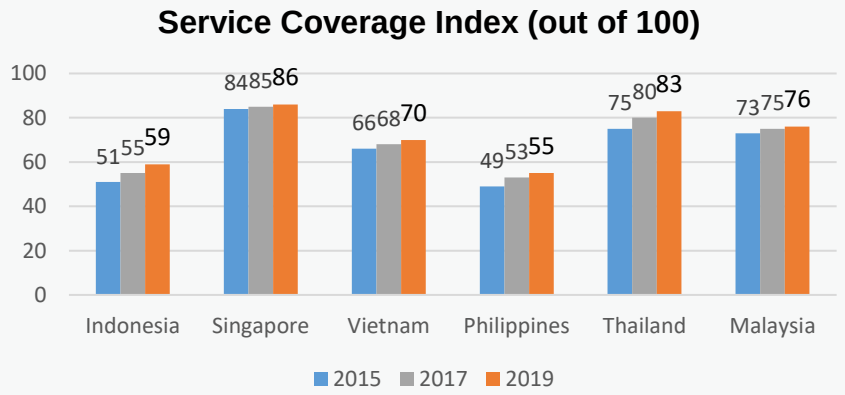
Resilient economy on track of recovery: In the past 20 years (2000-2020), annual GDP growth was **7.1%** on average. Although the COVID-19 pandemic has impacted the economic performance of the ASEAN countries, the region's GDP growth is on track to recovery.

A rising middle class: 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 $300b middle-class disposable income.

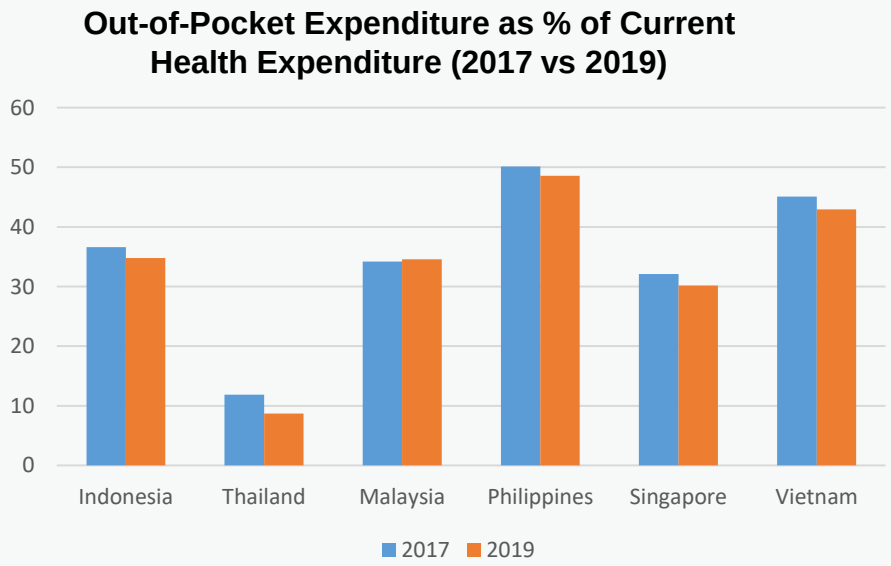


Source: WHO, Population Division. World population Prospect, 2019; International Monetary Fund, WEO Database, GDP per capita in countries 2021
** The GDP Per capital data of Thailand, Vietnam and Malaysia are IMF estimations.*

The Universal Health Coverage (UHC) Measures in ASEAN Countries are 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.



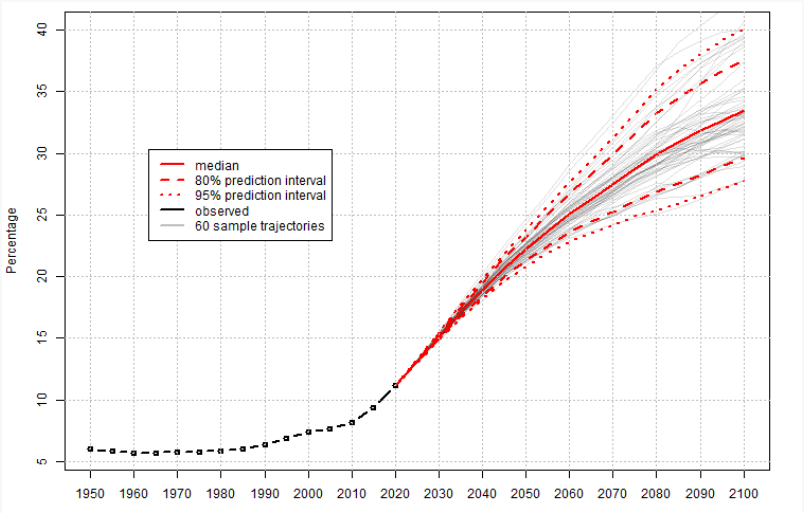
Vietnam	Resolution of the Central Committee of the Communist Party of Vietnam has commitment to move towards UHC. Social health insurance coverage is targeted at 95% by 2025
Thailand	UHC since 2002
Malaysia	UHC using public providers and general government budget since 1980s
Philippines	Expansion of 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 Programs of MediSave, MediShield and MediFund since the 1980s

5 out of 6 countries has seen **reductions** in out-of-pocket health expenditure from 2017 to 2019, which demonstrates **improvement in the affordability** of healthcare services in these countries

Source: 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

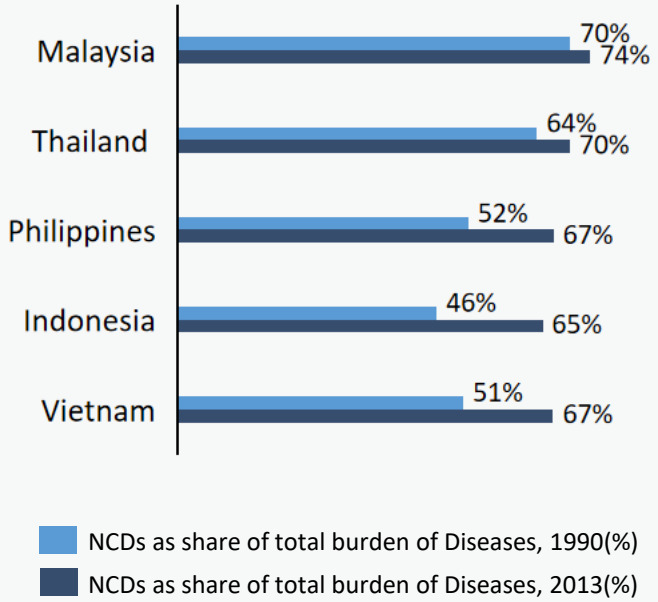
An Aging Population Combined with Epidemiological Shift to NCDs have Contributed to Increasing Health Expenditures

Aging Trend



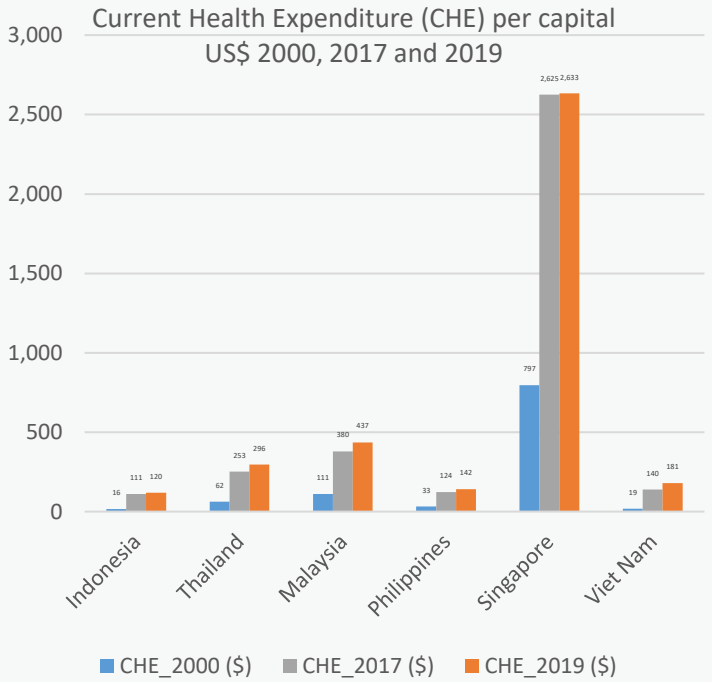
Over 20% of ASEAN population would be over 60 years old by 2050, compared with just over 10% in 2020

Epidemiological Shift to non-communicable Diseases (NCDs)



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

Healthcare Expenditures

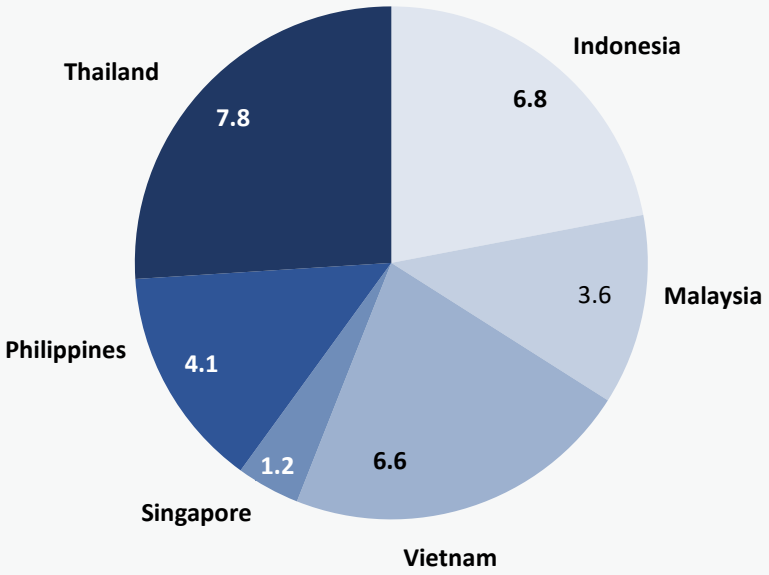


Current public health expenditure (CHE) per capita US$ continue to grow from 2000 to 2019

