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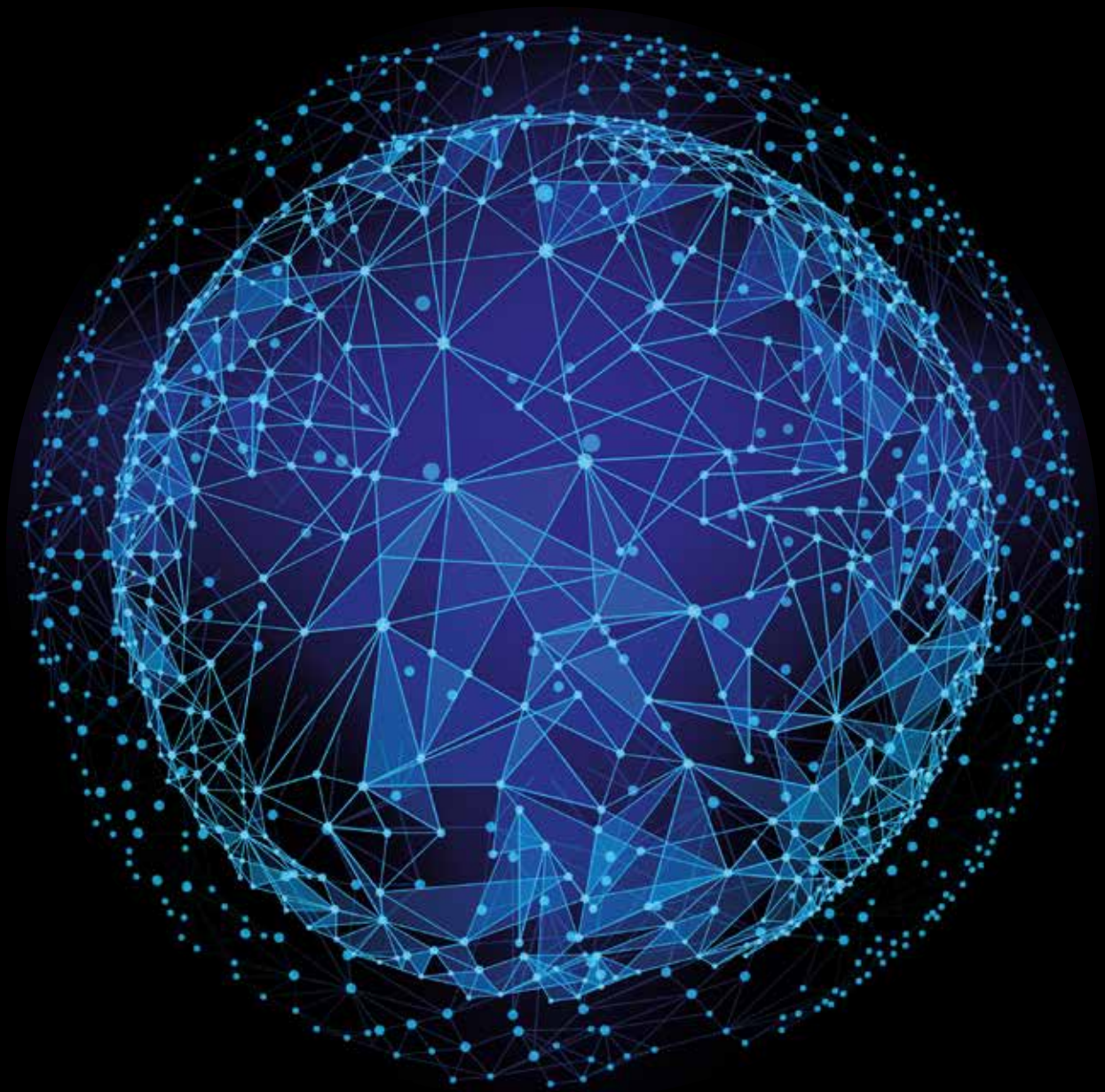

Fostering Biomedical Innovation & Excellence

Collaborating to enhance access to innovative medicines in Singapore

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List of abbreviations

COPD	Chronic Obstructive Pulmonary Disease
COO	Country of Origin
CPP	Certificate of Pharmaceutical Product
CT	Clinical Trials
GDP	Gross Domestic Product
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IMs	Innovative Medicines
IP	Intellectual Property
MAF	Medication Assistance Fund
NDA	New Drug Application
PPP	Public-Private Partnerships
PTE	Patent Term Extension
QALY	Quality-Adjusted Life Year
R&D	Research and Development
SDL	Standard Drug List

Singapore institutions, agencies and committees

ACE	Agency for Care Effectiveness
CFE	Committee on the Future Economy
DAC	Drug Advisory Committee
EDB	Economic Development Board
HSA	Health Science Authority
HBMS	Health and Biomedical Sciences
MOH	Ministry of Health
MTI	Ministry of Trade and Industry
NMRC	National Medical Research Council
RIE2020	Research, Innovation and Enterprise 2020 Plan
SCRI	Singapore Clinical Research Institute

Foreign institutions

FDA	Food and Drug Administration, United States
HIRA	Health Insurance Review and Assessment, South Korea
NICE	National Institute for Health and Care Excellence, United Kingdom
OECD	Organisation for Economic Cooperation and Development
PBAC	Pharmaceutical Benefits Advisory Committee, Australia
PHARMAC	Pharmaceutical Management Agency, New Zealand
WHO	World Health Organisation

This study was conducted by Deloitte and commissioned by the Singapore Association of Pharmaceutical Industries (SAPI).

About SAPI

SAPI is comprised of 36 global pharmaceutical companies who share the goal of making innovative medicines (IMs) accessible to patients in Singapore. It aims to achieve this through sustainable and valued partnership with healthcare professionals and providers, government, payers, and patient group stakeholders. This goal is in line with the Ministry of Health (MOH)'s Healthcare 2020 vision of better patient care, as well as Singapore's vision of becoming a biomedical hub.

The aim of this thought paper, assisted by surveys, interviews and research conducted by Deloitte, is to deliver valuable insights and suggestions that are in line with the government's aspirations and patients' benefits. The industry hopes to facilitate better access for the people of Singapore to a broader choice of innovative, life-changing medicines, as well as empower the broader healthcare system to deliver better patient care.

1. Executive Summary

Singapore, home to a population of 5.6 million people, is known for its small but internationally competitive open market. The country is politically stable, with a technocratic approach towards economic management with a long track record of success. In the Biopharmaceutical Competitiveness & Investment Survey in 2016, Singapore was ranked as the most competitive market in attracting biopharmaceutical investments amongst newcomer markets, ahead of South Korea, Taiwan and Israel.[1]

Singapore is also one of the most attractive countries for companies to invest and global talents to work in the metropolitan city, and continues to receive accolades for its highly structured and efficient system. However, there is still room for improvement in the entire biopharmaceutical value chain in terms of market access for innovative medicines (IMs). In early 2017, Deloitte was commissioned by the Singapore Association of Pharmaceutical Industries (SAPI) to assess the role of IMs and the current barriers for patients to access them, including the funding mechanisms that would facilitate IMs usage in Singapore.

Figure 1 Illustration of an IM's lifecycle from bench-to-bedside

We mapped the interactions between IMs, pharmaceutical companies and various stakeholders in the biomedical ecosystem from bench-to-bedside (Figure 1). What became apparent was the extensive footprint pharmaceutical companies actually have in Singapore, not just on providing treatment options to physicians and patients, but also in terms of local manufacturing's contribution to the economy, a myriad of joint research partnerships with local research institutions and contribution of tens of thousands of jobs to the local economy.

These were a direct result of a coordinated government policy to attract such foreign investments. In Singapore's bid to achieve and maintain its competitiveness, growth and reputation as an Innovation and Intellectual Property (IP) hub, the country had rolled out various policies and funding to support this drive. Underpinning these recently was the S$19 billion Research, Innovation and Enterprise 2020 Plan (RIE2020) in 2016, with the health and biomedical sciences (HBMS) domain-related projects receiving a sizable proportion of funding of 21%, or S$4 billion over the next 5 years.

In mapping the role of IMs in the healthcare space, healthcare and medical research trends in Singapore are also changing, such as a rapidly aging population and an increasing burden of chronic diseases. In Singapore, on top of healthcare policies of 3Ms (Medisave, Medishield and Medifund), healthcare policy themes include the "iron triangle of healthcare" over access, quality and cost, the Healthcare Masterplan 2020 announced in 2012, Medishield Life in 2015, and more recently the "3 Beyonds" announced in 2016.

[1] Pugatch Consilium. Biopharmaceutical Competitiveness & Investment Survey, 2016.

Deloitte sought to provide an objective third party review of the current status of IM access by identifying existing issues and understanding the perceptions of the pharmaceutical companies. Our survey centred around three general topics across the drug's lifecycle: "What is your companies' footprint?", "What are your existing perceptions of Singapore?", and "What can be better done?". Most of the respondents were Singapore country leaders, supported by their regional teams on data and perceptions on manufacturing and R&D. Based on these results, Deloitte then conducted interviews with the respondents to either clarify data, or deep-dived for insights on a particular subject the respondent might have mentioned.

The results were insightful, including actual experience of the existing processes and interactions between regulators and healthcare providers. For many of the issues raised, there has been on-going measures to address them, and gradual progress was already observable. These included insights around:

- Drug formulary listing practices in public hospitals;
- Process of how government determines drug subsidies;
- Challenges in conducting clinical trials in Singapore;
- Patent term extensions for innovation; and
- Impact of market registration timeliness on a global supply chain

In looking to balance the viewpoints from the industry, Deloitte also sought interviews with national regulators, hospitals and other stakeholders, including the Economic Development Board (EDB), the Ministry of Health (MOH), Health Science Authority (HSA), and the Agency for Care Effectiveness (ACE) to understand the status, concerns and challenges faced.

Through our surveys, interviews and research/benchmarks, we gathered 3 main insights. These are:

1. Many industry leaders echoed that while Singapore remains competitive globally, our country's competitors are catching up in attracting investments in R&D, manufacturing and commercial activities. There is a need to review Singapore's strategies to adapt to the global climate and headwinds.
2. Furthermore, many expressed an inconsistency in the nation-wide aspiration towards a global biomedical and innovative hub, yet concerns exist in promoting innovative medical treatments in the ecosystem, particularly in the public sector. These are reflected in the insights described in Section 5 of this Paper.
3. Last but not least, it is also perceived that there is room for more dialogues and collaboration between the public sector and industry, which is also evident from our benchmarking study with other mature regulatory agencies in other countries. The industry has thus far expressed interest in playing a part in collaboratively resolving these issues. On top of that, Deloitte further explores possible partnership models seen in other parts of the world, in the form of alternate innovative pricing and access models, and collaborative learning and programmes (Section 6).

Through the identification of these issues, the various stakeholders can jointly work together with a strong forward-looking view to address access to IMs, to help physicians and patients in Singapore. Singapore can thus remain competitive, and at the same time achieve greater long-term value and sustainability for healthcare systems and the overall nation's economy and population health.

2. Introduction

2.1 Singapore's pharmaceutical and biotechnology industry achievements

Looking back across 50 years of economic development, Singapore's ability to attract the pharmaceutical and biotechnology industry is undoubtedly a huge success story, with Singapore now hosting leading global biomedical science companies, research institutions and manufacturing plants across the pharmaceutical value chain.

Singapore has also developed its reputation as a producer of global biomedical products and rapidly, a global innovation hub, despite strong competition from other countries. This is due in no small part to attractive, comprehensive and coordinated government policies across economic and innovation fronts. In 2016, Singapore was ranked the most competitive market in attracting biopharmaceutical investments amongst newcomer markets, ahead of South Korea, Taiwan and Israel[2]; and in 2017 ranked 7th on the Global Innovation Index, right behind US (4th) and UK (5th) and Denmark (6th).[3]

Biopharmaceutical manufacturing is a key economic pillar in Singapore. There are more than 50 manufacturing plants with a total projected output of close to S$30 billion, accounting for 21.8%[4] of projected Singapore manufacturing activity and hiring 20,676 employees in the process. Specifically for pharmaceutical manufacturing, the remuneration and value-add per worker is projected to be one of the highest among all manufacturing sectors, earning S$102,000 (3rd) and producing S$1,704,000 per worker (1st) in 2016.[4 5] Pharmaceutical companies such as GSK, Baxter and Roche launched their first-in-Asia commercial production facilities in 2009, while other firms such as Merck, Pfizer, Sanofi and Abbott have also setup their global manufacturing base in Singapore.[6]

Singapore also hosts more than 30 **regional headquarters** for biopharmaceutical, medical technology and devices companies, employing more than 7,600 employees.[4] Critically these are high quality jobs and equips the local workforce with valuable skillsets. Despite high workforce costs, Singapore remains an attractive location due to a stable political landscape, attractive government policies, as well as an ability to draw global and regional talent.

The vibrant biomedical sciences **research and development ecosystem** of more than 50 R&D centres[4] could not have been possible without the right policies, funding and dedicated regulatory bodies implementing on the ground and providing support. Additional to academic research and medical centres, further PPPs with global pharmaceutical companies such as Novartis, Roche and MSD also helped to establish regional research and clinical trials centres, boosting research capabilities in Singapore.[4]

[2] Pugatch Consilium. Biopharmaceutical Competitiveness & Investment (BCI) Survey, 2016.
[3] Cornell University, INSEAD, and World Intellectual Property Organization. The Global Innovation Index 2017: Innovation Feeding the World, 2017.
[4] Ministry of Trade and Industry. Table A9.3 - Principal Statistics of Manufacturing by Industry Cluster, 2016p. Accessed 7 Jul 2017, from https://www.mti.gov.sg/ResearchRoom/Pages/Economic-Survey-of-Singapore-2016.aspx.
[5] Economic Development Board. Presentation: Sustaining Pharmaceutical Operations in Asia, Singapore as a Case Study, undated.
[6] The Economist Intelligence Unit. Industry Report Healthcare Singapore, 3rd Quarter 2017.

However, Singapore cannot afford to be complacent and needs to continuously review its competitiveness against other countries also seeking the benefits of biomedical investment. In Asia, South Korea and Taiwan have established an equally competitive and attractive clinical research and biomedical investment environment[7], while Thailand is advancing in clinical research via strong government engagement and support.[8] In the global context, US leads the pack with world renowned bio-clusters such as Cambridge/Boston, Massachusetts and San Francisco. If Singapore were to be compared by population and economy size, Ireland is a similarly attractive destination for pharmaceutical companies.

	Ireland	Singapore
General	• Population of 4.8 million (2016) • GDP of S$400.6 billion (2016)	• Population of 5.6 million (2016) • GDP of S$404.7 billion (2016)
Lays claim to	• 75+ pharmaceutical companies operate in Ireland	• More than 50 global biomedical sciences companies based in Singapore
Manufacturing output	• 40 Food and Drug Administration (FDA)-approved plants with a total annual export of €39 billion (S$61 billion) • 7th largest exporter of medicinal and pharmaceutical products in 2014	• More than 50 manufacturing plants with a total output of S$30 billion
R&D investments	• Cross-sector government research funding of €8 billion (S$12.5 billion). No known specific biomedical funding. • Science Foundation Ireland funds basic research especially in cancer, autoimmune diseases and Alzheimer's • National Institute for Bioprocess Research and Training costing €60 million to train 2,000 personnel	• 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 • Clinical trials supported by in-house Investigational Medicine Units in public hospitals and the Singapore Clinical Research Institute (SCRI) • Various research institutions fostered by Agency for Science, Technology and Research (A*STAR) and PPPs
Collaborative Clusters	• Dublin, Cork, Silgo, Waterford and Mayo	• Biopolis, Tuas Biomedical park, Science Park

Figure 2 Qualitative Comparison of Ireland and Singapore as leading bio-clusters. Foreign currency translations are rough approximations as of June 2017 and serve as a guide.[9 10 11]

[7] Pugatch Consilium. Biopharmaceutical Competitiveness & Investment (BCI) Survey, 2016.
[8] Clinical Leader. Thailand Puts Increased Focus On Clinical Trials, 2017. Accessed 19 Jun 2017, from https://www.clinicalleader.com/doc/thailand-puts-increased-focus-on-clinical-trials-0001
[9] Population and GDP figures from World Bank. Accessed 11 Jul 2017.
[10] Economic Development Board. Pharmaceuticals & Biotechnology, undated. Accessed 28 Jun 2017, from https://www.edb.gov.sg/content/edb/en/industries/industries/pharma-biotech.html
[11] IDA Ireland. Biopharmaceuticals, undated. Accessed 28 Jun 2017, from http://www.idaireland.com/business-in-ireland/industry-sectors/bio-pharmaceuticals/

Singapore's biomedical and innovation journey is the result of billions of dollars of investments over the last 25 years (Figure 3). In January 2016, the Singapore government further laid out the S$19 billion RIE2020, being the country's sixth five-year plan to invest in building R&D capabilities. The plan allocates S$4 billion (21%) to the HBMS strategic domain, underscoring Singapore's aspirations to be "*a leading centre that advances human health and wellness, and creates economic value for Singapore and Singaporeans through the pursuit of excellence in research and its applications*".

