RESEARCH ARTICLE

A study of new drug approval pattern of a Southeast Asian developed country from 2017 to 2021

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ABSTRACT

Background: The pattern of new drug approval is changing across the world as shown by the study using Center for Drug Evaluation and Research and European Medicines Agency data in US and UK with more drug approval for anti-cancer and immunomodulator drugs. There is a need to generate similar database for developed South East Asian countries too. **Aims and Objectives:** This study was conducted for one such country- Singapore for the new drug approval pattern of last 5 years (2017–2021). **Materials and Methods:** This was a pharmacoepidemiological study, in which government drug regulatory website data available in public domain was searched. The new drug approval data were classified according to active ingredient, drug approval date, new drug application category, indication of drugs, and World Health Organization Anatomic Thoracic Classification. **Results:** In this study, 418 new drug approvals were found in last 5 years in Singapore. From this maximum, drug approvals were given to anti-neoplastic and immunomodulator category drugs. In anti-neoplastic category new drugs approval few examples were Trastuzumab deruxtecan and Tucatinib for breast cancer therapy and Tepotinib and Capmatinib for non-small cell lung cancer therapy. **Conclusion:** This study shows that drug development in anti-cancer drug and immunomodulator is significant in Singapore. This trend is quite matching with other country such as US and UK.

KEY WORDS: New Drug Approval; Singapore; Health Science Authority

INTRODUCTION

New drug development is crucial for scientific progress of any country. Different countries have different unmet needs for new drug development that should be fulfilled by pharmaceutical industry. According to New drug and clinical trial rules 2019, new drug is defined as any active pharmaceutical ingredient or phytopharmaceutical drug which is not approved in that country or any approved drug having modified or new claim for indication, route of administration, dosage, and dosage form. As well as new drug is any new fixed dose combination of two approved drug or modified or new claim for indication, route of administration, dosage, and dosage form. It also includes a modified or sustained release form of a drug or novel drug delivery system of any approved drug. As well as a vaccine, r-DNA derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug.[1] The Singapore have Clinical Trial Guidance material that provides guidance to manufacturers, importers, and suppliers on the regulatory requirements relating to the import and supply of clinical research materials.[2]

Every country has the regulatory authority to check the authentic information regarding new drug approval and such information is available in public domain, for example, for US authentic information is available on Center for Drug

Evaluation and Research (CDER) website, established in 1987 under the US Food and Drug Administration (FDA).[3] Similarly for European union authentic data available on European medical agency (EMA) website[4] and for India it is Central drug standard control organization (CDSCO).[5]

The pharmaceutical sector and research and development remain strong pillar in Singapore economy. It contributes 5% of Singapore Gross Domestic Product (GDP). In 2021, pharmaceutical industry had contributed about 10.5 billion Singapore dollars (SGD) to the GDP which is significant increase from the previous year, that is, 8.77 billion SGD. The government of Singapore launches biomedical science initiative in 2000, that has amplified the pharmaceutical industry in the country.[6] Health science authority (HSA) is government authority for new drug approvals in Singapore. HSA had been formed on April 1, 2001, under the ministry of health and government of Singapore. This agency comprises three professional groups: the Health Products Regulation Group; Blood Services Group, and Applied Sciences Group. The Health Products Regulation Group ensures that medicines, innovative therapeutics, medical devices, and health-related products are wisely regulated and meet appropriate safety, quality, and efficacy standards. Its international partners include agencies such as the US FDA, Health Canada, Swissmedic, the Australian Therapeutic Goods Administration and China FDA.[7]

As a medical practitioner, it is important to know new drug approval pattern of the country so they can prescribe the relevant new medicine to the patient. As per a study, the drug approval process in India has more lag time as compared to developed countries such as US and UK which could lead to delay of few more years for the new drug to come out in market for the beneficiaries.[8] Study by Konwar *et al.* mentioned that absolute drug lag of CDSCO was 19 and 18 relative to the US FDA and Japan Pharmaceuticals and Medical Devices Agency (PMDA), respectively. The relative drug lag for the CDSCO vis a vis the US FDA, EMA, and PMDA was 43.2, 25.6, and 30.3 months, respectively.[9] For a Pharmaceutical industry, it is important to know new drug approval pattern of that particular country to remain relevant with the current trend in the pharmaceutical market. So study of drug approval pattern is important for various stakeholders of health-care delivery. Different studies conducted across the world have shown changing pattern of new drug approval with more number of anti-cancer and biologics being approved.[10]

Such studies have mainly been done in US FDA using CDER data, Japan using PMDA, European countries using EMA website data, and India using CDSCO. But similar baseline study is lacking in south east Asian developed country such as Singapore which formed the basis for our study. With Singapore becoming one of the fast growing countries in pharmaceutical engineering and export output of pharmaceutical products, it becomes imperative that a database is generated for its new drug approval pattern.