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

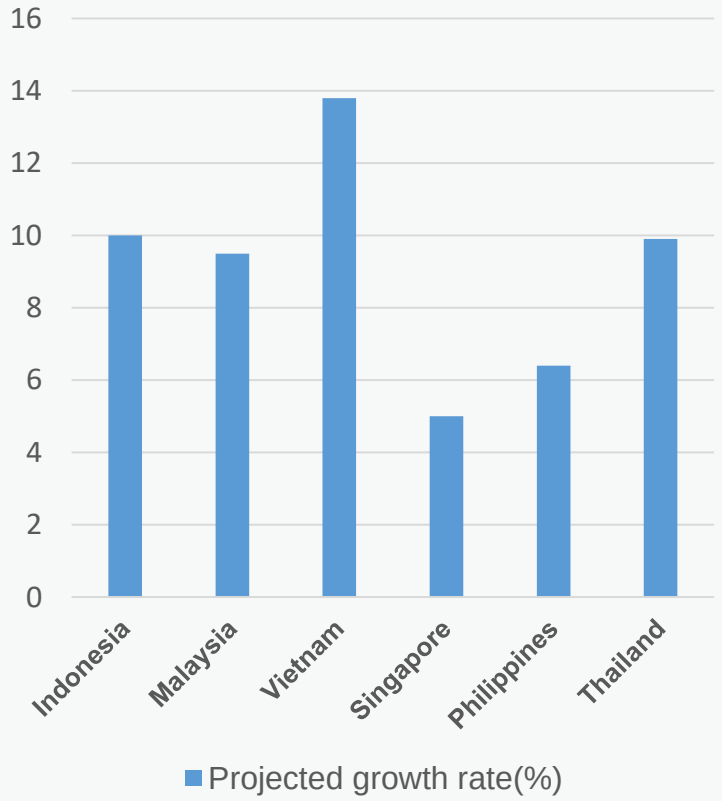
ASEAN Region has a Booming Pharmaceutical Industry with A Significant Amount of Imported Product Consumption

2019 Pharmaceutical Industry Market Size ($, Billion)

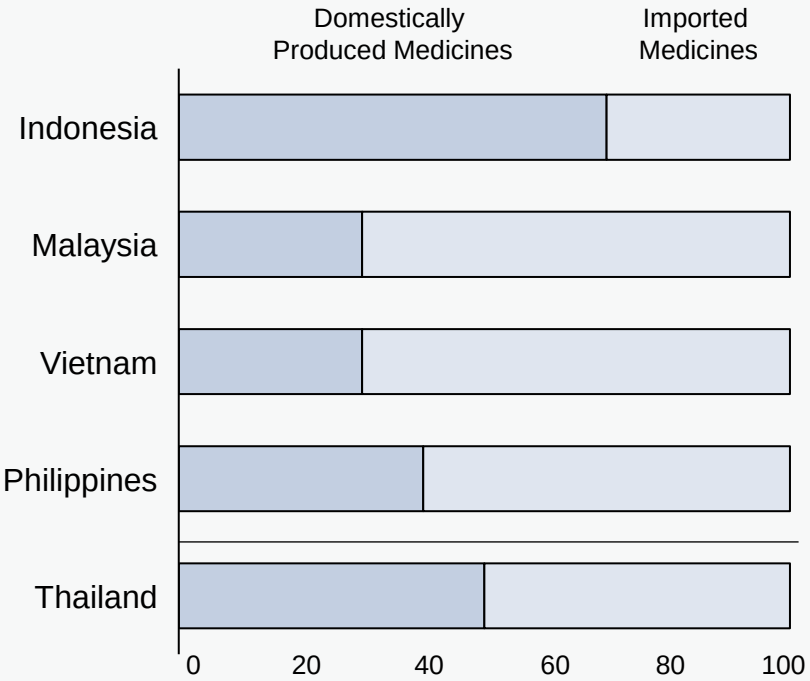


The total Pharmaceutical market size of the 6 ASEAN countries is **$30.1 billion** in 2019

Projected Growth Rate from 2019 to 2020 (%)



Pharma Consumption Domestic vs. Imported Medicines (value wise) %



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

ASEAN Countries are Building R&D Capacity to Support Drug Innovation

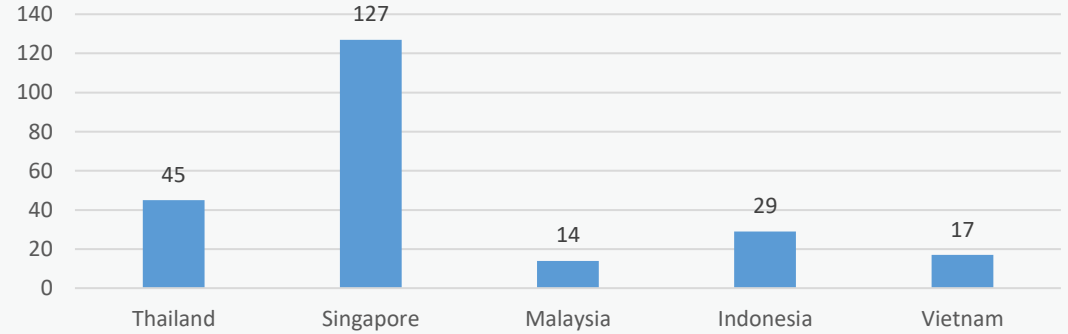
ASEAN countries have established institutions to drive and support R&D of innovative drugs

Country	Institute for new drug development	Est.
Singapore	Experimental Drug Development Centre (EDDC)	2019
Thailand	Chulalongkorn Drug Discovery and Drug Development Research Center	2017
Indonesia	Drug Development Research Center of IMERI (Indonesia medical education and research institute)	2017
Malaysia	National Institutes of Biotechnology Malaysia (NIBM)	2014
Vietnam	Institute of Biotechnology (IBT)	1993

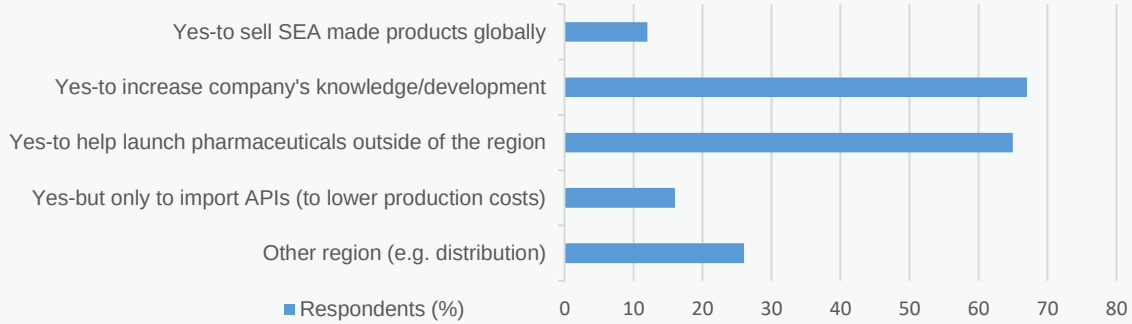
4 out of the Top 10 Global Top pharmaceutical companies' Asia pacific R&D center are in Singapore

	Location	Name
Johnson & Johnson, U.S.	Shanghai	**Asia Pacific Innovation Center**
Roche Holding AG, Switzerland	**Singapore**	**R&D center**
Pfizer Inc., U.S.	**Singapore**	**Manufacturing Technology and Development Centre**
AbbVie Inc., U.S.	Tokyo	**Research Center**
Novartis AG, U.S.	**Singapore**	**R&D Hub**
Bayer AG, Germany	**Singapore**	**Asia Pacific HQ**
Merck & Co. Inc., U.S.	Beijing, Shanghai, Taipei	**R&D Hub**
GlaxoSmithKline PLC, U.K.	Shanghai	**R&D center**
Bristol-Myers Squibb Co., U.S.	Tokyo	**R&D center**
Sanofi SA, France	Shanghai	**R&D center**

Number of new drugs under active development in selected top ASEAN companies, 2020



Local pharmaceuticals in ASEAN countries are looking forward to working with international partners



According to a survey conducted by CPhI in 2020 with 45 companies in 6 ASEAN countries, domestic manufacturers are looking forward to working with **international partners**, especially in **increasing knowledge and development of the company**

Source: ASEAN Investment Report 2019; FDI in Services: post COVID-19 opportunities and threats; May 2021Focus on Health Care, mapped with Statista's "2021 ranking of the global top 10 pharmaceutical and biotech companies based on revenue"; cortellis competitive intelligence, SEA: Pharmaceutical market landscape; CPhI Insights: ASEAN Pharma outlook

Section Summary – ASEAN is on the Rise: A Booming Market with Significant Potential

