Market & Regulatory Analysis of Singapore: An Epidemiological Study and Healthcare Research

Singapore is a fascinating country full of lively local cultures, rich history, amazing progress and also investment possibilities. Though physically small, the country is an economic giant. Singapore has become a flourishing country that excels in different sectors and is a model to developing nations. The country has also established strong fundamentals in healthcare excellence and providing universal coverage for Singaporeans with multiple layers of care. The standard of medical practice ranks among the best in the world. Singapore is committed to driving innovation that addresses the rising costs and inefficiencies in healthcare systems worldwide. The Ministry of Health (MOH) believes in ensuring quality and affordable basic medical service for all. The MOH also promotes healthy living and preventive health programmes, as well as maintaining high standards of living, clean water and hygiene, to achieve better health for all.

With a world-class infrastructure, a high level of human resources qualifications and a strong legal framework, Singapore offers an excellent environment for companies like CIDP to operate to their optimum level in research. In 2015, CIDP opened its fifth centre in Singapore, located in Biopolis, the heart of R&D for sciences, which is close to major universities, pharmaceutical industries and hospitals, as well as the Health Science Authority (HSA). CIDP has a dedicated department and a one-contact-person policy to deal with the regulatory submissions of clinical trials and ensure smooth communication with regulatory bodies and ethics committees. The cluster holds a strong knowledge of regulatory needs worldwide. As an example, CIDP has recently worked on the repositioning of a product from Asia to Europe for its commercialisation, in conformity with the European norms and standards.

1. Regulatory System and Clinical Trials in Singapore

1.1 Regulatory System

Singapore offers an excellent environment for clinical research and clinical trials. With an area of 719.1km² and a population of about 5.5 million inhabitants, the population in Singapore is mixed, consisting of Chinese (76 %), Malays (12 %), Indians (9 %) and other ethnicities (3 %). The country's health sector is divided in two, namely the public health sector and the private health sector – 80 % of the primary healthcare services are provided by private practitioners while the government polyclinics provide the remaining 20 %.

The healthcare regulatory framework in Singapore consists mainly of two parties, the regulator (comprising of MOH along with its statutory boards) and the regulated (comprising public and private providers). All healthcare facilities such as hospitals, medical centres, community health centres, nursing homes, clinics (including dental clinics) and clinical laboratories (x-ray laboratories) are required to apply for licence under the Private Hospital & Medical Clinics (PHMC) Acts / Regulations. All healthcare facilities are also required to maintain a good standard of medical/clinical service under PHMC Act/Regulations.

1.2 Clinical Trials

All clinical trials on medicinal products conducted in Singapore require clinical trial certificates (CTCs) from the Health Products Regulation Group (HPRG), Health Science Authority (HSA). With the increasing number of clinical trials research activities in Singapore, HPRG and HSA reviewed and updated the Medicines (Clinical Trials) Regulations in April 1998 and implemented the Singapore Guideline for Good Clinical Practice (SGGCP) on 1 August 1998. The SGGCP was adapted from the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP) Guidelines sets on ethical and scientific standards for the conduct of clinical trials, which also serves as an assurance that results obtained from clinical trials are credible.

The regulatory body responsible for clinical trials regulations in Singapore is the Health Science Authority (HSA) Register which was launched in September 2012. As can be seen in Table 1, there has been a rise in issuance of clinical trial certificates (CTCs) by HSA, which are needed before a trial can start.

Phase	2012	2013	2014
I	57	43	56
II	51	55	70
III	99	149	111
IV	43	50	43
Total	250	297	280

Table 1: Clinical trial certificates issued in Singapore from 2012 to 2014

Figure 1 gives an overview of the clinical trial therapeutic areas in 2014. The main therapeutic area for clinical trials revolves around 45 % in oncology, which is the leading cause of death in 2014, as reported by MOH, whereas 22 % are of other pathologies, namely dermatology, endocrinology, immunology etc.