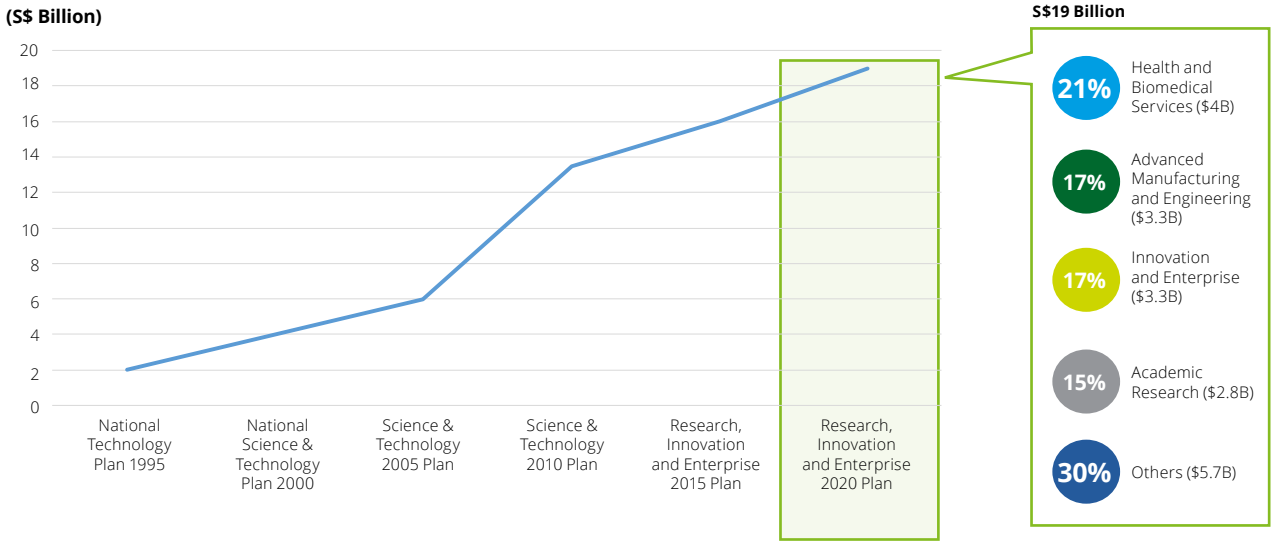


Figure 3 Public Investment in Research, Innovation & Enterprise in RIE2020[12]

These investments in biomedical and related sciences activities have contributed critically to Singapore's economy, generating 13% and 17% of R&D output and manufacturing value-add respectively in 2016 (Figure 4 and 5).[13] This vibrant ecosystem leads to 3 key benefits:

1. Through drug research, development and clinical trials, patients in Singapore are afforded early access to the most innovative therapies and medication;
2. Singapore continues to attract the brightest and most talented, transferring valuable know-how in management, manufacturing and clinical research to local Singaporeans; and
3. Putting Singapore on the global map as a leader of drug R&D in Asia and "punching above its weight" in bringing innovative therapies to the world.

[12] National Research Foundation. RIE2020 (undated). Accessed 11 Jun 2017, from https://www.nrf.gov.sg/rie2020
[13] Department of Statistics Singapore. Statistics by Theme (undated). Accessed 15 Jun 2017, from http://www.singstat.gov.sg/statistics/browse-by-theme

(S$ Billion)

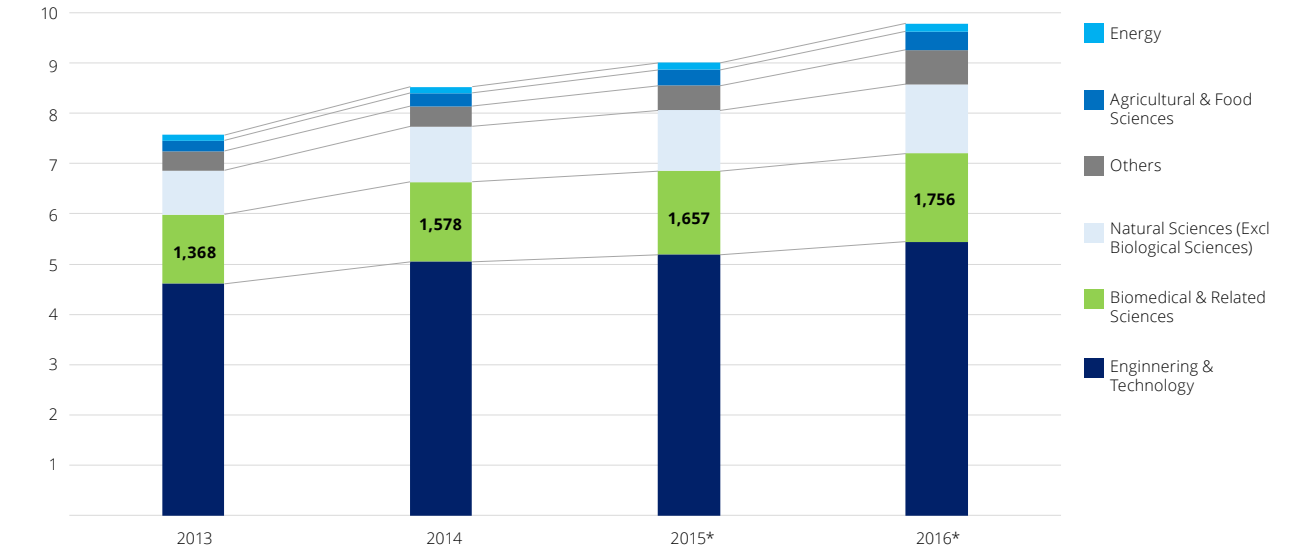


Figure 4 R&D output in Singapore between 2013 and 2016[13] [14]

(S$ Billion)

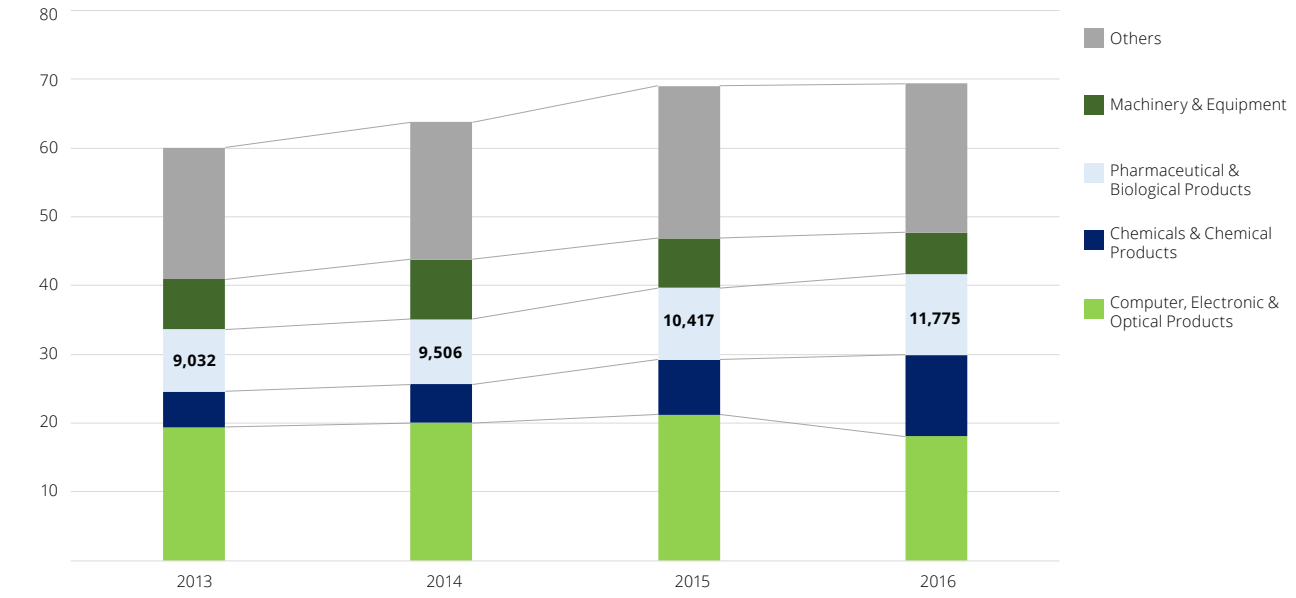


Figure 5 Manufacturing Value-add in Singapore between 2013 and 2016[13]

[14] Data for 2015 and 2016 were not available and extrapolated based on the average growth of the 5 preceding year (CAGR).

2.2 Singapore's medical achievements

Against the backdrop of Singapore's economical achievement, Singapore's healthcare system is also considered one of the most admired and most efficient systems in the world. Singapore boasts one of the highest life expectancies of 82.8 years and lowest infant mortality rate of 2.4 per 1,000 live births in 2016.

However, a rapidly aging population is of the top worries of the healthcare system, with the old age dependency ratio set to rise to 15.9% in 2021, from 12.3% in 2016. Furthermore, rate of diabetes are on the rise and the disease prevalence stood at 12.8% for 20 to 79 year olds in 2015, the 2nd highest rate for a developed country, behind the US.[15] In 2014, the Economist Intelligence Unit further listed Singapore as the 2nd best country for healthcare outcomes globally, closely behind Japan and ahead of South Korea.[16]

Thus far, the healthcare system has proven to be adaptive. Since MOH launched the Healthcare 2020 Masterplan in 2012 with the aim of improving healthcare quality, affordability and access, a slew of policies have been announced. These polices include:

- Public health insurance scheme i.e. MediShield Life to provide coverage from cradle to grave (affordability),
- An emphasis on growing medical and caregiver capacity (quality),
- Beefing up infrastructure and bed numbers, and
- Reviewing public healthcare clustering to provide seamless care between primary, community and tertiary hospitals (access).

In April 2016, MOH further outlined a policy move encapsulated in "3 Beyonds", being moving "beyond the hospital to the community"; "beyond quality to value"; and "beyond healthcare to health".

On "beyond quality to value", medicines are assessed based on its clinical and cost-effectiveness to improve overall healthcare outcomes and the patient's quality of life. Aligned to this was also the establishment of ACE under the MOH in 2015, deploying health technology assessment (HTA) methods which take into account expert opinion and scientific evidence to identity interventions that are clinically effective and offer the best value for patients. ACE enhances clinical decision-making and make subsidies recommendations to MOH's Drug Advisory Committee (DAC). The process includes two of the public subsidy mechanisms, the Standard Drug List (SDL) and Medical Assistance Fund (MAF). In May 2017, 11 Drug Guidances were released, detailing

- ACE's subsidy recommendation to DAC,
- Rationale for the subsidy recommendations, and
- Key clinical and economic evidence used for deliberation.

These subsidies have thus far acted as important considerations for clinicians' prescription decisions to patients receiving both IMs and generic drugs. In our interviews, Deloitte understands that the pharmaceutical industry has thus far had meaningful and constructive conversations with ACE and look forward to further development on this front.

Singapore's strong reputation for medical services and quality healthcare has also led to its reputation as a regional medical hub. Contributing factors include quality infrastructure, reliable medical services, and its cutting edge medical expertise in conducting complex procedures such as organ transplants, neurosurgery and cardiovascular surgery.[18] In 2014, Frost and Sullivan named Singapore the 4th ranked destination globally for foreign travellers seeking medical treatment based on patient volume, behind Thailand, Hungary and India, and ahead of Malaysia (5th) and South Korea (11th); while another study estimates that Singapore served more than 500,000 medical travellers in 2014.[19] [20]

[15] The Economic Intelligence Unit. Industry Report: Healthcare, 3rd Quarter 2017.
[16] The Economist Intelligence Unit. Health outcomes and cost: a 166-country comparison, 2014.
[17] Ministry of Health. Speech by Minister for Health, Mr Gan Kim Yong, at the MOH Committee of Supply Debate 2016, 13 Apr 2016. Accessed 9 Jun 2017, from https://www.moh.gov.sg/content/moh_web/home/pressRoom/speeches_d/2016/speech-by-minister-fo-health--mr-gan-kim-yong--at-the-moh-commit.html
[18] Singapore Business Review. Singapore named Asia's most expensive medical tourism destination: report, 25 Aug 2014. Accessed 28 Jun 2017, from http://sbr.com.sg/healthcare/in-focus/singapore-named-asia%E2%80%99s-most-expensive-medical-tourism-destination-report
[19] Forbes. Medical Tourism Gets a Facelift... and Perhaps a Pacemaker, 19 Aug 2014. Accessed 28 Jun 2017, from https://www.forbes.com/sites/reenitadas/2014/08/19/medical-tourism-gets-a-facelift-and-perhaps-a-pacemaker/#46cf292c391b
[20] The Straits Times. Medical tourism booms in Asia, with India, Malaysia, Singapore, Thailand leading the way, 22 Dec 2014. Accessed 28 Jun 2017, from http://www.straitstimes.com/asia/se-asia/medical-tourism-booms-in-asia-with-india-malaysia-singapore-thailand-leading-the-way

2.3 Interconnectedness of the biomedical science ecosystem

The footprint of pharmaceutical companies in the biomedical industry in Singapore is extensive and multi-faceted (Figure 6).

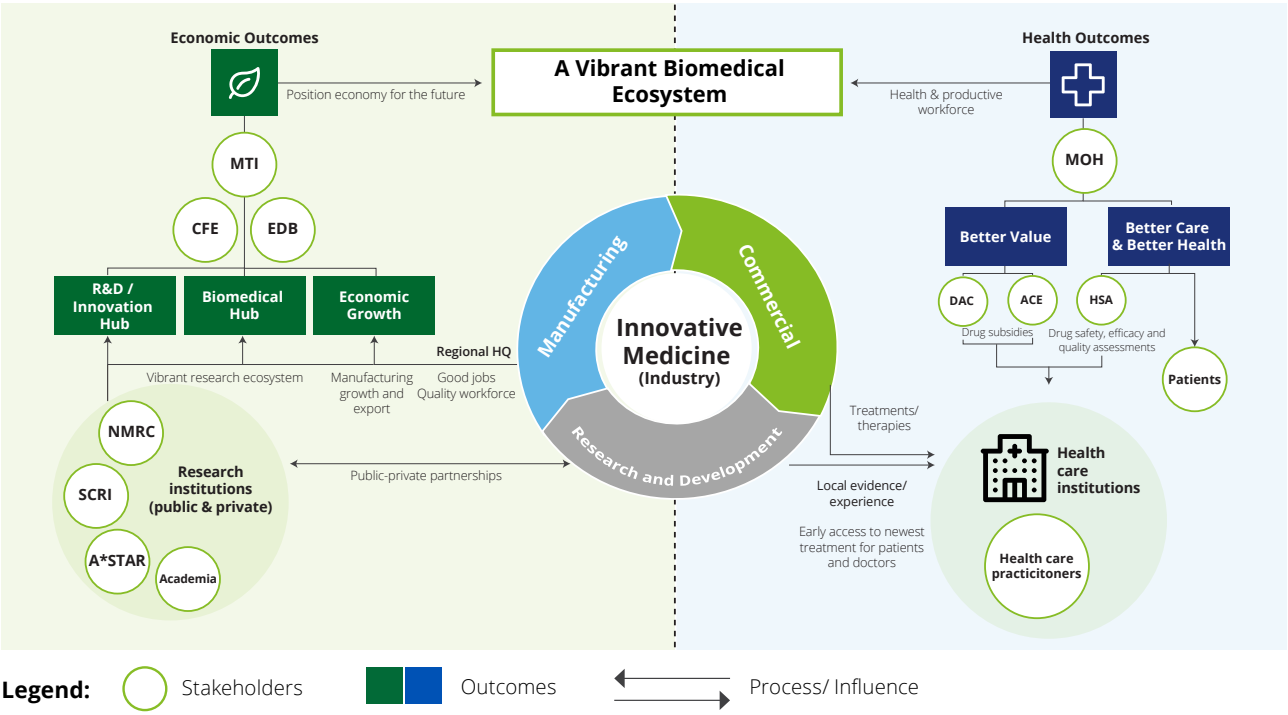


Figure 6 Economic and health value creation of IMs in the biomedical science ecosystem

The industry's impact in manufacturing and headquarters activities is substantial across the value chain, contributing good quality and knowledge-driven jobs, building a quality workforce, and adding value to the economy. On the R&D front, partnerships with public institutions have built a vibrant research ecosystem, positioning our economy in line with the desired outcomes for the future.