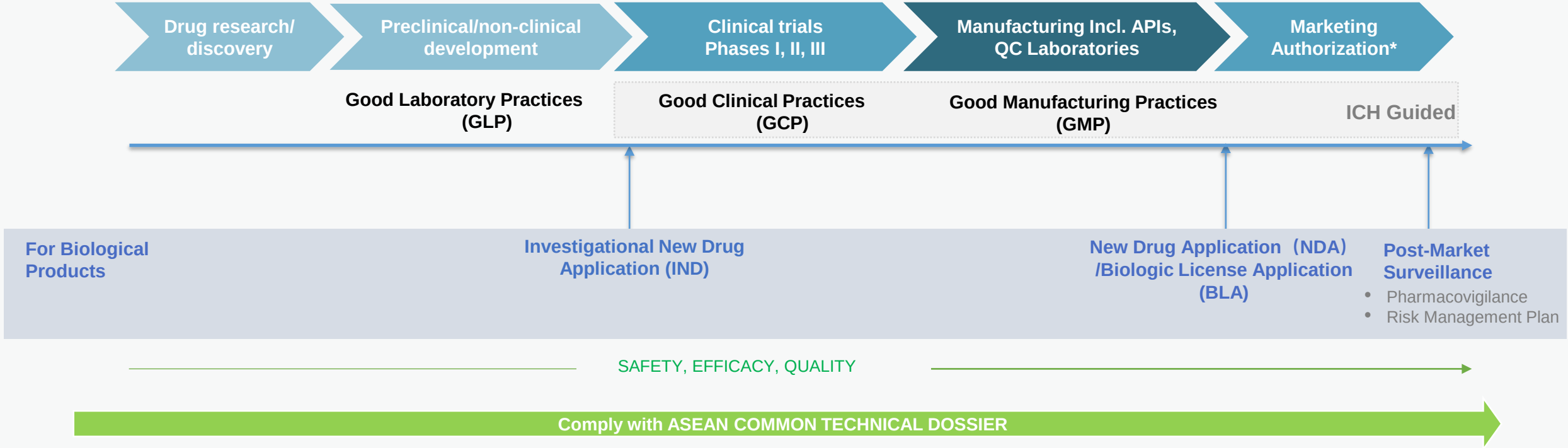
A booming market for the pharmaceutical sector	• Rapid economic growth, a gradual improvement in UHC, an aging population accompanied by an increase in the prevalence of non-communicable diseases have led to significant increase in healthcare expenditure in the region. • Heavy reliance on foreign medicines brings opportunities for foreign pharmaceutical companies already established in the ASEAN market, with room for new entrants to thrive.
An emerging region for new drug development	• Many global leading pharmaceutical companies have established R&D centers in the ASEAN region, especially in Singapore. • ASEAN countries have set up agencies to enhance new drug development capacity. • Local pharmaceutical companies are ready to cooperate with international partners.
Diverse levels of affordability could be a potential barrier	• Despite a gradual increase in UHC, significant differences exist in the levels of health coverage and out-of-pocket expenditure as a percentage of healthcare expenditures, affecting the affordability of innovative drugs and treatments.

Content

- ASEAN on the rise: booming market with significant potential
- **From drug discovery to market authorization: solidifying infrastructure and improving regulatory environment**
- Case studies of Chinese biopharmaceutical companies' expansion in ASEAN

Standard Drug Regulatory Framework

and how ASEAN countries fit into it



Guidelines	Singapore	Malaysia	Indonesia	Thailand	Vietnam	Philippines
GLP	OECD-MAD full adherent since 2010	OECD-MAD full adherent since 2013	N/A	OECD-MAD full adherent since 2020	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: The Organisation for Economic Co-operation and Development (OECD), National GLP Compliance Monitoring Programmes which participate in MAD; The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Members & Observers; The Pharmaceutical Inspection Co-operation Scheme (PIC/S), Members,;
** Normally GMP inspection is conducted before review of drug registration in ASEAN countries*

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Stage 1: Drug Research and Discovery

Singapore as the front-runner

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

Infrastructure

Singapore

- Various research institutions fostered by **Agency for Science, Technology and Research (A*STAR) : Experimental Drug Development Centre (EDDC)** as a national platform for drug discovery and development to channel high potential drug candidates.
- Well-equipped **R&D facilities in industrial parks** supported by the government: **Biopolis** is one of the government's key project that supports the biomedical industry as Singapore's key engine of economic growth. Located close to the National University of Singapore and the National University Hospital, it hosts leading public and private biomedical research institutions and organizations, and anchors the development of the **entire R&D value chain** of life sciences – from drug discovery, clinical development and medical technology research.
- **Biopharma MNCs established local labs:** More than 65 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.

Resources

Singapore

- **Talent Resources**: More than 2,000 top-level private-sector researchers in 30+ R&D centers, 7,600 employees in 80+ regional HQs and 24,000 workforces in BMS (biomedical science) sector in 2019. Singapore has set up various **awards** to attract researchers, engineers and scientists, such as NRF Investigatorship award, President's Science and Technology Awards (PSTA), Young Scientist Awards (YSA).
- **Funding resources: The RIE2025 Plan** lays the groundwork for the country's science and technology efforts and provides financial support for R&D with S$25 billion budget, covering the domain of Human health and potential (HHP).
- The **Singapore Therapeutics Development Review (STDR)** is a **funding scheme** implemented by A*STAR, which aims to identify potential high-value drug discovery and development projects, to render the right support and guidance to progress promising projects, and boost the quality and quantity of the biotech pipeline in Singapore.

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.
- The **collaboration of research institutes, hospitals and academic institutions** is also a model of partnership in Singapore in the R&D sector. **The Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT)** is a multi-agency effort led by A*STAR to deepen the understanding of cardiovascular (CV) disease progression in heart failure (HF).

Favorable Policy

Singapore

- **Tax incentives and schemes: R&D Enhanced Tax Deduction** up to 250 percent for qualifying R&D expenditure in Singapore, **IP Development Incentive (IDI)** offering 5-10 percent concessionary tax rate of qualifying IP income, **Approved Royalties Incentive (ARI)** offering reduced or nil withholding tax on qualifying royalty for R&D activity, **Research Incentive Scheme for Companies (RISC) and Innovation Development Scheme (IDS)** providing grant for companies to conduct or expand R&D activities, **Training Grant for Company (TGC)** for manpower building in Singapore **and Tech@SG Programme** for Employment Pass applications in collaboration with Ministry of Manpower (MOM).

Opportunities

- ***Singapore** is a leader in R&D in the ASEAN region, with well-developed infrastructure and abundant resources.*

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

Stage 1: Drug Research and Discovery

Other ASEAN countries are developing rapidly

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

Infrastructure

Thailand

- **Excellent Center for Drug Discovery (ECDD)** is the collaborative efforts between **TCELS and Mahidol University** which operate in the field of Pharmaceutical research, drug discovery and molecular basis. ECDD equipped with high throughput and high content screening automation that provides the research community with cost-advantaged, high-technology instrumentation and services.

Malaysia

- **Malaysian Institute of Pharmaceuticals and Nutraceuticals (IPharm)** aims to be a Biotechnology's Centers of Excellence by exploiting megadiversity of Malaysian natural resources for the **development of new drugs**.
- Strong support through **biotech focused industry parks**: Bio-Xcell in Nusajaya in the Johor region, Penang Science Park and Kulim High Tech Park in the North-West of Peninsular Malaysia.

Resources

Thailand

- **Funding resources** for research: NSTDA Chair Grant and Wildly Important Goal Grant provided by National Research Council of Thailand (NRCT).

Indonesia

- By its **abundant natural resources of biodiversity** (more than 30,000 species of plants, among which 9,600 have medical benefits), Indonesia has an opportunity to develop marine bio discovery program, **biotechnology industry**, and **pharmaceutical industry**.

Malaysia

- Aimed at spurring innovation and acknowledging impactful community-centric initiatives, the PhAMA Awards were launched in 2014. It comprises two primary awards – **the Minister of Health Innovation & Research Award (MIRA)** and the **PhAMA President's Community Impact & Awareness Award (CIA).**

Partnership

Thailand

- TCELS, Department of Medical Sciences; Ministry of Public Health, Ramathibodi Hospital; Mahidol University, and Riken, Genome Research Institute, Japan, which have been collaborating **in genomic research** since 2006, joined hands to push for a pharmacogenomics network in Southeast Asia by inviting leading researchers from **Japan, Korea, Taiwan, Malaysia, Indonesian and Thailand to share knowledge and experience in pharmacogenomics research.**

Malaysia

- The **Shared Services Unit (SSU)** has an organizational structure that sees a **centralized center** servicing various parts of a company across a wider region. Focusing on the strategic use of key human resource personnel and information technology (IT) solutions within a regional hub, such arrangement allows for improved efficiency via the streamlining of standard operating procedures (SOP) and promotes a stronger inter-regional cooperation within a company.

Favorable Policy

Thailand

- 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.
- **'Thailand 4.0'** is an initiative launched by the Thai Government to shift the country from what is described as a 'manufacturing hub' to an 'innovation hub'. While not solely focused on pharma manufacturing, this initiative has already seen state-of-the-art facilities set up at the Thailand Science Park with clean rooms, sensitive labs and high-performance technologies

Malaysia

- Numerous tax incentives are ready to encourage companies and institutions to carry out R&D activities in Malaysia, such as **Pioneer Status (PS), Investment Tax Allowance (ITA), Double Deduction or Tax Exemption.**