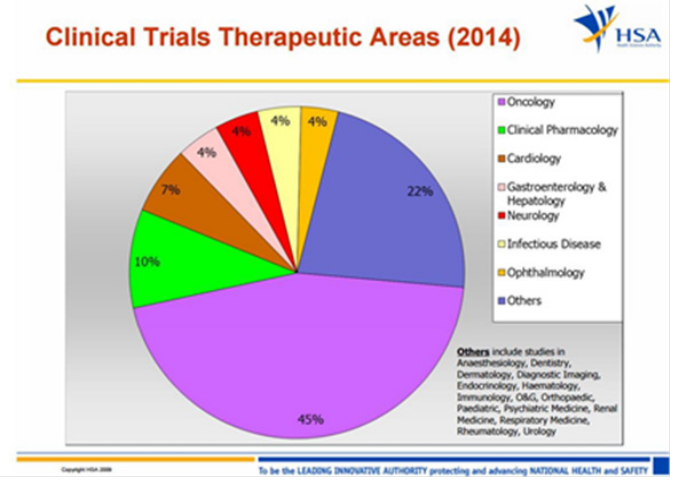
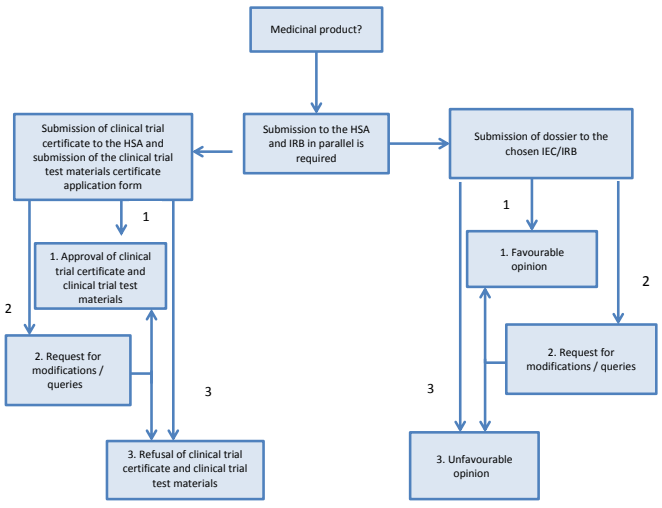


Figure 1: Singapore Clinical Trials Therapeutic Area in 2014

2.3 Submission Process of Study Dossier to Health Science Authority (HSA)

Before any clinical trials on medicinal products can be conducted, the principal investigator must obtain both ethics and regulatory approvals before initiating the study.

Parallel submissions should be made to both the regulatory body (HSA) and to the respective ethics committee (IRB). The regulatory (HSA) approval should be issued independent of the ethics (IRB) opinion. Figure 2 shows how to submit a study dossier to the Health Science Authority (HSA)



Clinical trial certificate issued within 30 days

The system of regulation requires that principal investigators (PIs) conducting clinical drug trials must obtain both ethics and regulatory approval before initiating a study. The ethics approval is from the chosen institutional review board (IRB). In order to receive regulatory approval from HSA to conduct clinical drug trials here, companies must provide relevant evidence that the investigational drug is acceptably safe and the design and conduct of the trial provide adequate levels of protection for participants. The regulatory approval, in the form of a clinical trial certificate (CTC), is issued to the PI of each trial site.

The target processing timelines in Figure 3 give an estimate of how long it would take HSA to process the related clinical trials applications in Singapore.

Type of Application		Target Processing Timeline (working days, excluding stop-clock time)
1	Application for Clinical Trial Certificate (CTC)	30
	Phase 1 clinical trials (solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interaction)	15
2	Extension of Clinical Trial	10
3	Application for Import of Clinical Trial Materials (CTM)	
	a) In conjunction with Application for CTC or Extension of Clinical Trial	As per (1) or (2)
	b) Subsequent application for approved clinical trial	3
4	Amendment of Protocol and/or Patient Informed Consent Form	15
5	Addition of Trial Site	10
6	Change of Principal Investigator	10

Import of Unregistered Medical Devices for Clinical Trials

Type of Application		Target Processing Timeline (working days, excluding stop-clock time)
1	Application for Import of Clinical Trial Materials (Medical Devices) (CTM-MD)	5

Figure 3: Target processing timelines

3. Types of Pathological Diseases in Singapore

According to international standards, Singapore has a good state of health. The boost in Singaporeans' health was largely caused by the high standards of education, good housing, safe water supply and sanitation, high quality medical services and the active promotion of preventive medicine.