Not only are pharmaceutical companies suppliers of IMs to healthcare systems, they are also medical educators to clinicians on recent diseases and drugs. As a result their business and commercial strategy has a direct impact on patient's health outcomes.

Biomedical companies also enhance treatment access to clinicians and patients by providing access to clinical trials setup to discover the latest life-saving medicinal products. These build on the existing roles played between the industry, government (e.g. HSA, DAC, ACE and MOH) and healthcare providers, to ascertain drug safety, quality, efficacy, and cost effectiveness, before being accessible by patients.

Furthermore, certain companies also provide patient access and compassionate programmes to help patients overcome financial challenges. This is especially true for "rare diseases", where one pharmaceutical company estimated its Patient Assistance Programmes covers up to 90% of patients in Singapore for a particular rare disease, and based on means testing, likely subsidise up to 35% of the medical bill.

The biomedical industry continues to work with various government and private stakeholders and contributes to multiple aspects of economy and health outcomes. In doing so, it is ultimately building a more vibrant biomedical ecosystem. The interconnectedness of the ecosystem means regulatory policies need to be coordinated across governmental agencies for a consistent message to existing and potential investors of the ecosystem, to maintain Singapore's competitiveness and global reputation as biomedical, innovation and IP hubs.

These significant achievements could not be made possible without the active engagement of IMs within the biomedical ecosystem. The next chapter explores the roles of IMs and its benefits to the ecosystem.

3. Role of Innovative Medicines in Singapore

IMs are medicines that are developed by researchers and pharmaceutical companies, and often mean meeting unmet medical needs, or new treatment options for patients with existing illnesses. IMs play an essential role in the entire healthcare ecosystem, by helping

- **Patients** live longer, healthier and more productive lives;
- **Healthcare** systems achieve long term value, and **national economies** achieve substainable gains.

3.1 Helping patients live longer, healthier and more productive lives

IMs are instrumental in providing new treatment options for patients to cure their disease or to improve their quality of life, across a wide range of illnesses (Figure 7).

Cardiovascular Disease
Innovative biopharmaceutical companies are currently developing 190 medicines to treat heart disease, stroke and other cardiovascular diseases. New PCSK9 inhibitors have revolutionized high cholesterol treatment

Diabetes
Between 2000 and 2012, new therapies contributed to a 48% and 31% decline in the diabetes death rate in Korea and Canda, respectively

Figure 7 Examples of IM helping patients achieve longer lives and lead productive lives[21]

Advances in cancer treatment, for example, have contributed to significant global mortality rate reduction of 12 – 27% between 1991 to 2014, and 2 out of 3 cancer patients have had their lives extended by a further 5 years with the new advanced treatment options. Furthermore, it was estimated that 4 out of 5 cancer patients were able to return to work following cancer treatment, enhancing the quality of life in their remaining years, as well.[21]

Vaccinations are commonly understood to be one of the most cost-effective treatment methods, supporting the reduction of healthcare costs. In Singapore, a pioneering vaccine project, the National Hepatitis B Vaccination Programme launched in 1985 and went on to be one of the most successful immunisation programmes in the world. It was a particularly impressive achievement considering it was initiated in a time when there were uncertainties around the benefits of immunisation.

[21] PhRMA. Prescription Medicines: International Costs in Context, Mar 2017.

Case Study:
Singapore's National Hepatitis B Vaccination Programme[22] [23]

On 1 October 1985, Singapore launched its National Hepatitis B Vaccination Programme, with the aim of covering over 95 percent of all newborns.

The programme achieved tremendous success since its introduction:

- Halving of acute viral hepatitis incidents from 10.4 to 4.5 per 100,000 between 1985 and 1995.
- The carrier rate fell to from 8-10 to 3 percent between 1980s and 1997.
- The incidence of primary liver cancer in men declined from 27.8 to 19 per 100,000 in 1988-1992.
- Present day, carrier rates have dropped to 2.4% and no child under 15 years has acute jaundice since 2005.

Prof. Gabriel Oon, the programme's principal investigator stated in its 25 anniversary celebration:

"*We were the first country in the world to embark on this vaccine, but this vaccine was also the first cancer vaccine intervention vaccine study to be conducted by International Agency for Research in Cancer, WHO and Singapore for cirrhosis and liver failures, and liver cancer, a top three killer in the world and the Asia pacific region to determine whether this vaccine would reduce the high incidence of acute jaundice cases… Today that answer is categorically YES.*

IARC/WHO Director Dr. Christopher Wild, in his congratulatory message describes this achievement as one of the greatest success stories of the last century of international collaboration. Today this vaccine has gone out to the poorest of the poor through international consortiums, and is saving the lives of these children."

Looking ahead, trends in treatments are poised to be ground breaking. For example, cancer research is bringing forth targeted approaches in specific genes, proteins or tissue environment, delivering better efficacy and lower toxicity, and allowing patients to feel and function better throughout the treatment process. Cancer immunotherapies have been heralded as "the most exciting advance in the treatment of tumours" and "the big hope is that… cancer is banished for good."[24] [25]

Similar to other developed countries, Singapore grapples with lifestyle related illnesses that have a huge public health impact, like diabetes and cardiovascular diseases, putting a significant burden on patients and healthcare systems alike. It is hopeful that a cure to chronic diseases, or at least slowing down the deterioration and long term complications of disease can be discovered and made accessible to everyone.

[22] Onn G, Kwek K. The Battle Against Hepatitis B: A Cancer Vaccine that transformed Singapore and the World, 2011.
[23] Onn G. Prof. Oon's speech 25 anniversary celebration of the successful National Hepatitis B Vaccine Programme…, 2 Oct 2010. Accessed 11 Jun 2017, from http://gabrieloon.com/Medical%20Research/Gabriels%20Book%20Launch%20&%20Speech.pdf
[24] Scientific American. Cancer Immunotherapy: The Cutting Edge Gets Sharper, 1 Oct 2015. Accessed 11 Jun 2017, from https://www.scientificamerican.com/article/cancer-immunotherapy-the-cutting-edge-gets-sharper/
[25] The Guardian. Immunotherapy: the big new hope for cancer treatment, Jun 2015. Accessed 11 Jun 2017, from https://www.theguardian.com/science/2015/jun/01/immunotherapy-the-big-new-hope-for-cancer-treatment

3.2 Helping healthcare systems and economies achieve sustainable gains

While IMs are commonly perceived to pose a huge cost burden on the healthcare system, many stakeholders are also realising that the value of IMs should not be seen in terms of its direct costs.

IMs may be perceived to be more expensive on a per-drug single-dosage basis, and though these may be earlier cost outlays, they bring about better intrinsic benefits in the longer term, over a lifetime or course of disease. For example, one may consider overall medical cost savings (e.g. reduced hospitalisation, re-admissions or supplementary medications), a better quality of life (e.g. less treatment discomfort or complications), and must not forget the indirect costs of illness and disability for the individual (e.g. ability to go back to work and lead productive lives).

For example, developments in diabetes treatments have now enabled patients to administer treatments at home instead of requiring hospital visits as in the past. Not only does this benefit the patients in terms of time and effort saved, this lessens the workload of healthcare administrators and avails them to provide more quality care to patients.

IMs have been further estimated to play a significant role not only in helping the patient, but helping the healthcare system save costs in the longer term (Figure 8). Certain diseases, especially chronic diseases, can also severely impact a country's long term productivity. For example, the Public Health Agency of Canada estimated that treatment of chronic disease consumes 67% of all direct healthcare costs, costing the Canadian economy C$190 billion (S$198 billion) annually. In this, only C$68 billion (S$71 billion) is attributed to treatment and the remainder to lost productivity (S$127 billion).[26]

New Cardiovascular Medicines Led to Direct Savings on Hospitalisations in 20 OECD Countries

Per capita expenditure on cardiovascular Direct Savings on hospitalisations would have been

$89 (70%) higher

in 2004 had new cardiovascular medicines not been introduced in the period 1995-2004

In the UK, a treatment delaying onset of dementia by 5 years would result in:

666,000
fewer people with dementia

566,000
fewer informal cares required

£21.2 billion
reduction in the cost of dementia

Figure 8 Examples of stronger healthcare savings through usage of IM[27] [28]

[26] Public Health Agency of Canada. Against the Growing Burden of Disease, undated. Accessed 15 Jun 2017, from http://www.ccgh-csih.ca/assets/Elmslie.pdf
[27] Lichtenberg. Have newer cardiovascular drugs reduced hospitalization? Evidence from longitudinal country-level data on 20 OECD Countries, 1995-2003, May 2008.
[28] Alzheimers Research UK. Defeat Dementia: The evidence and a vision for action, 2014. Accessed http://www.alzheimersresearchuk.org/wp-content/uploads/2015/01/Defeat-Dementia-policy-report.pdf

Further, to put healthcare costs in perspective, a study by Pharmaceutical Research and Manufacturers of America (PhRMA) showed that the cost of prescription medicines by 10 major countries (including US, UK, Japan, Australia, Korea and several EU nations) only ranged between 10 - 16% of the total national healthcare expenditure based on OECD Health Statistics data (2016)[21]. Last but not least, to understand the problem of healthcare costs, it may be also useful to review improper and unnecessary use of medicines, estimated by QuintilesIMS to cost the US a total of US$213 billion, or 8% of its healthcare spending in 2012.[29]

Singapore achieves its health outcomes through a modest health spend of 5.4% of GDP and a pharmaceutical spend of 8.3% of total healthcare cost (vs. OECD average of 8.9% and 16.3% respectively).[30] [31] However, recent changes to healthcare policies and infrastructure growth (as described in Chapter 2.2) have driven increased government spending, more than doubling the healthcare budget from S$4.7 billion in 2012 to S$11 billion in 2016. Sustainability of healthcare financing at the national level is certainly a concern.

Therefore it is critical to understand the policy stance of access to IMs in Singapore to better tackle this issue. This is discussed in the next Chapter.

[29] QuintilesIMS. Avoidable Costs in U.S. Healthcare, Jun 2013. Accessed 9 Jul 2017, from http://www.imshealth.com/files/web/IMSH%20Institute/Reports/Avoidable_Costs_in%20_US_Healthcare/IHII_AvoidableCosts_2013.pdf
[30] The Economic Intelligence Unit. Industry Report: Healthcare, 3rd Quarter 2017.
[31] OECD Health Statistics 2016.

4. Current Access to IMs in Singapore

The United Nations defines "access to medicine" as medicines that are continuously available and affordable at public or private health facilities.[32] As briefly mentioned in Chapter 2, access to IMs may start much earlier before the drug is available to public. For example, at the clinical trials stage, new or experimental drugs are first made available to patients in need or those who have run out of more standard treatment options. Therefore, reviewing patient's access to IM requires a holistic view, from research to commercialisation to post-launch market activities.

To understand the current access situation to IM in Singapore, Deloitte conducted primary research with relevant local government agencies and pharmaceutical industry executives via surveys and interviews. The aim was to determine their perceptions of Singapore as a commercial market for IMs and if they believed if access was being adequately given to the Singaporean population (refer to Appendix section 8.1 for more details).

Our survey results showed that Singapore is generally considered to be a strategic market for IMs (Figure 9). However, despite all the economic investments and progress outlined in manufacturing and R&D, 77% of Industry players surveyed think that Singapore's IM environment has disappointingly remained "about the same" or even "somewhat worse". "Market access and commercialisation", in particular, receives the lowest satisfaction scores from industry.

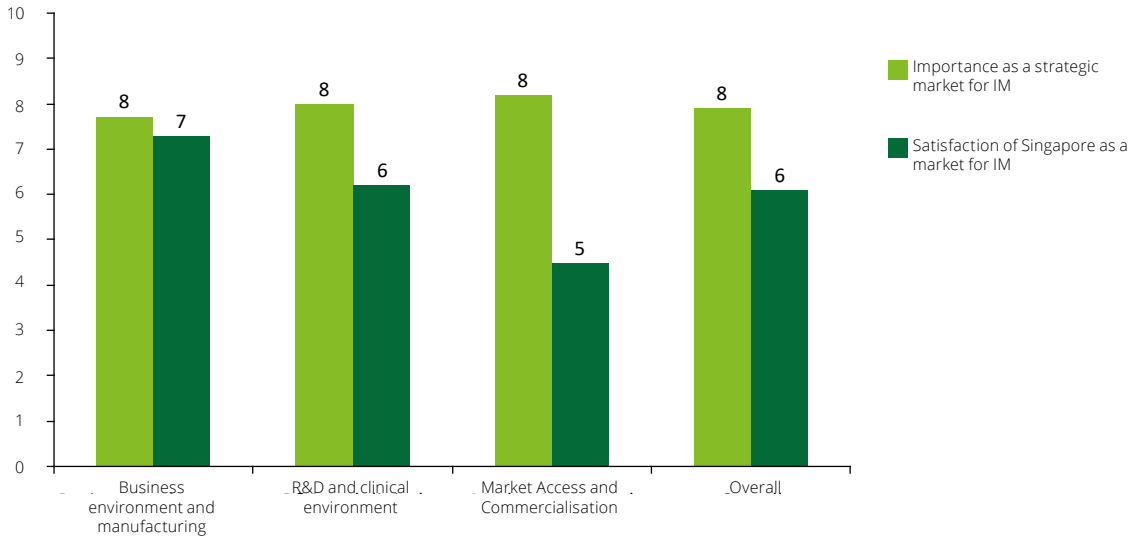
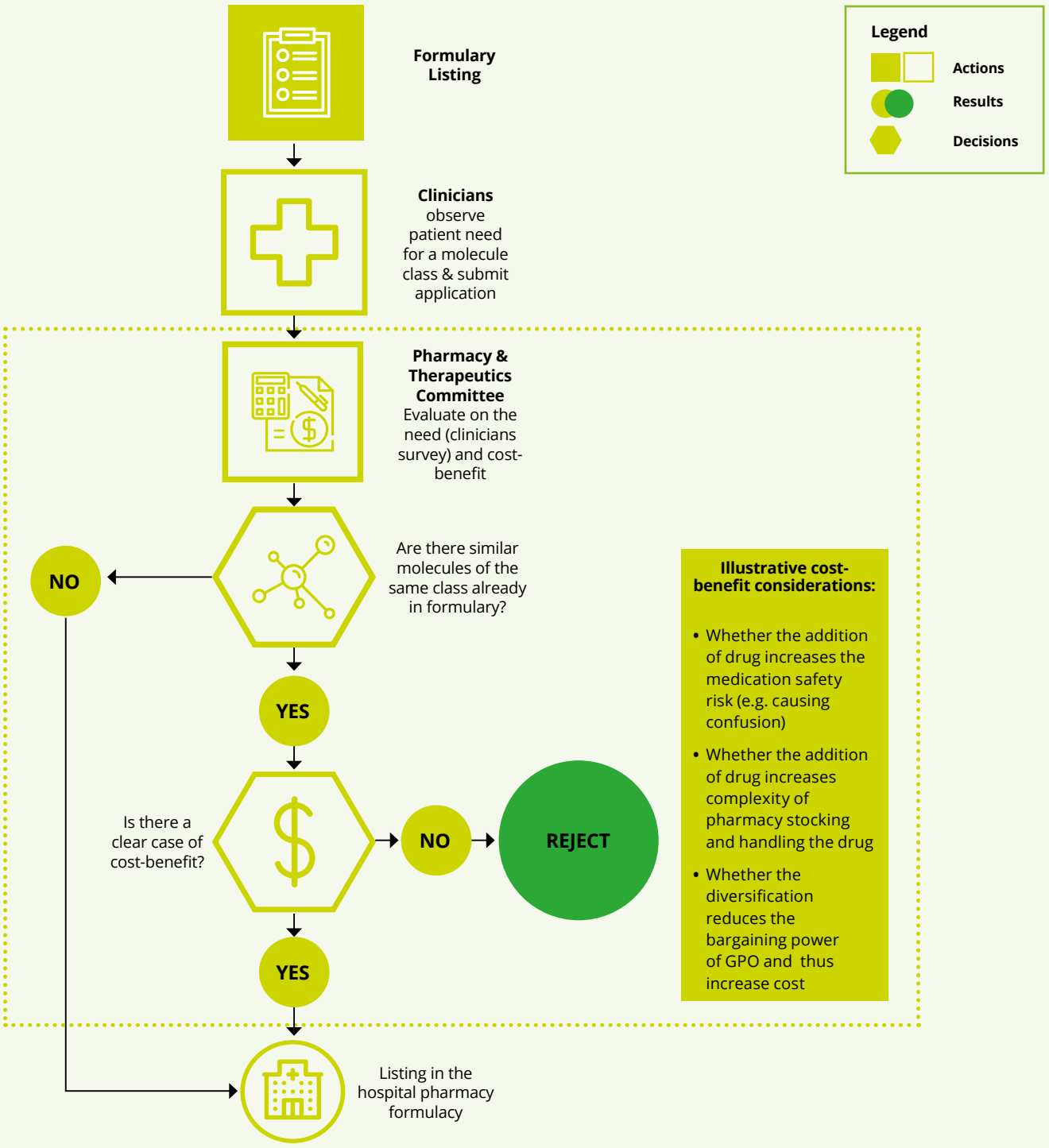


Figure 9 Deloitte survey: Singapore as a strategic market for IM, and its satisfaction levels

The following sections explore in depth the key issues behind the satisfaction levels in the R&D and commercialisation environment. This will be done by articulating the current access situations in Singapore, analysing possible root causes, and exploring viable solutions or understanding existing progress to address these challenges.