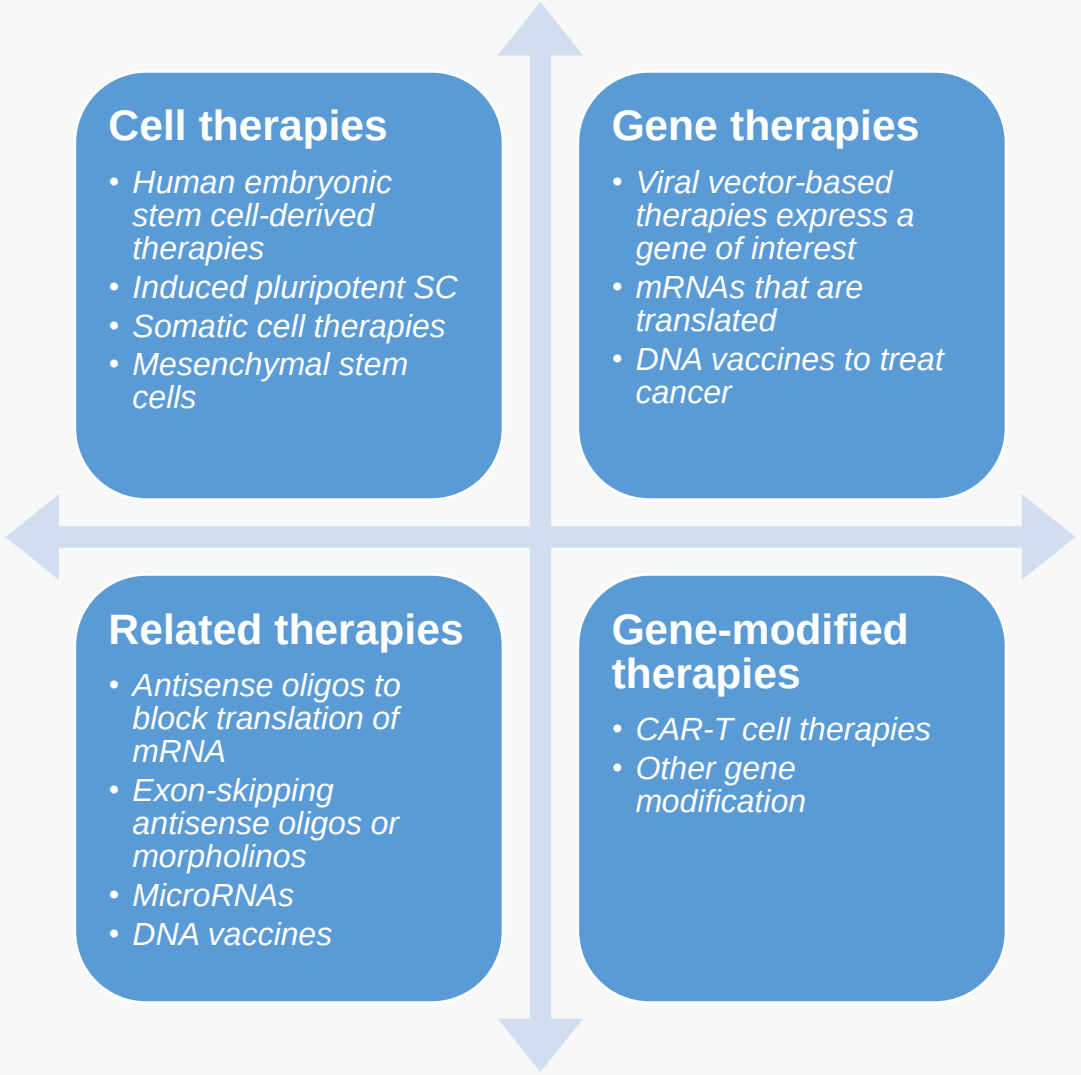
Opportunities

- *R&D in other ASEAN countries is gaining momentum in recent years, with **Thailand and Malaysia** being the more prominent examples. With various governments investing in developing R&D capacities, ASEAN countries have significant potential of becoming reliable local partners for multinationals.*

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

Stage 1: Drug Research and Discovery —— Advanced Therapy Products

Singapore and Thailand are leading in ASEAN



Singapore:

There have been notable development in cell-gene and immunotherapy areas in the last 5-10 years. The launch of the new national clinical GMP facility as part of ACTRIS **- Advanced Cell Therapy and Research Institute Singapore** will further accelerate cell therapy development in Singapore by providing end to end process development and clinical manufacturing infrastructure and capabilities.

CAR-T trials have been conducted in the hematological indications of leukemia and lymphoma in the large academic centers, including National Cancer Centre Singapore, Singapore General Hospital, KK Women's and Children's Hospital and National University Health System, Singapore.

Currently, there are 2 CTGTPs (Cell, tissue and gene therapy products) registered in Singapore by HSA**: KYMRIAH® and LUXTURNA®**

Thailand:

The Excellence Center for Advanced Therapy Medicinal Products (EC-ATMPs), under the King Chulalongkorn Memorial Hospital was established in 2018. It aims to develop and innovate advanced therapy medicinal products and provide training and promote regenerative medicine & tissue engineering education.

GMP cell and gene production unit (CPU) has been established in Thailand Science Park, Pathum Thani, which serves as high quality facility for R&D and clinical trial products and can also cope with the expansion of the prototype to commercial both for cell and gene therapy products.

Source: Thailand Excellence Center for Advanced Therapy Medicinal Products, https://chulalongkornhospital.go.th/kcmh/en/ec/excellence-center-for-advanced-therapy-medicinal-products/ ; Advanced Cell Therapy and Research Institute Singapore, https://www.actris.sg/about-us/

Stage 2&3: Conducting Clinical Trials in ASEAN

Key strengths of ASEAN as a place for conducting clinical trials

Investigational New Drug Application (IND)

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

General advantages:

Faster patient recruitment (compared with the U.S.)

- **A large patient pool**, low penetration rate and a disease landscape similar with the West
- Limited governmental security or insurance reimbursement stimulates greater motivation to participate

Favorable regulations and regional collaborations:

- Cross regional acceptance of ASEAN Common Technical Dossier (ACTD) for regulation harmonization and ICH E17 for supporting the use of multi-regional clinical trials (MRCTs)
- Singapore Clinical Research Institute (SCRI) is an **ASEAN hub** for clinical research excellence, leading more than 15 clinical research networks of different diseases, including cancer, ophthalmology, pediatrics and internal medicine. More information can be found on https://www.scri.edu.sg/

Selected Countries' highlights:

A cost-saving clinical trial market (**Thailand** as an example)

- Up **to 50%** trial costs could be saved in Thailand when as compared to US or Europe: Investigator and site fees for providing trial-related medication and investigations are 50% cheaper. Hospitalization costs are a third of that in the US or Europe. Domestic travel costs and support services are also less expensive.

High-level human resource with strong IP protection and legal environment: (**Singapore** as an example)

- Abundant high-level talent resource with recognized clinical research quality
- Strong principle investigator (PI) expertise and well-developed specialized disease centers
- Strong IP protection with lower legal liability compared to the U.S.

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	Completed application without queries can be approved within 30 working days.	The purported timeline is 60 days for the whole process	Clinical Trial Certificate (CTC) and Clinical Trial Authorization (CTA): 30 working days; 60 days for cell and tissue products.	IRB: institute EC 2-3 months/ Central EC CREF 5-6 months EC-MOPH 7-8 months	Registering clinical trial: 70 working days in total. Approving clinical trial: 30 days after receipt of eligible application, ASTT submits to MOH Minister for approval

** For detailed timeline of IND application, please refer to APAC PMRE Regulatory 2022 published by APAC PMRE working group.*
Source: Frost & Sullivan, APAC Analysis Report ver.2021; clinicalleader.com; ASK Health Analysis

Stage 2&3: Conducting Clinical Trials in ASEAN——Advanced Therapy Products

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

Singapore HSA regulations for clinical trials

Product type	Key regulation	Submission route	Key regulations for CRM (clinical research materials)	licensing requirements for CTGTP import, wholesale and manufacture
Class 1 CTGTPs*	*Human Biomedical Research Act*	Not regulated by HSA		The regulatory control of a manufacturer, importer or wholesaler is dependent on the **degree of manipulation** of the CTGTP which they are dealing in.
Class 2 CTGTPs	*Health Products Act and Health Products (Clinical Trials) Regulations*	Clinical Trial Authorization **(CTA)** or Clinical Trial Notification **(CTN)**	Health Products (Clinical Research Materials) Regulations	

New Clinical Trial Authorization (CTA) or Clinical Trial Notification (CTN) submission for CTGTPs

	CTA	CTN
When does it apply	A trial investigating one or more locally unregistered therapeutic products or Class 2 CTGTPs, or unapproved use of a locally registered product.	A trial of locally registered therapeutic products or Class 2 CTGTPs used in accordance with their local approved labels.
Turn-around-time	**30 working days, or 15 working days for Phase 1 trials solely to evaluate bioequivalence**, bioavailability, food effect or drug-drug interactions. **60 working days** for Class 2 CTGTP trials.	**5 working days**

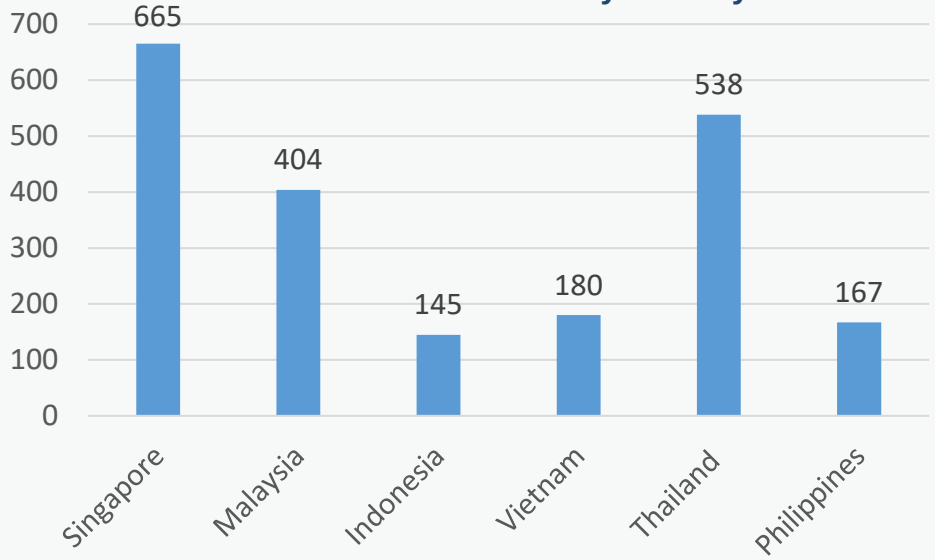
** HSA's classification of class 1 and 2 CTGTPs on https://www.hsa.gov.sg/ctgtp/regulatory-overview*
Source: Frost & Sullivan, APAC Analysis Report ver.2021; clinicalleader.com; ASK Health Analysis

Stage 2&3: Conducting Clinical Trial in ASEAN

Singapore and Thailand are in leading places

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

Number of Clinical Trials By Country*



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.

Number of Clinical Trials By Phase

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.*

** The number variates as the trial status changes. The data present here comes from a search in March 2022, with search tags of: "recruiting", "enrolling by invitation", "active, nor recruiting".*
Source: Clinical trial.gov; ASK Health Analysis.

Stage 4: Manufacturing - About Good Manufacturing Practice (GMP)

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

GMP is a vital component of Quality Assurance to ensure that therapeutic products are consistently produced with the quality standards appropriate for their intended use. All manufacturers, including assemblers of therapeutic products intended for ASEAN countries, are required to conform to the GMP standard.

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), comprising 54 authorities, is an international scheme aiming at harmonizing inspection of manufacturing facilities. In ASEAN, **Indonesia, Malaysia, Thailand and Singapore** are members of PIC/S. They benefit by avoiding duplication of GMP inspections within these countries, which facilitates quick trade for medicinal product across this region.