3.1 Non-communicable diseases (NCDs)

The leading causes of morbidity and mortality are major non-communicable diseases such as cancer, coronary heart disease, stroke, pneumonia, diabetes, hypertension and injuries. NCDs greatly contribute to the disease burden in Singapore. MOH and the Health Promotion Board (HPB) have taken steps to promote healthy living in Singapore by introducing the "Healthy Living Master Plan" in 2014.

3.1.1 Cancer

As a developed country, Singapore is no stranger to cancer, as it was the leading cause of death in 2014, with a high percentage of 29.4% reported by MOH. Cancer is on the rise in Singapore – especially those linked to modern lifestyles, including smoking and eating too much. According to the Director of the National Cancer Centre Singapore, Professor Soo Khee Chee, Singapore's aging population contributes to the high mortality rate from

cancer. One factor that increases the chances of cancer is smoking, according to Professor Soo. Even though the overall rate of smoking is decreasing, there is a trend of younger people taking it up, with the HPB figures from 2010 showing that 16 % of young people aged 18 to 29 years old smoked regularly, up from 12 % in 2004. Tables 2 and 3, respectively, show the number of cancer cases by year from 2010 to 2014 and the incidence of cancer by gender from 2010 to 2014.

Year of diagnosis	2010	2011	2012	2013	2014	2010-2014
No. of notifications	11,431	11,726	12,295	12,651	13,416	61,519

Gender	Number	%
Male	29,750	48.4
Female	31,769	51.6

Table 3: incidence of cancer by gender, 2010 to 2014

3.1.2 Pneumonia

Pneumonia is responsible for 19 % of deaths in Singapore. Theoretically, it is generally not a severe disease as it is the inflammation of lungs due to infection, which in most cases are bacterial. Even so, it can become very serious and life-threatening. Elderly people with chronic pulmonary diseases, diabetes and congestive heart failure are more at risk to develop pneumonia.

3.1.3 Ischemic Heart Diseases

According to the Singapore Heart Foundation, 15 people die from cardiovascular disease, including ischemic heart disease, in Singapore every day. Cardiovascular disease accounted for 29.9 % of all deaths in 2014. This means one out of three deaths in Singapore is due to heart diseases or stroke.**3.2 Communicable Diseases**

In 2014 was a critical year for communicable diseases on both the global and local front. The MOH faced the resurgence of infectious diseases such as Middle Eastern Respiratory Syndrome (MERS) and Ebola Virus Disease (EVD). The outbreak of these diseases globally serves as a lesson to Singapore to underline the importance of maintaining vigilance and preparedness for new and emerging infectious diseases.

On the local front, dengue fever (DF) dengue haemorrhagic fever (DHF), tuberculosis (TB) and human immunodeficiency virus (HIV) were a few of the causes of illness in Singapore. Figure 4 (below) gives a clear overview of the communicable diseases situation in Singapore in 2014.

3.2.1 Dengue Fever (DF) / Dengue Haemorrhagic Fever (DHF)

DF / DHF posed a burden of communicable disease in Singapore; following the record dengue epidemic seen in 2013, the number of DF/DHF cases remained high in 2014 with 18,326 laboratory cases of DF/DHF reported. There were six deaths due to dengue in 2014. The main circulating serotype was DENV-1. Mosquito larval source reduction remains the mainstay of vector-borne disease control, and this approach requires active community participation. Public health education continues to be coordinated by the National Environmental Agency (NEA) with support by MOH.

3.2.2 Tuberculosis (TB)

The incidence of tuberculosis (TB) among residents and long-staying non-residents continued to decline from 37.6 in 2013 to 36.9 in 2014. Measures to strengthen case detection and treatment have been rolled out progressively to enhance the Singapore TB Elimination Programme (STEP) following a review in 2012, which addressed key challenges for TB control: delayed diagnosis of infectious TB cases and the non-compliance with the complete treatment regimen until a full cure.