[32] United Nations Development Group. Indicators for Monitoring the Millennium Development Goals, 2003.



NB: The evaluation criteria is meant as a sample (as provided by one institution). This does not represent criteria of all hospitals in Singapore.
NB. Manufacturers may also submit application, but Deloitte understood only 1 out of all public sector hospitals.

Figure 10 Process Overview: IMs' access in Public health systems via drug formulary listing (adapted based on Deloitte interviews with stakeholders)

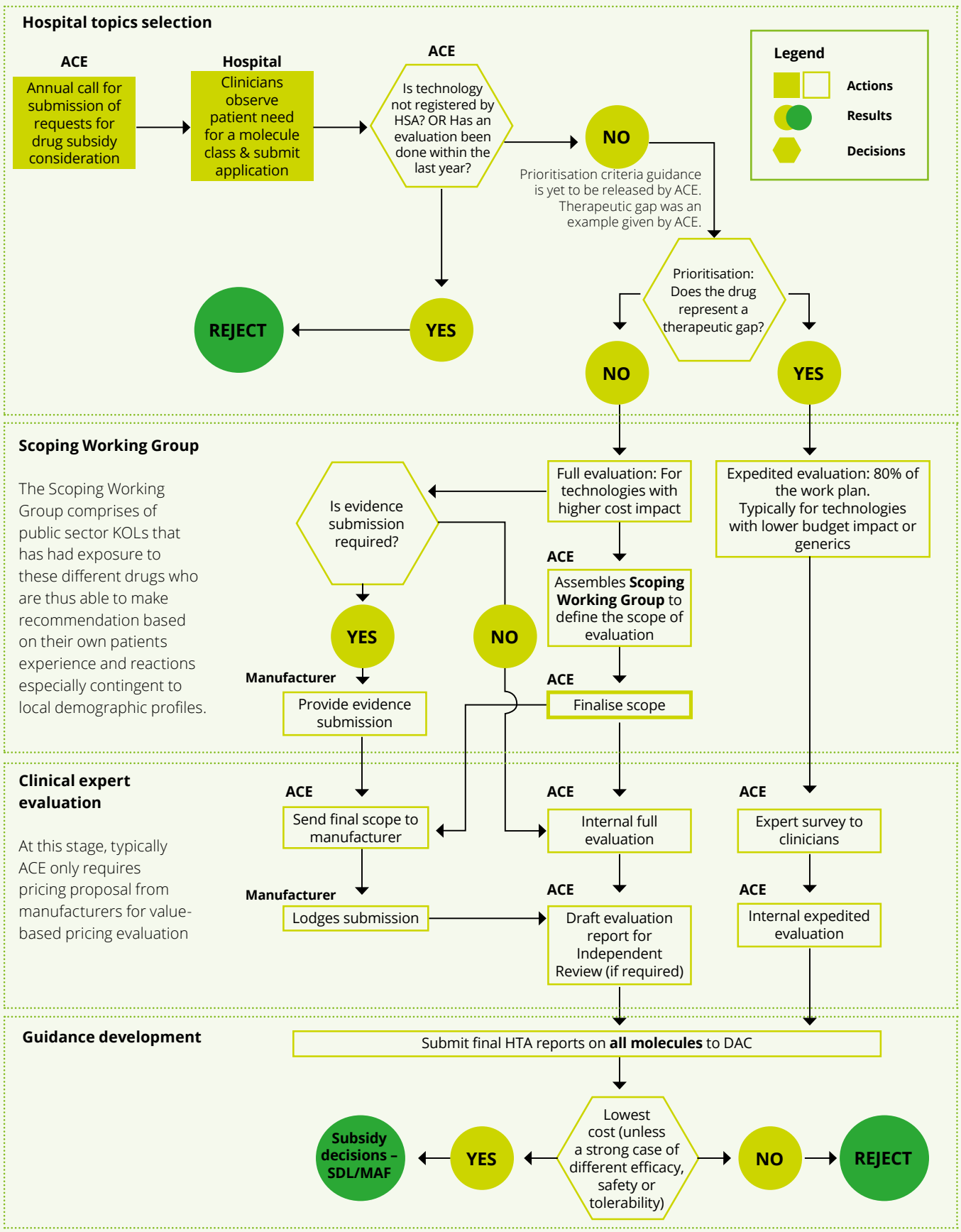


Figure 11: Process Overview: IM access in public subsidy system for application to the SDL/MAF under ACE/DAC)[33]

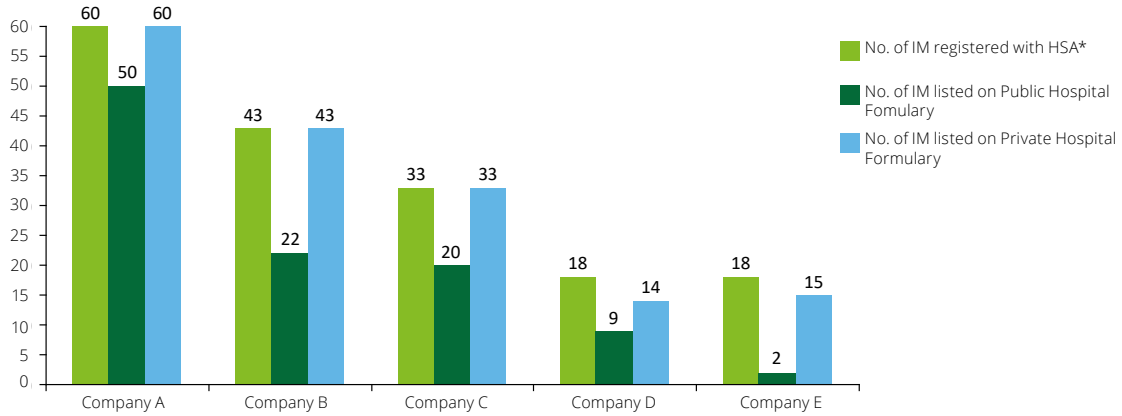
[33] ACE Industry Briefing, May 2017

4.1 Broadening public formulary access

Strengthening equitable access of IMs between private and public patients

While Singapore does not have universal healthcare, the public health system is heavily subsidised, with 80% of the acute patients seeking care in public hospitals.[34] The private health system in Singapore however operates largely in a free market and most of the patients pay out-of-pocket or are covered under private insurance.

In Singapore, prescription and usage of drugs in hospitals and polyclinics (both IMs and generics) generally adhere to the institution's drug formulary list. While listing of IMs in a private hospital's formulary is comparatively immediate after HSA's approval, the same listing process in a public hospital's formulary is often more limited for public sector patients (Figure 12).



NB: * IMs registered with HSA and with commercial intent only

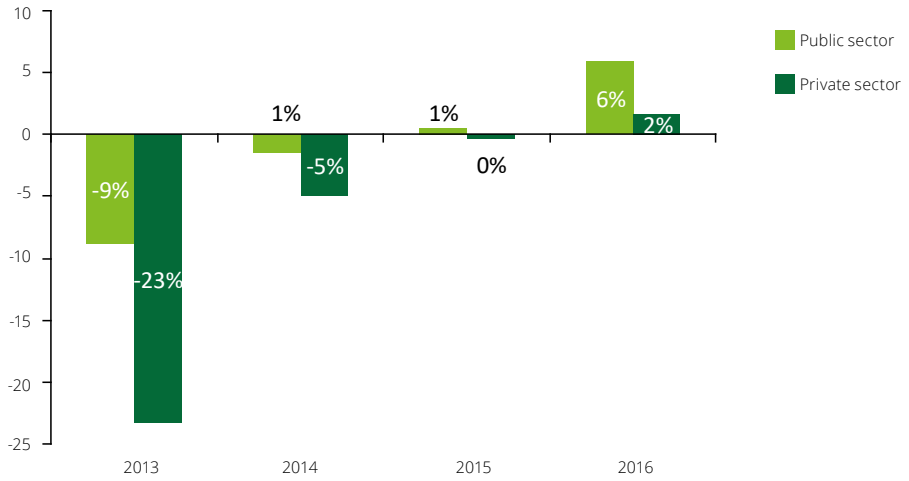
Figure 12 Deloitte survey: Total number of IM products registered with HSA and listed on hospital formulary. Data correct as of Jun 2017.

Furthermore, as mentioned in Chapter 2, the government has recently and rapidly increased public spending in healthcare with increased subvention to public hospitals, broadened coverage of MediShield Life and increased infrastructure spending for new hospitals. The funding is now further extended to the primary care sector which are majority private patients, with the formation of Primary Care Networks among General Practitioners (GPs) and the Community Health Assist Scheme (CHAS) that enable private patients to enjoy subsidised drugs that were only accessible in public sector. This funding support coupled with the re-clustering of public healthcare institutions into three clusters, and more coordinated government-led efforts to tackle chronic diseases at community level (e.g. War on Diabetes), may lead to an increasing shift of private patients to the subsidised public sector in the near future due to private-public sector integration at primary care level.

[34] Singapore Ministry of Health. Costs and Financing, 2017. Accessed 13 Jun 2017, from https://www.moh.gov.sg/content/moh_web/home/costs_and_financing.html

The trend is reflected in Figure 13, where public sector pharmaceutical sales growth has been outpacing private sector growth since 2013.

Growth / %



NB. Public sector includes restructured hospitals and polyclinics.
Private sector includes private hospitals and clinics, excludes retail pharmacy.

Figure 13 Pharmaceutical sales growth from key pharmaceutical distributors in Singapore

By connecting these trends together, there is a looming possibility that a larger pool of patients will not be able to benefit from the choice and range of access to the newest drugs, due to the shift of patients into the public sector. It is worth further considering if strengthening patient access to IMs in public sector is necessary to enable equitable care for the population at large, for public and private sector patients alike.

In strengthening access to IMs in the public sector, Deloitte's survey flagged sentiment around the formulary listing process in terms of consistency and transparency of the evaluation process and limited product listed in public hospitals. These topics will be reviewed in the next sections.

Enhancing Consistency and Transparency of the Listing Process in Public Formularies

Our assessment and interviews reflected that public hospital listings across different public institutions varied in accessibility and timeliness (Figure 14). Based on industry-provided data, the selective availability of a range of medicines across Singapore's public hospitals and polyclinics is notable. While it could demonstrate a lack of patient demand for these products in some institutions, the varying level of access across public hospitals and polyclinics poses the question of medical choices available to the patient at that point of consultation, if the hospital/polyclinic visited had no/limited options available; and the inconvenience and hardship to the patient (if he/she was even made aware) of visiting another hospital/polyclinic for it.

Therapeutic class	Available products in the market, in order of year of HSA approval	Access to public hospitals		Access to polyclinics		Year of MAF/SDL Listing, if any
		First year of listing	No. of public hospitals listed as of June 2017	First Year of listing	No. of polyclinics listed as of June 2017	
	Year	Year	Number	Year	Number	Year
Management options for chronic obstructive pulmonary disease (COPD)						
Inhaled corticosteroid and a long-acting beta-agonist (ICS/ LABA)	1999	2000	8	2003	19	2015
	2001	2002	8	2005	19	2015
	2015	2016	4	Not available	Not available	Not listed
	2015	2017	2	Not available	Not available	Not listed
Long-acting muscarinic antagonist (LAMA)	2009	2010	7	2011	19	Not listed
	2013	2014	3	Not available	Not available	Not listed
	2015	2017	1	Not available	Not available	Not listed
LABA/LAMA	2014	2014	6	Not available	Not available	Not listed
	2015	2016	1	Not available	Not available	Not listed
	2016	2016	3	Not available	Not available	Not listed
Management options for Type 2 diabetes mellitus						
Sodium glucose cotransporter-2 (SGLT2) inhibitors	2014	2014	3	Not available	Not available	Not listed
	2014	2014	7	2017	19	2017
	2014	2015	4	Not available	Not available	Not listed
Dipeptidyl peptidase-4 (DPP-4) inhibitors	2007	2008	7	2012	19	Not listed
	2008	2009	4	Not available	Not available	Not listed
	2010	2011	Subsequently delisted	Not available	Not available	Not listed
	2012	2012	7	2015	19	Not listed
	2015	Not available	Not available	Not available	Not available	Not listed

Figure 14 New drug access journey timelines for selected chronic diseases in Singapore's public healthcare sector. Data as of July 2017.

Our interviews indicated that these access and timeliness variances could be improved by a more standardised evaluation process across the healthcare institutions, and having more industry engagement during the drug's evaluation into the public formularies.

Singapore's public healthcare institutions each exercises their own autonomy, maintaining formulary lists independently with undisclosed evaluation criteria, with evaluations performed under closed-door circumstances by the individual hospital's Pharmacy and Therapeutics committees.

Deloitte understood that with the exception of one institution, the formulary listing process in a public hospital (Figure 10) would have limited direct industry involvement throughout the initiation and evaluation process. Requests to initiate evaluations are generally limited to healthcare practitioners, and the industry having to rely on these practitioners to communicate supporting medical/clinical data.

Again, there are possibilities to improve the standardization and transparency of the formulary listing processes across Singapore's public hospitals, and better industry engagement in the initiation and evaluation process. Certainly, the industry are able to provide the essential data for drug cost-benefit evaluations and increased engagement would facilitate faster access for a larger number of patients.

Broadening medicinal choices for patients and physicians

In public healthcare systems, the breadth of access of IM is also restricted since the institutions often limit the listing to one to two molecules within the same therapeutic class. However, patients may not all respond in the same way to the same medicine. As such each individual patient may require physicians to prescribe products from different manufacturers even within therapeutic classes, to test which would be most effective. With such limitations, patients are hence denied of medicinal choices and effective treatment options.

Figure 10 demonstrates some typical considerations, with several stakeholders interviewed citing non-clinical concerns or administrative limitations, such as medication safety risk, inventory space and logistics constraints. However, other stakeholders have expressed such issues should not be a primary reason for limiting medication choices to patients.

Given the growth of new diagnostic and informatics approaches, better understanding of the molecular basis of diseases and new drug evaluation methodologies (e.g. usage of real world evidence), each new therapy should be evaluated on its own merits, including for new indications as they are discovered to create more effective treatment choices for patients. A broader treatment option range will help clinicians who are also regional Key Opinion Leaders (KOLs) in their respective fields to access and clinically try out more treatment options, and understand patients' response and treatment effectiveness in the local patient demography. Given Singapore's vision as a biomedical science hub, this also provides the platform for hypothesis generation and further scientific outcomes for local clinicians.

Moving forward, re-clustering into integrated Regional Health Systems and the proposed implementation of a National Drug Formulary (as laid out in the National Pharmacy Strategy) may potentially enable more transparency in the listing process. Not only does the Strategy aim to consolidate the listing requirements from various hospitals, it also aims to enhance supply chain and vendor management IT systems in public sector, potentially resolving some of the above-mentioned issues. These are helpful solutions that will help enhance the patient and physician access to IMs in public healthcare system.

4.2 Open conversations with industry and public in subsidy considerations

The Singaporean healthcare system separates the role of "payers" (patients, insurance and ACE/DAC), "regulators" (HSA), and "formularies" (individual hospitals). In public sector, subsidies mechanisms i.e. SDL and MAF play a critical role in drug prescription considerations. Deloitte understood that the lists currently contain mainly generics and IMs that are nearing patent expiry.

In reviewing subsidy systems, Singapore's evaluation process was benchmarked against countries with perceived mature assessment processes/bodies in the United Kingdom, Australia, New Zealand and South Korea (Figure 15). The caveat here, as with all other regulatory systems, is the need to cater to the requirements of the local landscape and societal values and openness. As such there appears to be no definitive right or wrong in terms of how an assessment process should be implemented and this benchmarking study merely reviews differences in processes and consideration.