The ASEAN Sectoral MRA on GMP Inspection of Manufacturers of Medicinal Products is an agreement signed by the Economic Ministers of **10 ASEAN countries**, which aims to facilitate the movement of medicinal product in ASEAN through the mutual exchange and recognition of GMP inspection reports and certificates. The scope of the MRA is restricted only to medicinal products in finished dosage forms for human use. The scope may be extended to include biologics at a later stage.

Overseas manufacturers who intend to register therapeutic products in a PIC/S member state may be subjected to a GMP conformity assessment by the relevant regulatory authorities of the member state.

Overseas manufacturers that have been previously audited and found to conform to Good Manufacturing Practice (GMP) standards by at least one PIC/S member authority

These manufacturers may submit GMP evidence such as a valid GMP certificate, for evaluation. An on-site GMP audit is NOT required if the submitted evidence is found to be acceptable. However, the PIC/s member authority reserves the right to conduct an on-site audit of an overseas manufacturing site, where necessary.

Overseas manufacturers that have NOT been previously audited and found to conform to GMP standards by at least one PICS/S member authority will be subjected to an on-site audit by GMP auditors to assess their compliance to the PIC/S Guide to GMP for Medicinal Products

An application to request for an overseas audit has to be filed together with the submission of a Quality System Dossier, which is a set of documents and information that provides a comprehensive overview of the manufacturing site, site facilities, quality system of the manufacturing operations.

Source: PIC/S Website, https://picscheme.org/en/about; Health Sciences Authority (HSA), Singapore; The ASEAN Secretariat, Frequently Asked Questions on the ASEAN Mutual Recognition Arrangement (MRA) on GMP Inspection of Manufacturers of Medical Products

Stage 4: Manufacturing

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

Singapore

Policy/ Incentives
Biopharmaceutical manufacturing research programs have been set up by A*STAR to sustain this industry through activities such as generation of novel cell lines and biomolecules and cell therapy manufacturing R&D. Pharma Innovation Program Singapore (PIPS) for small molecule drug manufacturing is under way to include manufacturing of biologics (BioPIPS).

Manufacturing Infrastructure
With 9 leading biopharmaceutical companies already established manufacturing operations, Singapore is home to more than 60 pharmaceutical and MedTech manufacturing plants hiring 24000 employees. Biologics is key to Singapore's manufacturing industry Vision 2030. The Tuas Biomedical Park has attracted global pharmaceutical companies by providing high standard infrastructure, talents, and third-party services.

Malaysia

Policy/ Incentives
Following the crisis of COVID-19, the government looks to support local manufacturers and encourage foreign investment in pharmaceutical manufacturing with tax incentives.

Manufacturing Infrastructure
Manufacturers of biological drugs include **Alpha Biologics Sdn Bhd, Pharmaniaga** and **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.

Thailand

Policy/ Incentives
The Thai government aims to attract foreign firms and enhance the competitiveness of the local drug sector. Companies engaged in the manufacturing of pharmaceutical products and APIs are eligible for tax holidays and non-tax benefits.

Manufacturing Infrastructure
Manufacturers include The Government Pharmaceutical Organization **(GPO)**; **Thai Red Cross** -Vaccines and blood products; **Siam Bioscience** - biosimilar drugs; **Austrianova**-cell therapy; **TCELS CPU**-gene therapy products, etc.

Indonesia

Policy/ Incentives
The government has taken Steps to develop local manufacturing capacity for medicines, as well as attracting foreign investment. Foreign investors are permitted to own up to 100% of pharmaceutical businesses.

Manufacturing Infrastructure
There are more than 210 pharmaceutical companies in Indonesia, of which 70% are domestic, mostly producing essential drugs:
Kalbe Farma in 2016 established the country's first biotechnology-based drugs facility;
PT Bio Farma is a State Owned Enterprise with good vaccines and biologics drug substance and drug product capacities;
PT Etana Biotechnologies Indonesia is a producer of biopharmaceuticals.

Philippines

Policy/ Incentives
Under the Corporate Income Tax and Incentives Rationalization Act (CITIRA), government offers up to 50% deduction for reinvesting profits in the manufacturing industry. In 2021, the government approved the expansion of the Bulacan Industrial City where a new pharmaceutical manufacturing zone is set to rise.

Manufacturing Infrastructure
14 of the world's top 20 pharma companies, including the UK's GSK, currently operate manufacturing facilities here, 40 out of 61 licensed pharmaceutical manufacturers are GMP certified.

Vietnam

Policy/ Incentives
Vietnam's "National Master Plan for the Vietnamese Pharmaceutical Industry Development to 2020 with a Vision to 2030" aims to build production capabilities for vaccines and biological products for epidemic prevention.

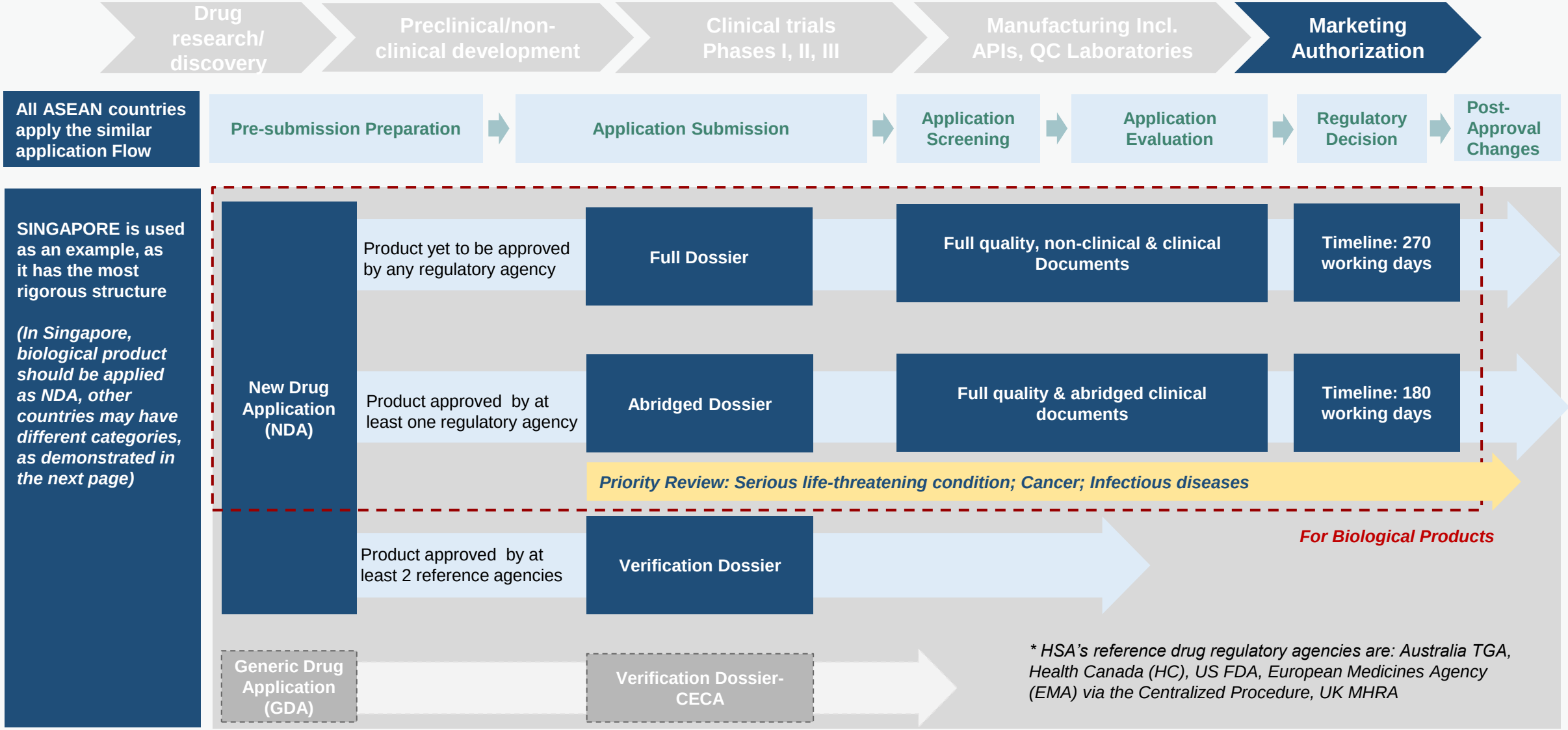
Manufacturing Infrastructure
180 pharmaceutical manufacturers has more than 220 manufacturing units achieving GMP certificates.
Major producer of biologics include **Institute of Vaccines and Medical Biologicals** under the Ministry of Health and three other manufacturers.