Infectious disease notifications and deaths in 2014

Diseases	No. of notified cases	No. of Deaths+	Morbidity rate*	Mortality rate*
Air-/Droplet-Borne Diseases				
Hand, Foot and Mouth Disease	22,171	0	405.3	0.0
Measles	142	0	2.6	0.0
Meningococcal Infection	9	0	0.2	0.0
Mumps	478	0	8.7	0.0
Rubella	17	0	0.3	0.0
Vector-Borne/Zoonotic Diseases				
Chikungunya Fever	182	0	3.3	0.0
Dengue Fever/Dengue Haemorrhagic Fever	18,326	6	335.2	0.1
Malaria	62	1	1.1	0.0
Food-/Water-Borne Diseases				
Campylobacteriosis	435	0	8.0	0.0
Cholera	2	0	0.0	0.0
Hepatitis A	73	0	1.3	0.0
Hepatitis E	68	0	1.2	0.0
Paratyphoid	19	0	0.3	0.0
Salmonellosis	1,920	0	35.1	0.0
Typhoid	58	0	1.1	0.0
Blood-Borne Diseases				
Hepatitis B	48	0	0.9	0.0
Hepatitis C	5	0	0.1	0.0
Environmental-Related Diseases				
Legionellosis	37	0	0.7	0.0
Melioidosis	34	1	0.6	0.0
HIV/AIDS, STIs, TB & Leprosy				
HIV/AIDS**	456	87	11.9	2.2
STIs	10,183	0	186.2	0.0
Tuberculosis***	2,018	55	36.9	1.4
Leprosy	6	0	0.0	0.0

+Source: Registry of Births & Deaths
*Rates per 100,000 population, based on estimated mid-year total population, 2014 (Source: Singapore Department of Statistics)
** Refers to Singaporeans/PR cases
*** Refers to Singaporeans/PR cases & long staying foreigners

Figure 4: Overview of communicable diseases situation in Singapore 2014

3.3 Human Immunodeficiency Virus (HIV)

In Singapore, the number of newly-reported HIV cases in 2014 was 456 cases, which was similar to the number reported in 2013 (454 cases). This brings the number of cases per million population to 117.8. In 2014, 117 cases of AIDs were reported, including 116 with AIDS diagnosis of HIV infection and one previously diagnosed asymptomatic HIV-infected patient who progressed to AIDS. The 116 cases with AIDS diagnosis comprised 25 % of the newly-reported cases.

49 % of the newly-reported cases presented with late-stage HIV infection. MOH has added three clinics to the list of private clinics offering anonymous testing services, to enhance the accessibility to voluntary testing.

In previous years, HIV/AIDS cases were predominantly male, with a male-to-female ratio of 12:1. In 2014, the highest notification rates were observed for males in the 30-39 years age group, and for females in the 50-59 years age group, as shown in Figure 5.

Age					Notification rate per million population*		
	Male	Female	Total	(%)	Male	Female	Total
0 - 14	0	0	0	0%	0.0	0.0	0.0
15-19	6	1	7	2%	47.4	8.3	28.3
20-29	82	2	84	18%	312.7	7.5	158.6
30-39	108	8	116	25%	380.4	25.8	195.2
40-49	101	9	110	24%	328.4	28.4	176.1
50-59	80	9	89	20%	264.0	29.9	147.4
60 & above	45	5	50	11%	145.6	14.1	75.4
Total	422	34	456	100%	223.8	17.4	118.8

*Rates are based on 2014mid-year Singapore resident population
(Source: Singapore Department of Statistics)

Figure 5: Age-gender distribution and age-specific notification rates of HIV/AIDS among Singapore residents, 2014

Regulatory bodies aim at ensuring the safety of all medicinal products and services that are offered on a particular market, and at the same time providing the best health services for the public. Thus, a close collaboration of all stakeholders in the healthcare system will only be beneficial in translational research by bridging this gap between basic research and clinical care. As an international CRO which pioneered cosmetic and pharmaceutical R&D in Mauritius with over 12 years of experience in clinical research, CIDP has a team of 160 staff members, consisting of doctors, pharmacists, project managers, clinical research assistants, biostatisticians, biologists, chemists, data managers... and has built over the years an international network of investigators who are highly qualified and have contributed to the successful conduct of clinical trials. The state-of-the-art offices and equipment reflect CIDP's high quality standards.

In Mauritius, the BIOPARK where CIDP is located will host in a few weeks a CMO (contract manufacturing organisation) which will allow the pharmaceutical industry to reach a combined CRO / CMO service. An original and innovative proposal which will enable laboratories to save time in the development of a product by ensuring European quality standards set by CIDP.

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