Month/Year	Singapore	United Kingdom	New Zealand	Australia	South Korea
Subsidy governing body	DAC / ACE	NICE	PHARMAC	PBAC	HIRA
ICER threshold (2016)	No fixed threshold value	£20,000 to £30,000 / QALY	No fixed threshold value	No fixed threshold value	US$20,000 / QALY
Initiation of the process	Healthcare professionals, but industry may be invited to submit data for comparative purposes	Appraisal Committee, including the NHS, academia and pharmaceutical supplier	Anyone - a patient, a health professional, or a pharmaceutical supplier - can make a funding application	Medical practitioners (specialists, general practitioners and clinical pharmacologists), pharmacists	Health professionals only
Public and industry involvement in decision making	Closed group decision making based on consensus by DAC No public nor industry involvement in decision	Pharmaceutical suppliers, health professionals, consumer groups and patients	Pharmaceutical suppliers, health professionals, consumer groups and patients	Consumers, health economists and industry representatives	No public nor industry involvement in decision
Feedback to decisions	Currently no official avenue for feedback from industry nor public	Decision making normally based on consensus during the committee meetings, which includes a variety of stakeholders	Welcomes feedback from public domain by publishing announcements online	Input from sponsors through submissions and relevant stakeholders, both clinical and consumer-based, through stakeholder meetings	Feedback from benefit claim review
Transparency	Guidelines and Drug Guidances have been progressively released since May 2017	A structured abstract made available for public disclosure	Practise under the Official Information Act and Privacy Act to provide access to information	Information provided to the PBAC can form part of the PBAC Minutes, the PBAC Outcomes and the Public Summary Document	The assessment plan is released on the HIRA website and media two months prior to the actual assessment

Figure 15 Benchmarking on subsidy evaluation methods and transparency in five countries[35 36 37 38]

Our benchmark results indicated that the process in Singapore and other mature assessment processes, differ in mainly two areas:

- How the regulatory bodies engage with industry/public at its initiation, pre- and post-decision making processes; and
- The intention to limit subsidy choices to one medication for a given therapeutic class.

The following sections review issues around these topics.

[35] PBS guideline. Accessed 08 July 2017, from http://www.pbs.gov.au/industry/listing/procedure-guidance/files/procedure-guidance-listing-medicines-on-the-pbs.pdf
[36] NICE guideline. Accessed 08 July 2017, from https://www.nice.org.uk/process/pmg19/chapter/
[37] PHARMAC guideline. Accessed 08 July 2017, from https://www.pharmac.govt.nz/medicines/how-medicines-are-funded/
[38] HIRA guideline. Accessed 08 July 2017, from https://www.hira.or.kr/eng/ebook/00_Page_img/extra/00.pdf

Increasing industry and public engagements

In recent years, the subsidy review process has been evolving, and the setup of ACE in 2015 to assess a drug's cost-effectiveness has facilitated decisions to subsidise IMs such as NOAC and SGLT2. Industry interviewees have also seen an increased interest by MOH to enhance transparency and industry engagement. ACE has been commended as being progressive, actively engaging stakeholders including the physicians and industry on its processes and methodologies. Comparatively, some countries may not have similar openness and interactions.

Nonetheless, interviewees still note that ACE can further increase interactions with the industry outside of price submissions. As demonstrated in Figure 11 and Figure 15, industry interactions remain limited and when benchmarked against other countries differ in the (lack of) involvement in the initiation and subsidy decision input processes. A possible reason is that the drug effectiveness data considered by ACE as part of their Incremental Cost-Effectiveness Ratio (ICER)[39] assessments would have been submitted by clinicians within the initial dossier application. Our benchmarking further demonstrated a lack of mechanism for the public to initiate a drug subsidy listing process, nor to provide feedback on the outcomes.

Understandably, an increase in public or industry involvement may require additional resources and lead to process complications. However, increased industry engagement will help facilitate and expedite the evaluation process: especially with industry providing dossiers with improved alignment to ACE requirements, a better understanding of HTA models employed, and mechanisms to provide feedback on the technical insufficiencies if any.

In our interactions as well, the industry has been open to share with ACE their regulatory expertise and knowledge, especially from their experience with more mature countries. This is because HTA is still an advanced and state-of-art topic, with a well-known lack of regulatory expertise in Singapore and the region.

> Transparency is important for several reasons: “First, the availability of detailed information about a drug's benefits and harms would allow interested individuals to review and analyse trial data themselves. If independent analysts come to the same conclusions as regulators and other decision-making bodies, confidence in the decision-making process would increase.
>
> Second, a lack of transparency always gives the impression that something is being hidden. The drug evaluation system would be perceived as being more legitimate if the public were aware of how and why decisions are made and had an opportunity to provide input.
>
> (Thirdly,) Governments might also benefit from increased public trust.
>
> Finally, increased scrutiny of the decision-making process might lead to better decisions.”
>
> **Dhalla and Laupacis, 2008[40]**

[39] ICER: A statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a healthcare intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. In HTA case, the effect is measured by Quality-adjusted life years (QALYs) gained. ICER's use means that price is a key concern and since evidence is already submitted at the initiation, the Industries' involvement is limited to price negotiations at a later stage.

[40] Dhalla I., Laupacis, A. Moving from opacity to transparency in pharmaceutical policy, 2008. Accessed from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2228347/
Irfan Dhalla and Andreas Laupacis are with the Department of Medicine, St. Michael's Hospital and the University of Toronto. Andreas Laupacis is also with the Keenan Research Centre at the Li Ka Shing Knowledge Institute of St. Michael's Hospital and the Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario

Increasing subsidized choices

While the industry welcomes assessment based on HTA, our interviews revealed perceptions that ACE's assessment too often became a discussion on price, before submission to DAC for final subsidy decisions. Often, it seemed that only one medication brand is selected at a time, typically the lowest priced drug, in order to contain costs and spur pricing competition, overshadowing the HTA merit of the drug's itself.

Providing an alternative view, New Zealand's PHARMAC was successful in using a similar mechanism whereby one brand was selected and given sole supply rights for a determined period of time to control the country's pharmaceutical expenditure and significantly manage prescription costs as compared to other OECD countries.[41] In recent years, however, PHARMAC have started to give more choices to patients by funding several medications for the same condition, allowing more patients to access IMs (case study: More treatments funded for respiratory disease).

With broader access, more patients will be able to benefit from the latest treatments available, and the increase in patient volume may potentially reduce costs due to economies of scale.

Case Study:
More treatments funded for respiratory disease[42]

PHARMAC is funding six new medicines that will improve treatment options for people with COPD.

COPD is a respiratory condition that is one of the leading causes of death in New Zealand.

Director of Operations Sarah Fitt says the new products and changes to prescribing rules increase treatment options for people with COPD.

"PHARMAC currently funds four products specifically for COPD. The new agreements grow this number significantly, giving choice to patients and clinicians treating them," says Sarah Fitt. "The agreements also enable PHARMAC to list some of the products without restriction which will mean that some people currently unable to access funded treatment will be able to do so."

"As a result we're expecting the number of people receiving funded treatment for COPD to more than double over the next five years."

Currently about 22,000 New Zealanders receive funded treatment for COPD.

Depending on uptake rates of the new products, PHARMAC estimates that savings could be in the region of NZ$10 million over five years. This is because price concessions that PHARMAC has obtained with broader patient volume due to expanded choices, will generate savings in the long term for the country.

With broader access, more patients will be able to benefit from the latest treatments available, and the increase in patient volume will potentially drive down cost further due to economies of scale.

[41] PHARMAC implemented a sole supply rights tendering system, and had been rejecting inclusion of new drugs on the schedule when it deems the market is sufficiently provided for, i.e., limiting choices of molecules in the same class. BMJ. How New Zealand has contained expenditure on drugs, 2010.
[42] PHARMAC. More treatments funded for respiratory disease, 2016. Accessed 15 Jun 17, from https://www.pharmac.govt.nz/news/media-2016-02-09-copd-treatments/

4.3 Promoting clinical trials in Singapore

Despite the limited population pool, Singapore remains consistently recognised as one of the top destinations to conduct clinical trials, for its high quality sites and globally-renowned investigators. However, 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 (Figure 16).

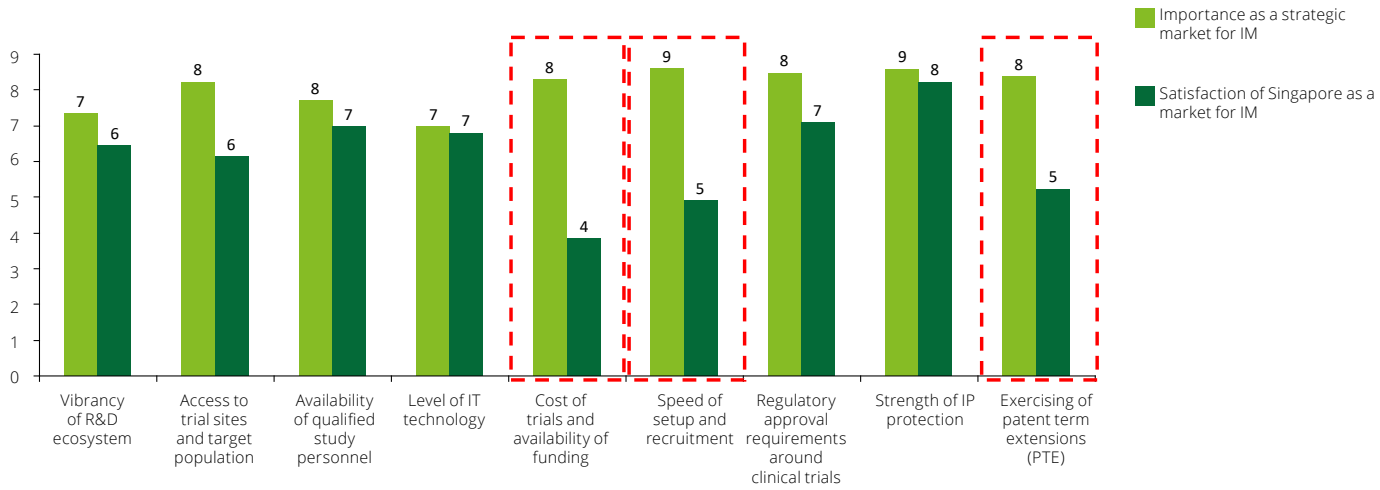


Figure 16 Deloitte survey: R&D and Clinical trials environment in Singapore

Data from a study by one pharmaceutical company (Figure 17) further showed the costs of study per patient/visit in Singapore are the highest across regional clinical research competitor countries (Australia, South Korea, Taiwan and Thailand). The costs of conducting trials on a "per patient" basis in Singapore is almost double the cost in Thailand, and significantly more expensive than mature economies such as Australia and Korea.

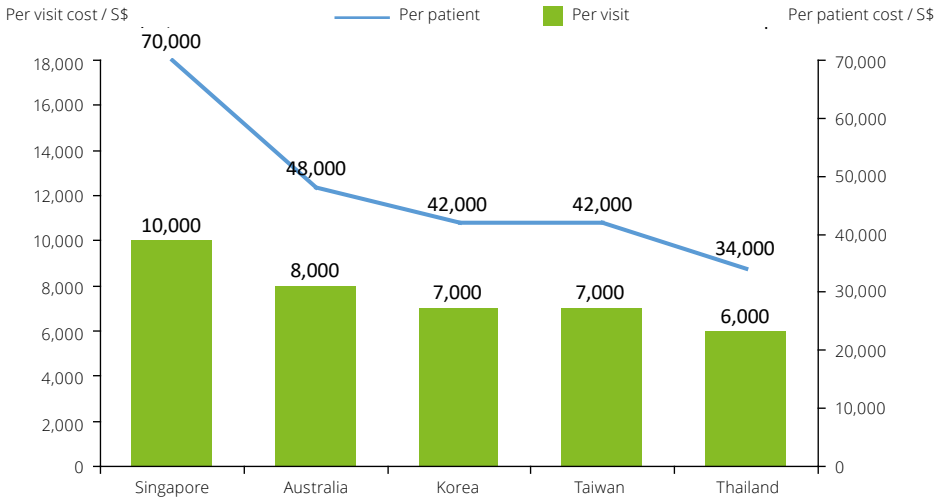


Figure 17 Cost comparison of a same study across 5 countries in Asia Pacific, 2016

One key reason behind the high cost in Singapore, besides the high administrative and resource costs, is that patients enrolled into clinical trials are not covered by any form of government subsidies, i.e., patients are charged at "Class A" rates[43], and the entire costs are borne by pharmaceutical companies. As compared to neighbouring countries such as Korea and Taiwan, where the National Health Insurance covers the "standard of care"[44], pharmaceutical companies only need to cover for the extra costs incurred. Should the standard of care be covered by the national insurance (or in Singapore's case, by government subsidy), cost of conducting trials can be reduced significantly.

Another aspect raised in our interviews are situations whereby certain individual study sites (public hospitals) may increase the laboratory and imaging fees during the trial period as these fees are benchmarked against the increasing investigational fees of the hospitals for their general pool of patients. This is especially challenging to researchers to manage costs over long term studies where investigators and patients are "locked" to that site. Certainly, fair market value justification and clear transparency would be desirable to better manage per patient costs in Singapore. For example, Deloitte understood that certain institutions do provide full transparency by breaking down administrative fees, providing industry clarity on how better to manage trial costs.

Difficulties in speed of setup and recruitment were also noted, mainly due to a lack of coordinated setup and infrastructure. This opportunity cost of delays, with already inherent challenges on patient enrolment and retention only discourages researchers from conducting large scale trials in Singapore.

When asked to compare Singapore's competitiveness with other countries, respondents indicate that some countries (consistently mentioned - South Korea, Taiwan and Thailand) are catching up on researcher capabilities at much lower costs, with coordinated policy positions to attract investments. These regional competitors are putting Singapore's status and reputation as biomedical hub under threat, even if not now, in 5-10 years.

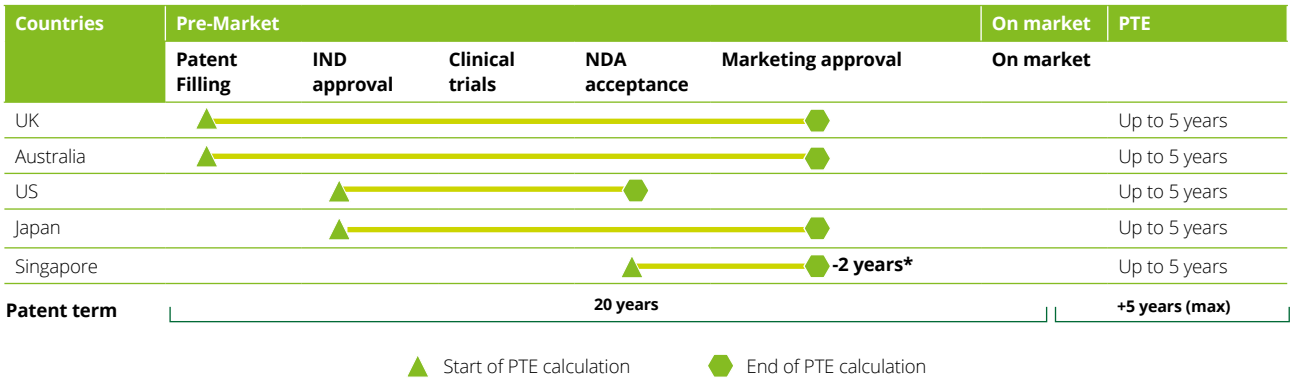
Fortunately, our interviews also revealed that government agencies such as EDB, SCRI and NMRC are studying strategies on various measures, including possibility of having a pre-agreed trial fee for an agreed duration at the sites when the contract is signed instead of the potential variability of fees due to inflation during the trial period, and also a potential to cover cost of investigations and drugs for patients which are part of their standard of care. It is also encouraging that 43% of industry respondents in our survey were willing to help, and offered streamlining of internal process, implementing digital technology and sharing economies of scale as ways to facilitate this. It is possible to find collaborative solutions to encourage conducting more clinical trials in Singapore, and for all stakeholders to work together.

[43] Class A: Highest class of ward in a public hospital where patients do not enjoy any government subsidy for inpatient stay.
[44] While the level to which standard of care is provided in different countries is still debatable, in this Position Paper, standard of care is defined as the minimum level of care provided by a National Insurance Scheme.

4.4 Aligning Singapore's patent term extensions towards a global Innovation hub

Singapore rightfully prides itself as a centre for world-class clinical research and clinical trials in the region, and an IP policy that is consistent with this will reinforce the attractiveness of Singapore as a biomedical science hub. A well-designed and effective PTE mechanism is an important element of a strong IP system as it gives additional exclusivity to biomedical sector and thus encourages investment in biomedical R&D. Section 36A(5) of the Singapore Patents Act recognises that a proprietor of a pharmaceutical patent should be compensated for any delay caused by the "process of obtaining marketing approval" for a pharmaceutical product.

Clinical trials – whether conducted in Singapore or elsewhere – represent an integral and indispensable part of the marketing approval process. Many developed country IP regimes include clinical trials when calculating patent term extension periods (e.g. European Economic Area, Switzerland, Australia, Japan, US, South Korea).[45,46,47,48,49] In Singapore, however, clinical trial period is not included in the PTE consideration (Figure 18).