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 growing capacity. While higher in cost, Singapore offers high quality manufacturing capability.*
Challenges: *With the exception of Singapore, the lack of comprehensive industry ecosystems in most of the ASEAN countries may be a hurdle for foreign companies to establish manufacturing facilities.*

*Source: EDB; A*STAR, ASEAN Briefing; THAILAND PHARMA MARKET & REGULATORY REPORT; Association of Southeast Asian Nations: Investing in ASEAN 2021I2022; 2020 KPMG Report: Value of Innovation; ASK Health Analysis*

Stage 5: Marketing Authorization (Drug Registration)

General processes



Source: Health Science Authority (HSA), Singapore

Stage 5: Marketing Authorization (Drug Registration)——Advanced Therapy Products

Registration pathways for class 2 CGTPs

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

Pre-submission Preparation → Application Submission → Application Screening → Application Evaluation → Regulatory Decision → Post-Approval Changes

	Singapore	Malaysia
Regulating agency	HSA	NPRA
Categorization model (risk-based approach)	Class 1/**Class 2 CTGTPs**	Class Ⅰ/**Class Ⅱ CGTPs**
Latest regulation	*Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021*	*Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia*
Fast-track regulations	• Conditional registration with post-approval commitments • The import and supply of unregistered Class 2 CTGTP through **Special Access Route**	Conditional approval and/or priority review
Abridged evaluation timeline	**50 days (screening) +180 days (evaluation)**	**120 days (evaluation)**
Inspection	GMP+GDP (good distribution practice)	GMP+GDP

Source: Health Science Authority (HSA), Singapore; NPRA, Malaysia

Stage 5: Marketing Authorization

Countries differ in application protocol, timeline, and other requirements

Item	Content	Indonesia	Malaysia	Philippines
Regulatory Agency		National Agency of Drug and Food Control	National Pharma Control Bureau	Bureau of Food and Drugs
NDA	Acceptance of CTD format	ACTD format and ICH-CTD format are both acceptable	ACTD format: the online product registration application is based on ACTD format.	ACTD or ICH-CTD
	Timeline	300 working days for New Drug, Biological Product, major variation (new indication/ posology)	Biological products : 254 days	New Chemical Entities for Biologicals, Vaccines (except cancer drugs) -180 working days; 240 for cancer drugs
	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.	Overseas clinical trial data is acceptable.
	Requirement of domestic clinical data for NDA application, if there is foreign data	Not necessary, unless for TB program and for family planning program	Not necessary	No necessary
	Requirement of CPP Certificates of Pharmaceutical Product	Yes, reference countries include: EU, US, Australia, Canada, England & Japan. Applicant can choose 1 country as reference and submit one CPP	Yes: CPP from the competent authority in the country of origin	Yes, one CPP is required to be submitted from the source or any reference country.
	Other requirements	-Specific country requirement on product labeling on product package; -GMP certificate and Manufacturing license are required for non registered overseas factories	Other requirements are as noted in the Drug Registration Guidance Documented DRGD issued by NPRD of Malaysia	-Reference Standard Sample (at least 300 mg) subject to FDA advise. -Compliance to foreign GMP requirements (from FDA) for foreign manufacturing site
	Priority Review System	-Reliance system with 120 working days, refer to BPOM regulation No. 15 Year 2019 -Refer to BPOM regulation No. 27 year 2020 on 2nd amendment to Regulation of HEAD BOPM No. 24 (Emergency Use Authorization)	-Products intended for Unmet medical needs; life-saving with no treatment locally available; treatment/prevention in pandemic situation; emergency supply; - Product which is the first *generic/ biosimilar product, or the first locally manufactured generic/biosimilar product.	-Products manufactured exclusively for export -New drug products considered to be a major therapeutic advance -First 5 products of newly-licensed establishments -Government projects -Imported pre-qualified vaccines
Post-Market Approval	Risk Management Plan (RMP)	RMP Requirement will be included in the Pharmacovigilance Guideline under revision by BPOM	RMP required for New Drug Products/Biologics, and in certain cases, new indications	Required. No local format, but Philippines FDA recommends compliance with EU format

Source: Association APAC: Pharmaceutical Market Regulatory Environment in Asia 2021 (APAC PMRE) Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies

Stage 5: Marketing Authorization

Countries differ in application protocol, timeline, and other requirements

Item	Content	Singapore	Thailand	Vietnam
Regulatory Agency		Health Science Authority (HSA)	Thai FDA	Drug Administration Vietnam(DAV)
NDA	Acceptance of CTD format	ACTD or ICH-CTD	eCTD for NCE & New Biologics/Vaccines; eCTD or hard copy and either ACTD or CTD format for other products	ACTD and ICH-CTD format
	Timeline	Screening: 50 working days Evaluation: Full dossier: 270 working days Abridged: 180 working days Verification: 60 working days	Timeframe for approval: New Biological products – 220 working days Vaccine - 280 working days Biosimilar: 230	Within 12 months
	Approval can be obtained by utilizing foreign clinical trial data	Overseas clinical trial data is acceptable.	Yes	Yes, the clinical data included in clinical documents must be in line with guidelines of ICH, Vietnam Ministry of Health or other organizations recognized by Vietnam
	Requirement of domestic clinical data for NDA application, if there is foreign data	Not necessary	Not necessary.	Not necessary
	Requirement of CPP Certificates of Pharmaceutical Product	Submission of CPP is not compulsory as a form of proof of approval. The form of proof of approval must come in the form of an official approval letter or equivalent document	Yes, 1 CPP from manufacturing country. The product details has to be supplemented with the CPP	Yes, 1 CPP issued by the competent authority of the manufacturing country AND 1 CPP issued by one of the reference authorities or Stringent Regulatory Authorities (SRA)
	Other requirements	Singapore-Specific Annex is required for submission of risk management plan in support of NDA applications	n/a	Site master file, Labeling, Package Insert, COA for Drug Substance and Drug Product, Trademark.
	Priority Review System	Priority review system or pathway is only applicable to 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, anti-cancer or product in need as per endorsed from Thai FDA. Abridged Evaluation (not all are priority review): effective from 1 Oct 2015 by referring to the approval & evaluation from one of the reference agencies.	-Orphan drug; -Drugs to support emergency requirements -Drugs produced domestically on new GMP-conforming manufacturing lines -Vaccines prequalified by WHO -Special therapeutic drugs with special dosage form to which there are no more than two similar drugs
Post-Market Approval	Risk Management Plan (RMP)	All new drug applications type 1 (NDA-1) and biosimilar product must submit RMP	Guideline on RMP for biological product list announced by FDA for NDA	Not mandatory

Source: Association APAC: Pharmaceutical Market Regulatory Environment in Asia 2021 (APAC PMRE) Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies

Stage 5: Marketing Authorization

ASEAN countries have more divergence than similarities

Similarities

Application Type

NDA for Biological product, biosimilars are not considered generic drugs.

ACTD/CTD Acceptability

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

Fast-track approval

All countries have established formal or informal priority approval systems or abridged evaluation systems, though with different qualification requirement for priority approval.

Clinical Trial Data

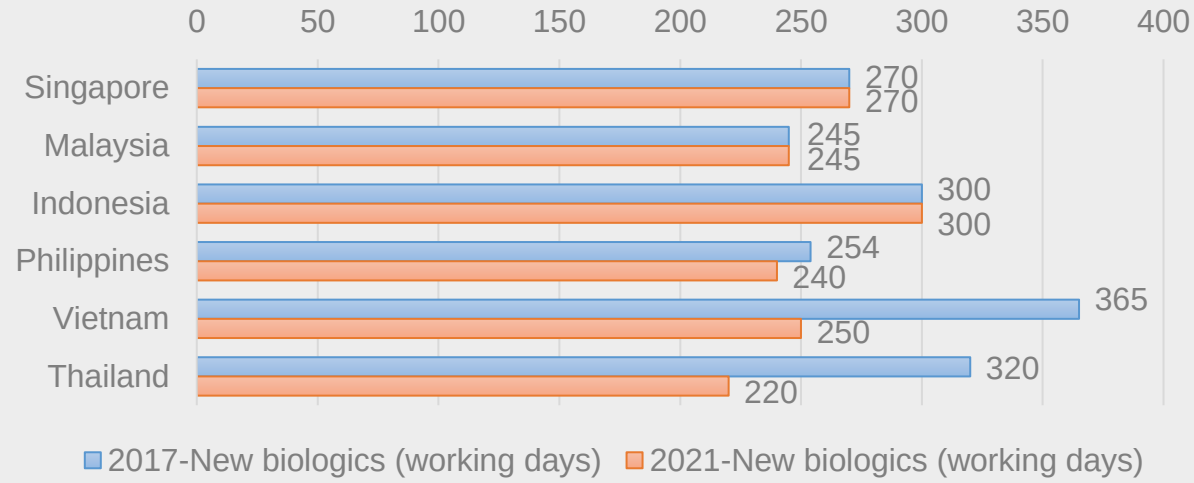
For NDA, all countries accept foreign clinical data in the drug registration process; generally speaking, foreign biomedicines are not required to submit local clinical data.

Certificate of Pharmaceutical Products (CPPs)

For product registration, CPPs from country of origin is generally required in WHO format with samples and labels.

Divergence

NDA Approval Review Time



Product Labelling

Product labels in English are acceptable only in Singapore.
Product labels in English and local languages are accepted in Malaysia and the Philippines.
For Indonesia and Thailand and Vietnam, product labels must be accompanied with their local languages.

Additional requirements

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

Source: Association APAC: Pharmaceutical Market Regulatory Environment in Asia 2021 (APAC PMRE) Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies; The Regulatory Affairs Professionals Society, The Drug Regulatory Landscape in the ASEAN Region (2018)

Regional Harmonization on Pharmaceutical Regulation

Harmonization efforts in the region

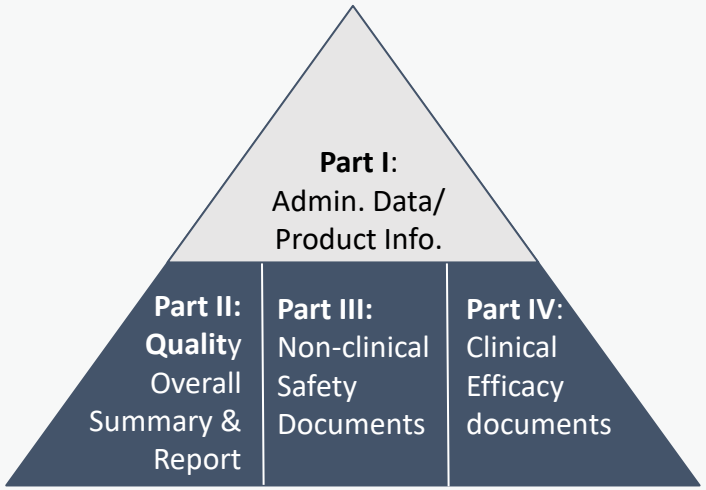
Background

ASEAN Free Trade Area (AFTA)

- A collective effort by ASEAN to reduce or 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, with an objective to have regional guidelines along with synchronization with ICH guidelines



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.
- 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

Source: https://asean.org/book/asean-common-technical-dossier/

Regional Harmonization on Pharmaceutical Regulation

Regional harmonization programs that have achieved partial results

Project Orbis

As an initiative of the FDA Oncology Center of Excellence (OCE), It 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 (HC)**, **Singapore's Health Sciences Authority (HSA)**, **Switzerland's Swissmedic, Brazil's National Health Surveillance Agency (ANVISA), Israel Ministry of Health (MOH) Pharmaceutical Administration and United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA).**
- 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. So far, **22** drugs have been approved.

APEC Life Sciences Innovation Forum — Regulatory Harmonization Steering Committee (RHSC)

Established by APEC Leaders in 2002, the **Life Sciences Innovation Forum (LSIF)** has since grown to become APEC's leading initiative on health and health sciences innovation.

The Regulatory Harmonization Steering Committee (RHSC) was formed in June 2009 under the auspices of the APEC LSIF to promote a strategic approach to regulatory harmonization by undertaking activities of greatest value to regulatory authorities and regulated industries. It is a network of regulatory experts from regulatory agencies in APEC economies, industry and academia with the vision of achieving **greater regulatory convergence** within the APEC economies by 2020.

The RHSC identifies **Priority Work Areas (PWA)** in the medical product sectors of pharmaceuticals (advanced therapy products and biotherapeutic products, e.g.) and medical devices where member economies believe would benefit from regulatory convergence. **Training Centers of Excellence for Regulatory Science (CoE)** are then commissioned by the RHSC to meet the training needs of member economies in the Priority Work Areas.

Source: US FDA, Duke-NUS CoRE； Health Science Authority (HSA), Singapore; https://www.apec.org/rhsc/rhsc-priority-work-areas

Regional Harmonization on Pharmaceutical Regulation

Regional harmonization programs that have achieved partial results

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)

ICH, founded in 1990, is an initiative that brings together **regulatory authorities and pharmaceutical industry** to discuss scientific and technical aspects of pharmaceutical product development and registration. **China** became regulatory member of ICH in 2017.

The mission of the ICH is to promote public health by achieving greater harmonization through the development of **technical Guidelines and requirements for pharmaceutical product registration.**

Members in ASEAN: **HSA, Singapore,**
Observers in ASEAN: **Indonesian FDA, Indonesia; NPRA, Malaysia**

The Pharmaceutical Inspection Co-operation Scheme （PIC/S)

PIC/S was established in 1995 as an extension to the Pharmaceutical Inspection Convention (PIC) of 1970. It is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. It is open to any Authority having a comparable GMP inspection system. PIC/S presently comprises **54 Participating Authorities** coming from all over the world (Europe, Africa, America, Asia and Australasia)

- PIC/S aims at **harmonizing** inspection procedures worldwide by developing common standards in the field of **GMP** and by providing training opportunities to inspectors
- PIC/S also aims at facilitating co-operation and networking between competent authorities, regional and international organizations, thus increasing mutual confidence
- These objectives are to be achieved by developing and promoting harmonized GMP standards and guidance documents; training competent authorities, in particular Inspectors; assessing (and reassessing) inspectorates and facilitating the co-operation and networking for competent authorities and international organizations.

Source: US FDA; Health Science Authority (HSA); Singapore; PIC/S website: https://picscheme.org/en/about

Regional Harmonization on Pharmaceutical Regulation

Regional harmonization programs that have achieved partial results

ASEAN Pharmaceutical Regulatory Framework (APRF) and ASEAN Pharmaceutical Regulatory Policy (APRP)

It has been recognized that in order to provide a structure and instruments to realize the free flow of safe, efficacious and quality pharmaceuticals in the region, as well as to facilitate access to needed pharmaceuticals and eliminate substandard and falsified products, adopting a common **APRP** is very important. In October 2021, Members of the Pharmaceutical Product Working Group (PPWG) and the ASEAN Health Cluster 3 (AHC 3) successfully concluded the deliberation of **APRP,** which is now under review by senior officials in the Economic and Health sectors preceding a formal adoption by ASEAN Member States.

The **APRF** elaborates on the governance, management structure, recognition, cooperation and coordination mechanisms that have to be developed to realize the targets of an integrated market. In December 2021, the two ASEAN bodies have agreed that the draft document is now sufficiently developed to permit a final domestic consultation and pave the way for formal adoption.

Duke-NUS CoRE: Centre of Regulatory Excellence

CoRE is the first dedicated Asian Centre targeted at meeting 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);
- aligning understanding and implementation of technical requirements and processes, and normalizing the baseline competency to facilitate convergence and regulatory cooperation through training and education;
- providing a platform to train regulatory professionals and bringing stakeholders together as a neutral entity;
- serving as an entry point for other global stakeholders to reach out to ASEAN regulatory environment e.g. DFAT RSP, WHO, DIA.

Source: Duke-NUS CoRE; https://ariseplus.asean.org/aprf-dec/

Section Summary: From Drug Discovery to Market Authorization

Drug Research and Discovery	Clinical Trials	Manufacturing Incl. APIs, QC Laboratories	Marketing Authorization	Regional Regulatory Harmonization
• Singapore is acknowledged as the front-runner of biological R&D, including advanced therapies. • Other ASEAN countries, especially Malaysia and Thailand, are continuously improving their capacities in drug research and discovery.	• ASEAN has a large, treatment-naive patient pool. • Regional clinical research networks have been established to enhance cooperation and facilitate patient recruitment.	• Singapore is leading the high-end pharmaceutical manufacturing in ASEAN, especially for biologics including advanced therapy. • Other countries like Malaysia, Indonesia and Thailand are gearing up to enhance manufacturing capacities.	• Regulations are being streamlined and reviewed to create a favorable environment for new drugs. • As the only ASEAN country that has joined ICH, Project Orbis, and PIC/S, Singapore serves as a bridge between global leading pharmaceutical players and the ASEAN market.	• More regional cooperation and regulatory harmonization mechanisms are emerging in ASEAN. • ASEAN has a partially harmonized manufacturing regulatory framework.

Content

- ASEAN on the rise: booming market with significant potential
- From drug discovery to market authorization: solidifying infrastructure and improving regulatory environment
- **Case studies of Chinese biopharmaceutical companies' expansion in ASEAN**

Chinese Biopharmaceutical Companies' expansion in the ASEAN region

The ASEAN region is becoming an emerging overseas destination for Chinese biopharmaceutical companies because of its diverse characteristics and unique advantages. They have adopted various development strategies to leverage the resources and advantages of the ASEAN region.

Several Chinese biopharmaceutical companies have registered their products in ASEAN countries and started the commercialization process through:

- Licensing-out to local partners – Innovent
- Building capacity to operate locally - Everest Medicines

Chinese biopharmaceutical companies are also making strategic moves in ASEAN through:

- Collaborating with local research institutions for drug development - Everest Medicines
- Conducting clinical trials - CANbridge Pharmaceutical and SINOVAC
- Establishing manufacturing facilities - GenScript
- Establishing a joint venture to enhance pharmaceutical products' international market access - Sinopharm

"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 Lead of a MNC Biopharmaceutical Company

Case Study

Licensing-out to pharmaceutical companies with presence in ASEAN

Overview

Currently, a number of Chinese biopharmaceutical companies have chosen to license out their pipelines or commercialized products to MNC or local companies in the ASEAN region.

Case Study: Innovent

Innovent (stock code 01803.HK） is a leading biopharmaceutical company in China with the mission is to develop, manufacture and commercialize high-quality innovative medicines for the treatment of cancer and other major diseases. Since its inception, Innovent has developed a fully-integrated multi-functional platform, which includes R&D, CMC (Chemistry, Manufacturing, and Controls), clinical development and commercialization capabilities. Leveraging the platform, the company has built a robust pipeline of 32 valuable assets in the fields of cancer, metabolic, autoimmune diseases and other major therapeutic areas, with 7 products, TYVYT® (sintilimab injection), BYVASDA® (bevacizumab injection), SULINNO® (adalimumab injection), HALPRYZA® (rituximab injection) officially approved for marketing in China.

Licensing-out to an ASEAN local partner

In January 2021, Innovent entered into an agreement with PT Etana Biotechnologies Indonesia (Etana) to out-license BYVASDA® (Bevacizumab Biosimilar)'s development and commercialization rights in Indonesia to Etana. Etana is committed to launch BYVASDA® in the local market. In return, Innovent will receive milestones for development and commercialization as well as double-digit royalties on net sales. Following BYVASDA® (Bevacizumab Biosimilar)'s breaking into the North America market in 2020, this collaboration will enable BYVASDA® to penetrate into a Southeast Asian market quickly and marked another solid step toward getting Innovent's innovative portfolio into the global market. On June 14, 2022, the licensed product Bevagen® (bevacizumab biosimilar) has been approved by the Indonesian Food and Drugs Authority (BPOM) for five indications.

In September 2021, Etana closed **a new round of financing**, by Legend Capital along with **Innovent** and a consortium led by UOB Venture Management (UOBVM). The funds will be used to further strengthen the company's production, registration, clinical and commercialization capabilities, promote the company's extensive and in-depth cooperation with biopharmaceutical companies, and lead the development of the Indonesian biopharmaceutical industry.

Source: Innovent website

Case Study

Building local capacity - new drug registration in the ASEAN region

Overview

Apart from licensing-out, some Chinese biopharmaceutical companies have established local operations in ASEAN to conduct drug registration and prepare for commercialization.

Case Study: Everest Medicines

Everest Medicines is a biopharmaceutical company focused on developing and commercializing transformative pharmaceutical products that address critical unmet medical needs for patients in Asian markets. Everest Medicines has built a portfolio of eleven potentially global first-in-class or best-in-class molecules, many of which are in late-stage clinical development. The Company's therapeutic areas of interest include oncology, autoimmune disorders, cardio-renal diseases and infectious diseases.

In January 2021, Everest Medicines initiated the submission of a New Drug Application (NDA) to HSA for sacituzumab govitecan-hziy (Trodelvy®) for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. In February 2022, the company received approved Trodelvy®(sacituzumab govitecan or SG) for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease. This marks the first drug approval of Trodelvy received by Everest. The Company expects a series of approvals for Trodelvy in its license territories in the coming year.

In addition to Singapore, Everest is closely coordinating with regulatory bodies in Greater China and South Korea to review its applications for Trodelvy for adult patients with unresectable locally advanced or metastatic TNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease.