NB: *PTE calculation is from HSA NDA acceptance to approval but exclude 2 years of review time.
The calculation methodologies shown are general cases. Actual start date of PTE calculation may vary in different situations. However, clinical trial period is always included during the PTE calculations in the above four countries (UK, Australia, US and Japan).
IND: Investigative New Drug

Figure 18 PTE calculation methodology in selected countries

[45] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (Codified version); see also "Public Policy Statement: Patent Term Extensions," Merck, 2011
[46] Australia Patents Act 1990 and Commonwealth of Australia, Explanatory Memorandum, Intellectual Property Laws Amendment Bill 1997. See also "How are Pharmaceutical Patent Term Extensions Justified? Australia's Evolving Scheme," C. Lawson, Journal of Law and Medicine, December 2013; and "Pharmaceutical Extensions in Australia: A Reference Guide," Pizzeys Patent and Trademark Attorneys.
[47] Article 67(2) of the Patent Act, Japan, and "Purport of the System of Patent Term Extensions," Government of Japan (English version), https://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/Guidelines/6.pdf . See also "Overview of the Patent Term Extension in Japan," Kawaguti & Partners, available at https://www.kawaguti.gr.jp/aboutlaw/jp_practices/01_1.html; and "Overview of Patent Term Extension in Japan," Anderson, Mori, and Tomotsune 2012.
[48] Patent Act of the Republic of Korea, Article 31(2), (3) or Article 42(1) of the Pharmaceutical Affairs Act; or Article 8(1), Article 16(1) and Article 17(1) of the Agrochemicals Management Act. See also "Patent Term Extension in Korea," American Intellectual Property Law Association, January 2014.
[49] 35 U.S.C. § 156. See also "Hatch Waxman Boot Camp," Mary Till, Legal Advisor, Office of Patent Legal Administration, United States Patent and Trademark Office, and "Public Policy Statement: Patent Term Extensions," Merck, 2011.

Aligning the developed IP regimes by extending the PTE in Singapore to include the clinical trials period, as is the case the other countries listed in Figure 18, will be beneficial. For one, this maintains Singapore's competitiveness in attracting foreign direct investment, since excluding the clinical testing phase from the calculation of term serves as a disincentive not only for filing patent applications in Singapore. Secondly, it can attract clinical trials which are demographically-pertinent in Singapore.

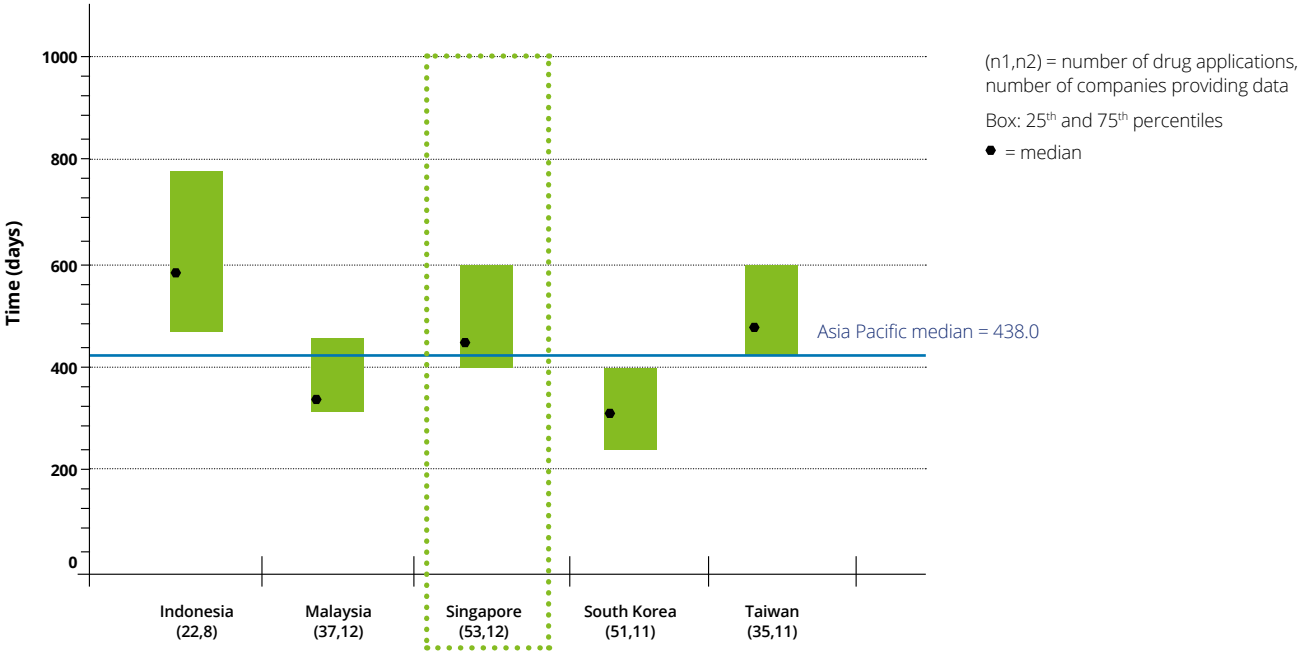
The Committee for the Future Economy (CFE), a 30-member committee comprising of public and private sectors was convened in 2016 to chart economic strategies for the next decade. In the 2017 report, the CFE identified IP as a key driver of Singapore' economic growth and a need for "a clear and ambitious IP strategy and a standardised IP protocol, which translates into speed, clarity and consistency in our approach to commercialising IP and creating enterprises".[50] In line with CFE's recommendation, Singapore needs to consider ways through which it can strengthen the IP protection for both local businesses and global companies who seek to establish innovative operations in Singapore.

[50] CFE. Report of the Committee on the Future Economy, Recommendation SC1.9, 2017.

4.5 Taking a holistic view of market registration and its far-reaching impact

HSA regulates market registration and authorises new drugs to be sold in Singapore. Generally HSA is perceived to have a transparent and productive working relationship with the industry, with opportunities for regular dialogue.

Globally, HSA's approval timelines remains competitive, being on the median for Asian countries (Figure 19): ahead of countries like Indonesia and Taiwan but notably behind countries such as Malaysia and South Korea. Nonetheless, the industry has noted HSA to be efficient and timely in the review process that the timelines are well-adhered to.



NB: Data are shown for NDAs that were approved between 1 Jan 2010 and 31 Dec 2014.
Chart time (days) includes industry's time to respond to queries (stop clock timing).

Figure 19 Country Regulator approval timelines across Asia Pacific[51]

An interesting observation noted by HSA is that NDA applications in Singapore have lagged behind the first worldwide regulatory submission to the FDA or European Medicines Agency (EMA) by up to 1 year. According to Deloitte's dialogues with industry regional heads, the delay indicates that Singapore was not one of the "wave 1" countries for drug launch for global pharmaceutical companies, and has lost its strategic value versus other markets.

[51] International Pharmaceutical Manufacturer Group (IPMG), Indonesia, 2016.

Verification route is less chosen

Currently, the industry can choose among 3 routes for submission of a New Drug Application (NDA) for regulatory approval. All timelines exclude screening periods and stop-clocks:

1. Full evaluation route that takes 270 days with no reference country approval required;
2. An abridged route that takes 180 days with 1 reference country approval required; and
3. A verification route that takes 60 days with 2 reference country's approval required.

Despite intending for the verification route to quicken drug access, a study conducted by industry of 28 NDAs in 2017 demonstrated that only 2 drugs (7%) were approved via the verification route. Similarly, HSA internal statistics showed that 85% of NDA were processed via the abridged route with the remaining 15% under full or verification route.[52]

Our discussions with HSA and the industry noted that currently, the verification route is less chosen, typically due to the need to follow more stringent requirements for a successful application. These issues include:

1. Time is required to obtain the reference authority's evaluation report.
2. It is restricted to limited indications.
3. Due to the restrictive qualifying requirements for the use of this route, some applications are instead re-routed as an abridged applications.
4. There is a requirement for a greater level of documentation compared to the abridged route.

In our interview with HSA, it was reflected that the verification route heavily leverages on the reference agency's technical assessment and approval. The pre-requisites are necessary to ensure products are of genuine same efficacy, safety and quality as approved by the reference agencies. HSA has also shared that some companies may apply for clinical uses modified from the reference agencies' approved use, or for manufacturing aspects that are of lower standards.

[52] HSA statistics.

Impact on pharmaceutical manufacturing as Country of Origin

The regulatory approval timeline has also an impact on pharmaceutical manufacturing. Certain countries requires a Certificate of Pharmaceutical Product (CPPs)[53] from the country of origin (COO) and/or the reference country(s) for importation. The speed of approval in Singapore therefore has an impact on the particular drug's market access to other countries, and hence its attractiveness as a pharmaceutical manufacturing site.

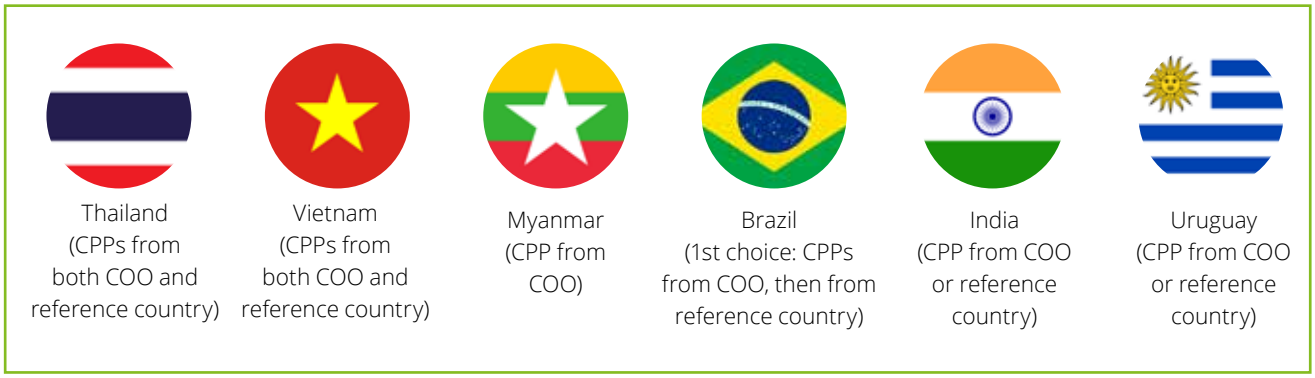


Figure 20 Importation requirements of selected countries with CPP requirements

In recent years, EDB and the industry have been partnering to explore and promote the newest drug manufacturing technologies and manufacturing of biologics and enzymatic products. As these new IMs emerge and production out of Singapore increases, local regulatory approval timelines will become critical for Singapore to successfully market itself as a as a key export country for drug manufacturing.

While there is a need for Singapore to maintain a competitive position, it remains equally important that HSA is able to ensure a quality review of medical safety, quality and efficacy, whilst mindful of the impact from market registration evaluation. Indeed, HSA and the industry has been in constant engagement to explore more efficient ways to conduct regulatory reviews, such as the working group in e-Labelling commencing in September 2017.

The CFE in 2017 identified medical devices as a key area of growth, given that it is rapidly growing and gaining strong traction in Singapore. As a result, HSA was supported and resourced to establish a "priority review" channel for new medical device applications. While this is a welcomed move, benefitting patients and ecosystem alike, it is necessary to consider that many advanced medical technologies and novel medical devices build upon new medicines and treatments by pharmaceutical companies, with a symbiotic relationship established between the industries e.g., companion diagnostics and new biologics drugs that require more targeted drug delivery systems. Through a strong partnership between the emerging med tech sector and the incumbent pharmaceutical industry, local med tech companies can be better enabled to develop expertise and enrich the value of their current product portfolio.

[53] The CPP is a certificate issued in a format recommended by the WHO which establishes the status of the pharmaceutical product and of the applicant in the exporting country. This is issued by the local health authorities and first needs to be registered locally.

5. Desired Outcomes – a Better Health and Economic Outcomes for a Vibrant Biomedical Ecosystem

Singapore's commitment towards establishing an efficient policy and infrastructure has compensated for its limited domestic market, and on numerous occasions has been quoted as one of the key attributes for attracting industry investments into the country's biomedical industry. The influx of pharmaceutical companies establishing regional headquarters, R&D centers and manufacturing plants over the past 20 years is a testament to Singapore's strong government policies and support. In contrast, an overly restrictive access environment and policies could make companies hesitate and resist future investment or expansion in Singapore.

Looking ahead, Singapore is expected to grapple with a multitude of market challenges to retain its global position in these aspects. Singapore's competitors are investing huge amounts of resources to develop their biomedical sectors and have been described by industry leaders to be equally competitive or mere years away. In order to better compete vis-à-vis its competitors, Singapore must constantly review its strategies to adapt to the current global climate and headwinds and assess areas of opportunities to take advantage of.

Furthermore, according to a published article in World Economic Forum, some countries may also establish market registration barriers such as drug importation quotas and local investment requirements in return for registration access, handicapping efficient downstream supply chains and public access to newer medications.[54] Although there are no outright market entry barriers in Singapore, some pharmaceutical companies have expressed that issues in funding and hospital access (mentioned in the earlier chapters) may be viewed as "barriers" compared to other countries. As mentioned previously, companies are no longer viewing Singapore as one of their priority markets for new drug launches. Effectively and in the longer run, Singaporean patients and doctors will face delayed access to innovative therapies and medicines, which will be detrimental to the patients, healthcare systems and economy, and may erode our leadership as a biomedical hub in the future.

Back home, the healthcare sector has undergone several waves of development and re-clustering to ensure better accessibility and more efficient allocation of resources. For many years, the MOH and the relevant agencies strove hard to contain costs while still achieving quality patient outcomes, via quality service provision or innovative treatment adoption. Indeed, "to be the world's most cost-effective healthcare system" used to be a tagline. However, one may consider if the emphasis on continued cost containment will stifle the vibrancy of biomedical innovation ecosystem, as Singapore's pool of medical KOLs shrink given the lack of exposure on the new innovative treatments. Without this exposure, medical doctors in Singapore may not get to study new treatment options and to influence on the global stage.

Last but not least, it is critical that policy decisions and initiatives are taken in the interest of enhancing quality, affordability, and access, and the interdependencies of each government policy need to be carefully and holistically aligned. Many industry leaders interviewed have pointed out the differing government policies: between the visions for Singapore as a global biomedical and innovation hubs, but not taken the opportunity to look beyond Singapore's own traditional management models in the healthcare system. These are minor "chips" to Singapore's reputation, which may add up in the longer run.

To further develop towards an Innovation hub, Singapore can potentially lead the way by adopting an innovative approaches towards policy making in the areas of market registration, access, subsidies, clinical trials and patent terms. Greater inter-agency communication and cohesion during policy making as well as more open and collaborative engagement with industry stakeholders can increase efficiency and effectiveness towards addressing specific national challenges, creating a win-win solution for all parties involved.

Riding on innovative and forward-looking policies such as Healthcare 2020 Masterplan, "3 Beyonds", RIE2020 and the CFE national initiatives, Singapore needs to also look to innovative approaches to continue improving an already vibrant biomedical ecosystem. These are reviewed in the next Chapter.

[54] World Economic Forum: Enabling Trade: Valuing Growth Opportunities 2013. Accessed on 5 July 2017, from http://reports.weforum.org/global-enabling-trade-2013/pharmaceuticals/.

6. Steps Forward - Working Hand in Hand

Some of the challenges faced by the healthcare system, for example, raising costs, are deeply rooted in the system and also prevalent in many other countries. Such challenges cannot be solved unilaterally and may require collaborative, joint and innovative approaches to resolve them. There are many innovative models currently implemented in other developed markets and Singapore may consider their adoption and lead in such innovative models:

6.1 Alternative innovative pricing models

Performance-based access agreements
To avoid inefficient spending on the treatment of patients who may not respond to a particular drug, these agreements are managed on a case-by-case basis and payment based on effective performance. Such an arrangement minimizes the risk of financing a technology that is not cost effective. In this manner, it may potentially improve the payer's willingness to finance the drug.

Case Study:
In the UK under J&J's mooted pay-for-performance scheme, patients undergo full course of bortezomib (Velcade) only if patients exhibited complete or partial response, and the cost is repaid to the patients after undergoing for four cycles of non-responsive treatments.[55]

In Singapore, healthcare institutions may be cost-conscious in advocating for the usage of IMs, and hence the adoption of performance-based pricing models can potentially alleviate some level of cost burden on the hospital and mitigate uncertainties towards the drug's effectiveness.