Everest Medicine is building a robust commercial presence in Asia Pacific markets. The company is well-positioned to accelerate quickly during the next phase of growth with an established commercial team, bridging the gap between patients with unmet medical needs and first-in-class biopharmaceutical innovation.

Source: Everest Medicines website

Case Study

Collaborating with local research institutions for drug development

Overview

At earlier stage of drug R&D, some Chinese players are making the strategic move of collaborating with local research institutions in ASEAN to develop innovative products.

Case Study: Everest Medicine

Everest Medicine ("Everest") and Singapore's Experimental Drug Development Centre ("EDDC") reached a global licensing agreement in January 2022, under which Everest will obtain exclusive worldwide rights to develop, manufacture and commercialize EDDC's series of viral 3C-like ("3CL") protease inhibitors as potentially best-in-class COVID-19 oral antiviral treatments.

"This is a prime example of the innovative risk-sharing relationship Everest is bringing about globally. We intend to bring the drug candidate quickly and efficiently through clinical trials, in order to deliver this novel oral antiviral treatment to patients during this time of limited therapeutic options" said Kerry Blanchard, MD, PhD, Chief Executive Officer of Everest Medicines

Under the terms of the agreement, Everest will obtain exclusive global rights to EDDC's series of 3CL protease inhibitors that have demonstrated potent in-vitro activity against SAR-CoV-2 (the virus that causes COVID-19) and its variants, as well as other coronaviruses such as MERS. Everest has full rights to sub-license the drug further and will receive full technology transfer. The lead compound is EDDC-2214, a novel and potent SARS-CoV-2 3CL protease inhibitor, which Everest will develop as an oral antiviral COVID-19 therapy. The main protease in SARS-CoV-2 is the 3CL protease. Compared to several other oral COVID-19 antivirals, EDDC-2214 exhibits better in-vitro potency and pre-clinical oral bioavailability. Clinical trials evaluating EDDC-2214 are expected to begin later this year.

EDDC is Singapore's national platform for drug discovery and development. EDDC aims to develop therapeutics and diagnostics that save and improve the lives of patients in Singapore, Asia and around the world. EDDC works collaboratively with public sector and industry partners to translate the great science arising from Singapore's biomedical and clinical sciences R&D into innovative healthcare solutions.

*Source: A*STAR Website*

Case Study

Conducting clinical trials in ASEAN countries

Overview

Chinese-origin biopharmaceutical companies are conducting both early stage and Phase III clinical trials in ASEAN.

Conduct early stage clinical trial in Singapore

Case Study：CANbridge Pharmaceutical

CANbridge Pharmaceuticals, Inc. (“CANbridge,” stock code 1228.HK) is a China-based global biopharmaceutical company committed to the research, development and commercialization of transformative rare disease and rare oncology therapies.

CANbridge was granted an IND by Singapore’s HSA in December 2020, on the Phase I safety trial of CAN106, a novel, long-acting, anti-C5 complement recombinant human monoclonal antibody. In February 2022, CANbridge announced top-line results from the Phase I single ascending dose (SAD) study of CAN106 in 31 healthy volunteers in Singapore. CAN106 was shown to be safe and well-tolerated with dose-dependent and linear pharmacokinetic exposure. The data also showed that free C5 and CH50 could be effectively inhibited. The clinical trial was conducted in the National University Hospital Singapore.

Based on the Singapore trial result, CANbridge designed the Phase Ib/II clinical trial for CAN106, which has been approved by China National Medical Products Administration. The trials have been commenced in patients with paroxysmal nocturnal hemoglobinuria (PNH).

Conduct phase III clinical trial in Indonesia

Case Study: Sinovac

Sinovac Biotech Ltd. (NASDAQ: SVA) (“Sinovac”), is a China-based biopharmaceutical company that focuses on the research, development, manufacturing and commercialization of vaccines that protect against human infectious diseases.

Sinovac conducted phase III clinical trials in Brazil, Turkey, **Indonesia**, and Chile for the vaccine against COVID-19, CoronaVac. The trial in Indonesia started in August 2020 was led by Padjajaran University (Unpad) Medical School professor Kusnandi Rusmil. Six locations chosen for the trials include Unpad Pendidikan Hospital, an Unpad campus, and four community health centers. In January 2021, Indonesia’s food and drug agency, BPOM, granted emergency use authorization to Sinovac’s vaccine against COVID-19 based on the interim data from the phase III trial in this country.

Sinovac has also signed agreements with Indonesia based PT Bio Farma for the supply, local production and technology licensing in respect of Sinovac’s inactivated vaccine candidate against COVID-19.

Source: CANbridge website; Sinovac website; Reuters; ASK Health analysis

Case Study

Establishing manufacturing facilities in ASEAN countries

Overview

Increasing interests have been observed among biopharmaceutical companies and CDMOs in establishing manufacturing facilities in the region, to support their business expansion to ASEAN countries and beyond.

Case Study: GenScript

GenScript Biotech Corporation (stock code 1548.HK) is the world's leading technology and service provider of life science R&D and manufacture. Built upon its solid gene synthesis technology, GenScript Biotech is divided into four major platforms including the life science service and product platform, the biologics contract development and manufacturing organization (CDMO) platform, the global cell therapy platform and the industrial synthesis biological product platform. GenScript Biotech's business operations span over 140 countries and regions worldwide with legal entities located in the US, Mainland China, Hong Kong, Japan, Singapore, the Netherlands and Ireland. GenScript Biotech provides premium, convenient and reliable services and products for over 180,000 customers.

Established a State-Of-Art Manufacturing Facility in Singapore to Strengthen Manufacturing Capability

GenScript opened a more than 30,000-square-feet facility for highly automated protein and gene preparation services in February 2022. The state-of-the-art site marks a significant expansion of the company's advanced protein and gene platforms, and is designed to provide high quality, fast-turnaround on products required for new vaccines and therapeutics development and innovations in life sciences. Supported by the Singapore's Economic Development Board (EDB), the new production site will support the Asia Pacific region and complements the current production sites in the United States and China.

"Singapore the home to GenScript's Asia Pacific headquarters, it is also a strategic location for us to expand our manufacturing capability to support the fast growing biotechnology industry. With the strong support from EDB, our new facility aims to be the center of a solid regional network to catalyze more collaboration, ultimately spurring more innovation and breakthrough life science. This demonstrated GenScript's commitment to build and develop the world leading enabling platform in serving science," said Dr. Ray Chen, President of Life Science Group, GenScript Biotech Corporation.

Source: GenScript website

Case Study

Establishing a joint venture (JV) in ASEAN to enhance pharmaceutical products' international market access

Overview

Early movers have also established JVs with other multinational players to enhance the international market access of their pharmaceutical products.

Case Study: China National Pharmaceutical Group corporation

China National Pharmaceutical Group Co., Ltd. ("Sinopharm") is a large healthcare group with a full chain in the industry covering R&D, manufacturing, logistics and distribution, retail chains, healthcare, engineering services, exhibitions and conferences, international business and financial services. China National Biotec Group (CNBG), a subsidiary of Sinopharm and the 6th largest vaccine manufacturer in the world, focuses on producing over 50 different human vaccines totaling 7 billion doses a year.

In November 2021, CNBG and Pasaca Capital Inc, the private equity firm that owns one of the worlds largest COVID-19 test providers, Innova Medical Group, Inc., announced the establishment of a global joint venture - Sino-Innovax Biotech Pte Ltd. The joint venture is based in **Singapore** with a focus on providing critical vaccines to the world population, including the highly sought-after World Health Organization ("WHO") approved COVID-19 vaccines. The joint venture will enable expanded access to much needed quality vaccines to those in less developed areas where cold supply chain is not available. The joint venture will initially focus on the manufacturing and global distribution of Sinopharm's virus inactivated COVID-19 vaccines and will include other vaccines currently produced or in development by CNBG.

Headquartered in Pasadena, CA, Pasaca Capital Inc. is an evergreen private equity investment firm focused on innovative technologies and products that benefit the world. With a focus on medical devices, pharmaceuticals, TMT, industrial & automation, and food ingredient sectors, Pasaca Capital seeks to improve the human condition globally. Pasaca portfolio companies operate in Europe, Middle East, SE Asia, and North America. Portfolio companies include Innova Medical Group Inc, Sweegen Inc, Meepo Inc., ATL Group Ltd, ASOCS, Caton Technology and others. Last week, Pasaca Capital was awarded Business of the Year by California State Assembly for its extraordinary contributions to the State of California and to the world.

"Sinopharm CNBG has been a major force in the global fight against COVID-19 pandemic and we are looking forward to working with Pasaca to expand our reach and help improve human conditions during COVID and beyond," said Mr. Yang Xiaoming, Chairman of CNBG.

Source: https://www.prnewswire.com/news-releases/pasaca-capital-inc-with-its-portfolio-company-innova-medical-group-establish-joint-venture-with-sinopharm-group-to-improve-access-to-covid-19-vaccines-301422575.htmlz

The Way Forward

- Despite the impact COVID-19 pandemic has on ASEAN countries, economic recovery in the region is gaining traction. Over the last two years, ASEAN countries have responded by increasing investments in the biopharmaceutical industry, accelerating policy innovations in new drug approval and surveillance, and removing regulatory barriers. All these measures enable international biopharmaceutical companies to continue growing in ASEAN.

- ASEAN is a vibrant and diversified market. From drug discovery to marketing authorization and commercialization, each of ASEAN countries have their unique set of advantages and challenges. To be successful in the region, Chinese biopharmaceutical companies need to carefully think through their objectives, plan for their points of entry and development paths, and consider building up a regional strategy by tapping on the strategic value offered by each country.

- China's pharmaceutical regulatory convergence and cooperation with other parts of the world are gaining momentum. The country has joined ICH in 2017, and is applying to join PIC/S. These efforts will gradually remove regulatory barriers for Chinese biopharmaceutical companies to expand internationally. Compared with 2020, a growing number of Chinese companies have made strategic progress to enter the ASEAN market. As the ASEAN region becomes increasingly attractive to Chinese biopharmaceutical companies, a rising number of which will position ASEAN as a priority market for their internationalization.

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