Coverage with evidence development
This scheme provides conditional reimbursement whilst collecting targeted drug and patient data in parallel, with the aim of reducing material uncertainty. Access to the product is temporary until new evidence emerges from the patient cohort over a defined period allows the regulators to make a final decision. Real world evidence could also potentially be used to provide insights into how a drug or drug class performs or is used in real-world medical settings. This model is becoming increasingly adopted in countries such as US, Australia, UK and Sweden.[56] [57] [58]

For Singapore, ACE can allow for greater certainty of the evaluation process prior to the recommendation of its cost effectiveness. To increase the success of such a model, Singapore healthcare providers can use clinical pathways to gather real world evidence on cost, outcomes and quality.[59] Technology and analytics can help support the collection of real world evidence and allow refinement of protocols to improve success.

Cost sharing
Similarly, the adoption of cost sharing would help to balance expectations and share risks between the hospitals and drug manufacturers. This is evident in cases where clinical data is insufficient to take an informed view on cost-effectiveness at the point of drug launch.

Case Study:
In Slovenia, an oncology medicine risk sharing scheme was set up in 2010 for Iressa (Gefitinib), a medicine from AstraZeneca. The scheme consists of a rebate plus free supply of the medicine for the first 2 months of treatment. It was used to measure the drug's short-term effectiveness, with respondents of the scheme covered by Social Health Insurance. The two main aims of introducing this scheme in Slovenia are to control overall budget and finance pharmaceutical which are considered or proven cost-effective.[60]

[55] APM Health Europe. J&J offers NHS performance-related payment for Velcade. 2007.
[56] Trueman P, Grainger DL, Downs KE. Coverage with evidence development: Applications and issues. International journal of technology assessment in healthcare, 2010.
[57] Mohr PE, Tunis SR. Pharmacoeconomics. Access with evidence development: The US experience, 2010.
[58] Jaroslawski S, Toumi M. BMX Health Service Resources. Market access agreements for pharmaceuticals in Europe: Diversity of approaches and underlying concepts. 2011.
[59] Deloitte. The evolution of oncology payment models: What can we learn from early experiments, undated.
[60] Andalusian School of Public Health. Experiences and impact of European Risk Sharing schemes focusing on oncology medicines, 2011.

Emulate pricing models from other industries

One approach by the med tech industry is "solutions pricing". Under this pricing model, companies shift from selling products and absorbing service as a cost, towards offering solutions for both products and services that the customer values together.[60]

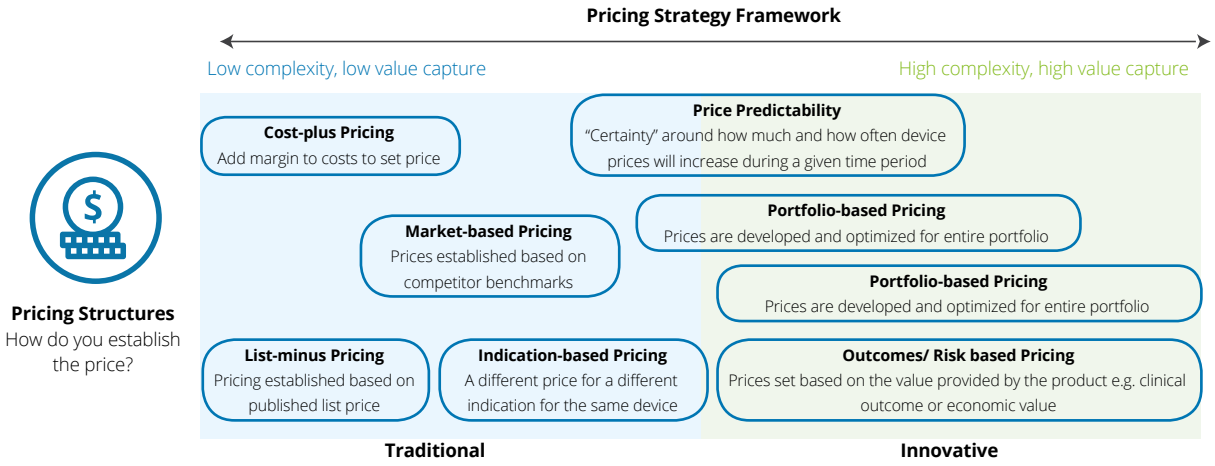


Figure 21 Examples of innovative pricing strategies in med tech

For Singapore, this can be applied to hospitals in which they can work with pharmaceutical companies to co-develop an integrated solutions so that the hospital is able to achieve better patient outcome at a higher cost efficiency. However, such an approach requires a good understanding of hospital workflows, clinician behaviour, clinical and economic data and technology capabilities to monitor the performance and measure the how well this solution is performing.

[61] Monitor Deloitte. Capturing the value of medtech ingenuity: The case for pricing innovation, undated.

6.2 Alternative access models

Adaptive licensing

Since 2010, HSA has been involved with Massachusetts Institute of Technology Centre for Biomedical Innovation's NEW Drug ParadigGmS (NEWDIGS) initiative to explore the possibility of implementing adaptive licensing model. Similar to CEDs as described earlier, adaptive licensing models allow restricted patient groups to get quicker access to IMs while HSA provides conditional approval and is able to get more substantial evidence for its internal assessment via the use of real world efficacy and safety monitoring data.[62]

HSA is keeping a watching brief on developments in real world evidence. Several concerns exists, including on the quality of patient data that will be gathered. Unlike clinical trials where the data is collected under a controlled environment, the variability of each patient's lifestyle and dietary habits complicates data collection and will require structured and robust data cleaning methods. This is nonetheless an area of great interest among global regulators and with high potential of resolving many existing problems.

Adoption of big data to harness real-time data sharing

In the US, a private and academic consortium established a cloud based platform called Cancer Outcomes Tracking and Analysis (COTA), to capture and analyze cancer patients with similar characteristics. This allowed clinicians and researchers to capture cancer sub-types and molecular characteristics, allowing for more accurate comparisons and retrospective insight into how patients with similar patient profiles were treated and what their outcomes were, thereby allowing for an informed clinical decision in real time.[63]

The use of big data has been increasingly popular as it may potentially unlock potential of enabling precision medicine and cost efficient care.[64] [65] Payers, governments, healthcare institutions and pharmaceutical companies can potentially work together to better use technology and analytics to better monitor the outcome of IMs if concerns exist over its treatment value. Such an approach ensures that IMs are given an equal chance for patient adoption but placed at lower risk for all parties.

[62] European Medicines Agency. European Medicines Agency launches adaptive licensing pilot project. 2014.
[63] Deloitte. The evolution of oncology payment models: What can we learn from early experiments? Undated. Accessed on 7 Jul 2017.
[64] Marketwired, COTA increases cross-industry support with the addition of Celgene, Foundation Medicien, Inc., HealthScape Advisors and Novartis as strategic investors. 2016. Accessed on 7 Jul 2017 from, http://www.marketwired.com/press-release/cota-increases-cross-industry-supportwith-addition-celgene-foundation-medicine-inc-2127749.htm
[65] GlobeNewswire. COTA Enters Innovative Collaboration to Enhance Outcomes and Drive Value-Based Cancer Care. 2016. Accessed on 7 Jul 2017 from, https://globenewswire.com/news-release/2016/01/28/805304/0/en/COTA-Enters-Innovative-Collaboration-to-Enhance-Outcomes-and-Drive-Value-Based-Cancer-Care.html

6.3 More collaborative learning and programmes

Cross border and sector partnerships can be explored in which knowledge sharing is further facilitated. Both HSA and ACE have expressed potential benefits in enhancing their regulatory abilities e.g. an increase in performance of sophisticated cost-benefit equations with improved design. Industry stakeholders can also play a part in co-developing a common learning platform for both parties to share their knowledge and expertise.

Case Study:
Working together on healthcare policy for better patient care[66]

Shire, together with patient groups and the specialty pharmacy community helped shape US healthcare legislations, the 21st Century Cures Act, which was passed in December 2016. Previously, the US federal health insurance programme (Medicare) provided insurance coverage for home infusion of drugs self-administered by a subcutaneous pump, but did not cover associated nursing and training. As a result of the efforts, beneficiaries can now receive training, nursing, and support services needed for self-infusion of medication.

More public platforms for dialogue between industry, MOH and other stakeholders such as doctors and patient groups can be arranged as well, to discuss on certain topics of population wellbeing. For example, in Australia, the Cancer Drugs Alliances work together with Federal and State Government as well as other stakeholder groups on timely and affordable access to new cancer medicines.

Furthermore, pharmaceutical companies can also work with ministries and agencies in public health promotion and health education programmes. For example, awareness and lifestyle changes early in life can make a difference in disease prevention and overall health. Industry partners can sponsor or support patient advocacy and support groups, for instance in cancer or diabetes, to promote regular disease screening and adoption of healthy eating habits and active lifestyles. With a better informed public population, patients will be empowered to make the right choices when it comes to choosing IMs or alternative types of therapies.

Case Study:
Healthy Heart Africa[67]

Healthy Heart Africa is AstraZeneca's programme launched in October 2014 with the aim of supporting Africa's health systems by investing in education, screening, reduced-cost treatment and control for patients with existing hypertension. Providers are trained and they support the development of guidelines that are appropriate for community-based implementation. Supply chain and distribution models are also developed to ensure access and affordability to healthcare.

Through PPPs, Healthy Heart Africa is able to create a sustainable healthcare model that has activated over 400 health facilities, screened over two million people and is now treating thousands of patients every day.

In summary, the abovementioned approaches may potentially address Singapore's challenges for IM, so that both government and industry stakeholders are able to achieve common grounds. Ultimately, the local population will be the final beneficiaries, gaining access to IMs via a series of innovative pricing, access models and public-private collaborations. These collaborative models contributes to further economical and health outcomes, strengthening our position as an innovative biomedical hub.

[66] Shire. Annual Responsibility Review 2016. Accessed on 28 Aug 2017, from https://www.shire.com/-/media/shire/shireglobal/shirecom/pdffiles/newsroom/global%20files/shire-annual-responsibility-review.pdf
[67] McKinsey & Company. Pharma's next challenge, 2015. Accessed on 5 Jul 2017, from http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-next-challenge

7. Conclusion

The story of Singapore's transformation from a mud-flat into the global metropolis it is now, within 50 years is nothing short of a modern day miracle.[68] The Singapore leadership had the foresight and resolution, and in the past 20 years have attracted the biomedical industry and transformed Singapore into a leading biomedical hub that hosts numerous global pharmaceutical regional headquarters, manufacturing plants and R&D facilities. This was not an easy journey and is something all Singaporeans can be proud of.

At the same time, Singaporeans today enjoy both quality and affordable healthcare - which in many other developed countries do not co-exist at equivalent levels. William Haseltine, in his book Affordable Excellence: The Singapore Healthcare Story spelt out three compelling qualities that he found to have enabled the Singapore's success: long-term political unity, ability to recognize and establish national priorities, and the consistent desire for collective well-being and social harmony of the country.[69]

As Singapore's economic competitors catch up, it is imperative for Singapore to enhance the existing system and business friendly policies to continue to strengthen its foothold. Also, with the silver tsunami upon us and rising affluence of local population, the expectations of quality care has risen much more quickly than the public system can respond to. As was the case years before, the foresight and resolution of Singapore's policy makers is once again being tested.

In order to achieve long term success, Singapore needs to constantly remember its hallmark qualities: boldness of vision, foresight and strong can-do spirit which are the key ingredients of its economic success and the foundation to maintain its competitiveness on a global scale.

Our review and analysis has led us to the following conclusions:

- IMs play a crucial role in Singapore's health outcomes and economic development.
- Given the socio-demographic shifts and evolving disease trends, the roles of IMs are ever more important. The healthcare outcomes include patients having longer lifespans, with a better quality of life, and healthcare systems and government ultimately also enjoy sustainable gains in the longer term.
- However, certain policies and regulatory processes in pockets of the ecosystem have weakened Singapore's attractiveness as a market and this impedes patient's access to newer, better and potentially more cost-effective therapies. These starts from clinical trials to registration, commercialisation, subsidy process and decisions, and eventually PTEs.
- Healthcare challenges faced by Singapore e.g. costs are common in many other countries. The best patient outcomes require stakeholders to look forward and collaborate, identifying and removing barriers, and developing multi-faceted and innovative approaches to resolve these problems.
- Key areas include having more dialogue and transparency in decision making, and streamlining duplicative processes and structures which result in system inefficiencies.
- The biomedical industry can and is ready to play a larger role and contribute on national healthcare and economic policies/ outcome discussions with the Singapore government. With a combination of expertise, it is in the mutual interests of all parties concerned.

The above suggestions support the various healthcare masterplans for better patient access, affordability and quality; and also reinforces Singapore's commitment in RIE2020 and CFE towards biomedical innovation. These initiatives can cement Singapore's position as a leading biomedical hub, provide the best IMs to patients, benefit our healthcare practitioners, systems, as well as provide a strong value proposition to government stakeholders.

[68] National Archives of Singapore. Transcript of a speech made by the prime minister, Mr Lee Kuan Yew. 1965. Accessed on 5 Jul 2017 from, http://www.nas.gov.sg/archivesonline/data/pdfdoc/lky19650912a.pdf
[69] Haseltine, W. Affordable Excellence: The Singapore Healthcare Story, 2013.

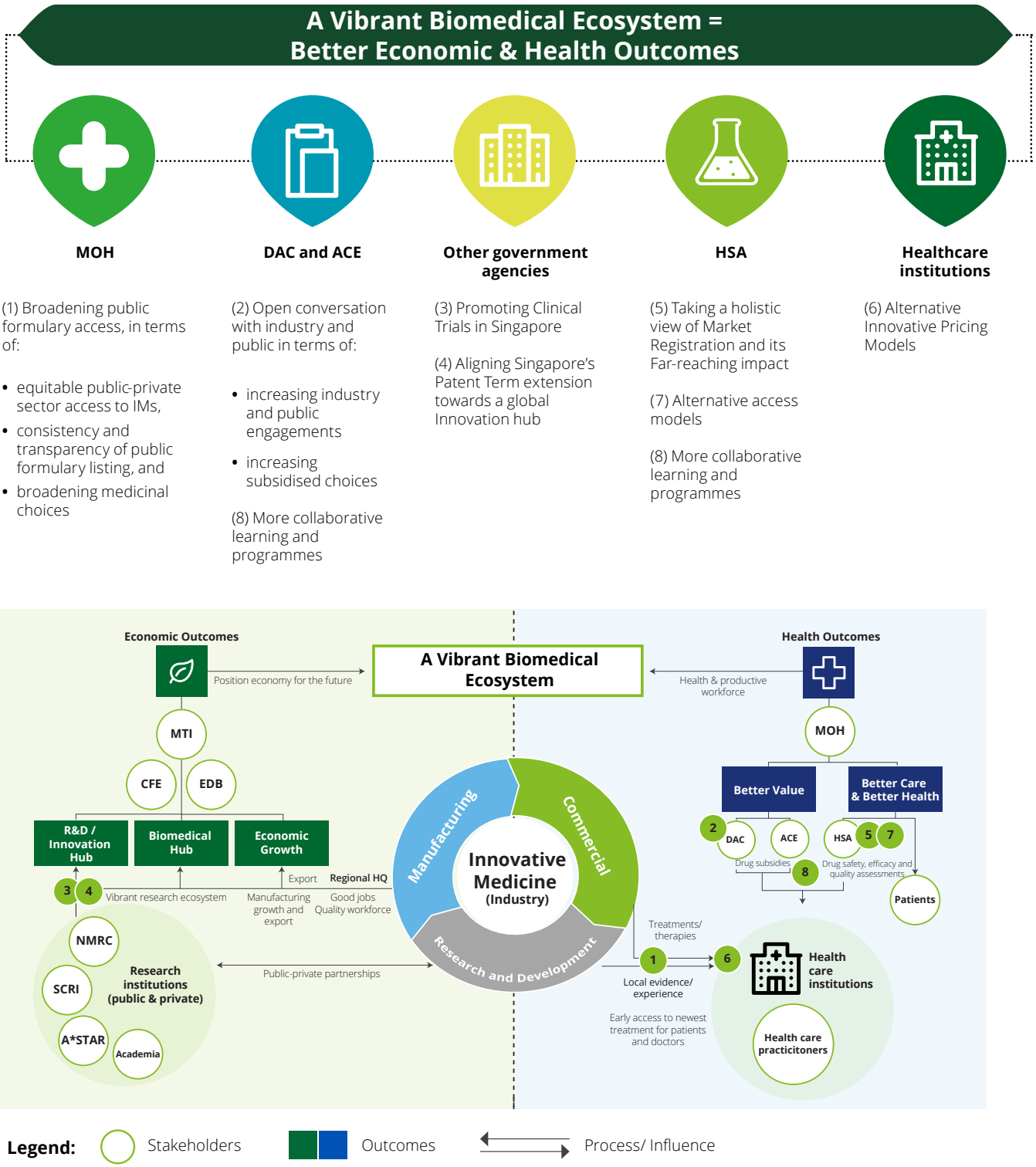


Figure 22 & 23 Suggestions to enhance access of IMs for a more vibrant biomedical ecosystem in Singapore

8. Appendix

8.1 Methodology

Deloitte was commissioned by SAPI to help develop this Thought Paper. In order to present a holistic view and a fair position, Deloitte implemented a three-ways approach to engage all the stakeholders in the ecosystem through surveys and interviews (primary research) and desktop research/benchmarks (secondary researches).

Survey amongst Industry members	Stakeholder Consultation	Secondary research
Tailored questionnaire covering selected areas, i.e. • Market Access, • Patent Protection, • Regulatory and • Clinical Trials to identify concerns and impediments towards an improved access and funding of IM and the potential impact on the patient	Interviews with hospital management, government agencies and/or academia to identify • Current access to IM • Current listing process in hospitals • Interview with patient associations to identify • Patient's journey to IM • Problems patients may encounter due to limited access to IM	Benchmarking with selected competitor countries • Macroeconomic and healthcare key indicatives • How regulatory approval of IM is prioritised • Current listing process in hospitals • Reimbursement process for IM in other countries • Benchmark the role and processes of ACE against similar bodies such as NICE, PHARMAC

Deloitte would also like to thank the following stakeholders in their participation in this study and their invaluable inputs in sharing information on the IM ecosystem (in alphabetical order):

Industry contributions (in alphabetical order):		Stakeholder interviewed (in alphabetical order):	
Pharmaceutical companies:	***Distributors:***	***Government agencies:***	***Hospitals, Academia and Patient Associations:***
Abbvie Actelion Astellas AstraZeneca Bayer Eisai GlaxoSmithKline Johnson & Johnson Kyowa Hakko Kirin Menarini Merck Novartis Pfizer Roche Sanofi Aventis Shire	DKSH LF Asia Zuellig Pharma	ACE EDB HSA MOH NMRC SCRI	Diabetes Society of Singapore (DSS) National University Hospital (NUH) National University of Singapore (NUS) – School of Public Health Singapore General Hospital (SGH)

This Thought Paper was also supported by Deloitte's Center of Regulatory Excellence (CORE) for Life Sciences, based out of the UK, for regulatory inputs and review.

About Deloitte CORE
Deloitte CORE provides advisory services to life sciences companies in assessing the impact of regulatory change on their business processes, governance, organisational structure and technology and supporting them to develop strategy and implementation. CORE bring the Firm's Life Sciences experts from across our global member firm network together. Our work is centred on understanding, implementing and training global regulatory change and our team of deeply experienced experts are skilled in achieving this.

8.2 Survey Questionnaire Sample

Survey Questionnaire for SAPI members

RESPONDENT PROFILE

Purpose: To ensure that correct respondents are interviewed

P1 Name of Respondent

P2 Organisation Name

P3 Email
Contact Number

P4 Latest Financial Year period
(and used as basis of data provided in survey)?

SECTION A: RESPONDENT BACKGROUND SCREENER

S1 Which department(s) are under your management? *Please choose all that applies*

- Clinical operations
- Manufacturing
- Reimbursement and market access
- Medical affairs
- Commercial
- Country operations
- Project management
- Others, pls specify

Others, pls specify:

S2 Which geographies do you cover under your portfolio? *Please choose all that applies*
Note: If the respondent does not cover Singapore, TERMINATE survey.

- SEA: Brunei
- SEA: Cambodia
- SEA: Indonesia
- SEA: Laos
- SEA: Malaysia
- SEA: Myanmar
- SEA: Philippines
- SEA: Singapore
- SEA: Thailand
- SEA: Vietnam
- Ex-SEA: Australia & New Zealand
- Ex-SEA: China
- Ex-SEA: India
- Ex-SEA: South Korea
- Others, pls specify

Others, pls specify:

SECTION B: ORGANISATION BACKGROUND

Purpose: To understand the current R&D manufacturing and commercial activities of the organisation

Q1 Kindly provide the **following statistics** in terms of your companies' activities for the last FY in Singapore only in terms of the following areas:

- R&D investment
- Manufacturing investment
- Manufacturing output
- Local pharmaceutical sales (IM only, excluding generics)
- Clinical Trials run

Q1.1 What was the YoY growth/decrease in the **last** 5 years (2012-2016)?
Q1.2 What is the expected YoY growth/decrease in the **next** 5 years (2017-2021)?

	Last FY SGD Mil	**Last 5 years** +/- %	**Next 5 years** +/- %
R&D investment			
Manufacturing investment			
Manufacturing output (sales value)			
Local pharmaceutical sales (IM only, excluding generics)			

	No.	+/- %	+/- %
No. of clinical trials run			

Q2 In the last FY, what is the **volume breakdown in clinical trials sponsored** by your company (inhouse + outsource) in Singapore?

Q2.1 How will you expect the trial volume breakdown to change in the **next** 5 years (2017-2021)?

	Last FY % Vol breakdown (Sum up to 100%)	**Next 5 yrs** % Vol breakdown (Sum up to 100%)
Phase I		
Phase II		
Phase III		
Phase IV		

Q3 As at the last FY end, how many **full-time equivalent (FTE) employees** did your organisation employ in Singapore?

Q3.1 How do you expect this to change in the **next** 5 years (+/- %) (2017-2021)?

	No. of FTEs #	**Next 5 yrs** +/- %
R&D		
Manufacturing		
Commercial *		
Regional HQ		

** Commercial includes all local functions pertaining to Singapore operations incl. Regulatory, Medical etc.*

SECTION C: PERCEPTIONS OF SINGAPORE'S OPPORTUNITIES, CHALLENGES AND COSTS FOR IM

Purpose: To understand perspectives and challenges companies faced when implementing IM strategy (clinical research and market access strategy) in Singapore

Q4 From a scale of 1-10 (1= not important at all, 10 = very important), **how strategic is Singapore** as a market for IM?
(Examples of strategic value (including but not limited to): big potential of un-tapped market, a gateway to Southeast Asia/Asia market, high quality of infrastructure and quality talent to leverage on for clinical research)

Strategic Level	

Q4.1 From a scale of 1-10 (1= not important at all, 10 = very important), how important are these factors for Singapore to become a strategic market for IM?

Business environment and manufacturing	
Country reputation and stability	
Favourable laws and regulations	
Availability of quality workforce	
Cost of workforce	
Cost of raw materials and import/export policies	
Tax and investment incentives	
Others, pls specify:	

R&D and clinical environment	
Vibrancy of R&D ecosystem	
Access to trial sites and target population	
Availability of qualified study personnel	
Level of IT technology	
Cost of trials and availability of funding	
Speed of setup and recruitment	
Regulatory approval requirements around clinical trials	
Strength of IP protection	
Exercising of patent term extensions (PTE)	
Others, pls specify:	

Market Access and Commercialisation	
Market size and competitive intensity	
Effectiveness of alternative NDA evaluation channels (e.g. abridged & verification route)	
Speed of NDA regulatory approval	
Transparency of NDA regulatory approval	
Streamlined/efficiency of NDA regulatory evaluation	
Regulatory policies promoting choice of IM	
Speed in DAC/ACE evaluations	
Transparency in DAC/ACE evaluations (incl. criteria)	
Transparency in public hospital GPO tendering policies	
Speed in public hospital drug listing decisions	
Transparency in public hospital drug listing process/decisions	
Availability and variety of healthcare subsidies	
Ease of govt. approval over new subsidy models	
Ease of IM inclusion into reimbursement system	
Regulations around patient access programs	
Others, pls specify:	

Q5 From a scale of 1-10 (1= least satisfied, 10 = most satisfied), how would you rate your **overall satisfaction level** in Singapore being a market for IM?

Satisfaction Level

Q5.1 From a scale of 1-10 (1= least satisfied, 10 = most satisfied), how would you rate your satisfaction level in the following attributes?

Business environment and manufacturing	
Country reputation and stability	
Favourable laws and regulations	
Availability of quality workforce	
Cost of workforce	
Cost of raw materials and import/export policies	
Tax and investment incentives	
Others, pls specify:	

R&D and clinical environment	
Vibrancy of R&D ecosystem	
Access to trial sites and target population	
Availability of qualified study personnel	
Level of IT technology	
Cost of trials and availability of funding	
Speed of setup and recruitment	
Regulatory approval requirements around clinical trials	
Strength of IP protection	
Exercising of patent term extensions (PTE)	
Others, pls specify:	

Market Access and Commercialisation	
Market size and competitive intensity	
Effectiveness of alternative NDA evaluation channels (e.g. abridged & verification route)	
Speed of NDA regulatory approval	
Transparency of NDA regulatory approval	
Streamlined/efficiency of NDA regulatory evaluation	
Regulatory policies promoting choice of IM	
Speed in DAC/ACE evaluations	
Transparency in DAC/ACE evaluations (incl. criteria)	
Transparency in public hospital GPO tendering policies	
Speed in public hospital drug listing decisions	
Transparency in public hospital drug listing process/decisions	
Availability and variety of healthcare subsidies	
Ease of govt. approval over new subsidy models	
Ease of IM inclusion into reimbursement system	
Regulations around patient access programs	
Others, pls specify:	

Q5.2 How is Singapore's IM environment today, compared to that of 5 years ago?

Q6 Looking at the IM life cycle, which of the following activities did your company incur the **greatest resources** (number of manpower hours x average personnel costs)?

Kindly rank the activities in order of highest costs incurred, with 1 being the highest cost and 10 being the lowest cost.

	Rank (1 to 10)
Submission of Investigational New Drug application	
Clinical trial agreement	
Ethics and regulatory review application	
NDA submission	
Interactions with DAC/ACE	
Drug Formulary Listing application	
Drug Formulary Listing evaluation with Public Hospitals P&T Committees	
Tendering and pricing negotiations with Public Hospital GPOs	
Filing patent applications	
Patent term extension (PTE) application	

Q7 What is the **time spent** (weeks) for clinical, market access and commercial processes for 3 most recent drugs marketed by your company?

	Case 1 Weeks	**Case 2** Weeks	**Case 3** Weeks
Name of IM product			
Submission of Investigational New Drug application			
Clinical trial agreement			
Ethics and regulatory review application			
NDA submission route (i.e. full/ abridged/ verification route)			
NDA evaluation			
Listing by DAC			
Listing on Drug Formulary with Public Hospitals			
Tendering and pricing negotiations with Public Hospital GPOs			
Filing patent applications			
Patent term extension (PTE) application			

Q8 As at the end of the recent FY, kindly disclose the **total number of IM products** registered with HSA and listed on hospital formulary listings (public and private)?

For example, 10 products registered with HSA, and 8 and 10 products listed with public and private hospitals respectively

	#
No. of IM registered with HSA*	
No. of IM listed on Public Hospital Formulary Listings	
No. of IM listed on Private Hospital Formulary Listings	

** Those IMs with market commercialisation intent only*

SECTION D: OPPORTUNITIES FOR IMPROVEMENT IN THE IM ECOSYSTEM

Purpose: To identify unmet needs and greenfield opportunities for improvement and collaboration within IM ecosystem

Q9 What do you think are the **top 3 measures** in each category that would facilitate a more vibrant IM ecosystem?
Kindly rank the activities in order of importance, with 1 being the most important.

Q9.1 Amongst the top measures chosen, kindly indicate (tick) which areas do you think your organization can contribute to improving IM ecosystem?

	Rank (Top 3 per category)	M/C *
Business environment and manufacturing		
Creating training and development opportunities		☐
Having less complex and bureaucratic processes		☐
Reducing the cost of doing business		☐
More conducive tax and investment incentives		☐
Flexibility to bring in foreign talents		☐
Critical thinking workforce capability		☐
Others pls, specify:		☐
R&D and clinical environment		
Better trained research workforce		☐
Better funding and process support for research		☐
More awareness campaigns for potential study subjects		☐
Longer IM patent terms		☐
IM patent term extensions (e.g. to include CT period)		☐
Lowered CT costs		☐
Faster study initiation timelines		☐
APAC hub capabilities to grow patient enrolment		☐
Others pls, specify:		☐
Market access and commercialisation		
Increased speed/transparency for NDA approval		☐
Relaxing of NDA approval policies and scrutiny		☐
More inclusion of IM into reimbursement system		☐
Speed and transparency of DAC/ACE evaluations		☐
Formulary listing policies that broadens access and promotes choice of IM		☐
Standardizing formulary listings across public hospitals and polyclinics		☐
More transparency in hospital tendering process		☐
Centralising existing GPOs/nation-wide GPO		☐
Guidelines on timing for formulary listing on hospitals		☐
Expanded drug options of similar NMEs		☐
Others pls, specify:		☐

** S/C – Single choice questions; M/C – Multiple choice questions*

Q10 Are there any other comments that you would like to share with us?

8.3 Strengths, Weakness, Opportunities and Threats Analysis

The following Strengths, Weakness, Opportunities and Threats (SWOT) Analysis was derived after stakeholder interviews, secondary research and benchmarking analysis of Singapore's biomedical landscape.[70]

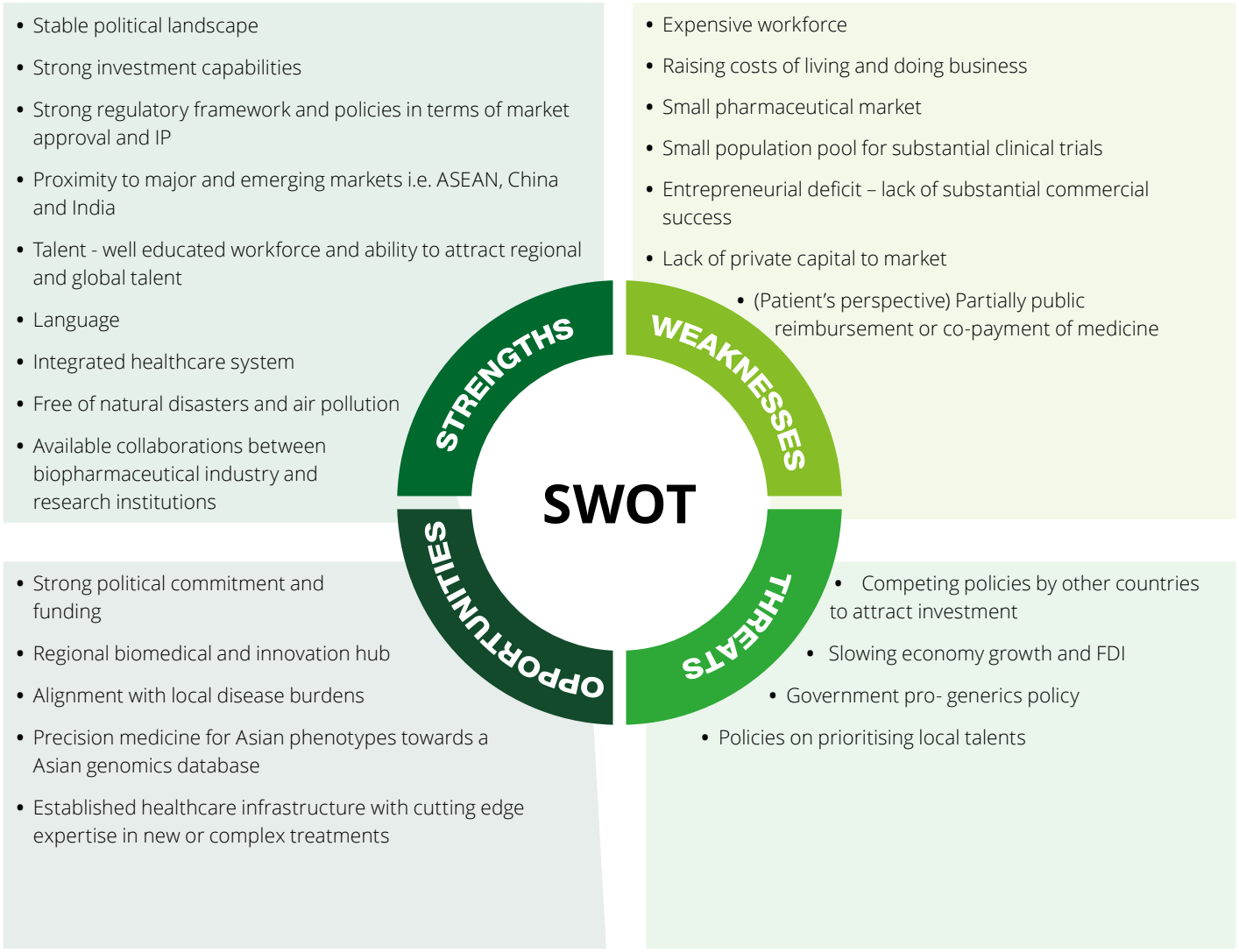


Figure 24 SWOT Analysis of Singapore' biomedical landscape

[70] The Economist Intelligence Unit. The Next Lap – Biosciences in Singapore 2025, 2015.

Deloitte.