MATERIALS AND METHODS

This was a pharmacoepidemiological retrospective observational type of study in which drug approval pattern of new drugs in Singapore was studied. Data available on official website of Singapore government health authority were searched.[7] The data were compiled for the duration of January 2017–December2021.

Data on the website was available in form of monthly approval which was then entered to Libre office calc spread sheet. The new approved drugs were classified based on different parameters such as active ingredient, drug approval date, new drug application (NDA) category, Indication of drugs, and the World Health Organization (WHO) Anatomic Thoracic Classification (ATC).

In Singapore any new drug or biologics approval is given through NDA. There are three categories in NDA.
1. NDA category one - for first strength of new chemical or biological entity which is not previously registered in Singapore
2. NDA category two - applicable to first strength of product previously registered in Singapore having new combination, new dosage, new formulation, new presentation, new route of administration, new indication, new dosage recommendation, and new patient population included
3. NDA category three - for any new subsequent strength of chemical or biological entity that was previously registered in Singapore under NDA 1 or 2.

A biosimilar product applies to a biological product demonstrated to be similar in physicochemical characteristics, biological activity, safety, and efficacy to an existing registered biological product. Biosimilar products are required to be submitted via NDA-2 or NDA-3. Here NDA 2 is for the first strength of a bio similar product with the same dosage form and route of administration as the Singapore reference biological product. And NDA 3 is for subsequent strengths of a biosimilar product that has been registered or has been submitted as an NDA-2. The product name, dosage form, indication, dosing regimen, and patient population should be the same as that for the NDA-2 submission. Hence, the data were classified in three types of NDA categories as described above.

In the WHO ATC classification, the active ingredients were classified in fourteen main anatomical or pharmacological groups. Active ingredient is also classified according to hierarchy in five different levels - from which we have used level one classification with fourteen main groups in

this study. The descriptive analysis of data was done using Libre office calc. As the new drug approval data are freely available in public domain of Government website, so ethical permission is not required.

RESULTS

There were total 418 new drugs which were approved in Singapore during period 2017–2021, with an average of 83.6 new drugs approved annually in last 5 years and 29 annual new drug approval in NDA 1 category [Figure 1].

On classification of all the drugs according to the WHO ATC classification, it was found that maximum number of new drugs approvals 129 (30.86%) were from anti-neoplastic and immunomodulating agent category which was followed by 47 (11.24%) new drug approvals in anti-infective category and 44 (10.53%) new drug approvals in nervous system category [Figure 2].

The data were also classified according to NDA category and it was found that maximum number of new drugs belonged to NDA-2 category- 178 (42.58%) new drug approval followed by NDA-1- 145 (34.69%) new drug approval and NDA-3 category- 95(22.73%) [Figure 3]. From these new approved drugs, 27 were new biological entity and 91 were new chemical entity.

There were 11 biosimilars approved in last 5 years. There were 47 new dosage forms and 36 new combinations approved of already approved drugs in Singapore under NDA 2 category. There were 95 approvals given to new subsequent strength of already approved new chemical/biological/Biosmilar entity under NDA 3 category.

We had classified new chemical entity/new biological entity approval in Singapore in last 5 years. Few example of new drug approval were – (a) breast cancer (Trastuzumab deruxtecan, Tucatinib), (b) non-small cell lung cancer (NSCLC) (Tepotinib, Capmatinib), (c) SARS-CoV-2 (Tozinameran, Remdesivir), (d) HIV 1 (Doravirine), (e) Complecated Intra-abdominal infection (Eravacycline, Avibactam sodium), (e) Depression (Esketamine, Brexpiprazole), (f) Asthma (Erdosteine, Benralizumab), and (g) Pulmonary Arterial Hypertension (Selexipag) [Table 1].

DISCUSSION

This retrospective observational study was conducted to know new drug approval pattern in Singapore in last 5 years. In our study, 83.6 is average annual new drug approval found in Singapore and 29 annual new drug approvals in NDA 1 category. In comparison CDER, USA approved 50 new drug in 2021 and 53 new drug in 2020 with last 5 year average approval of 51 new drugs per year.[11]
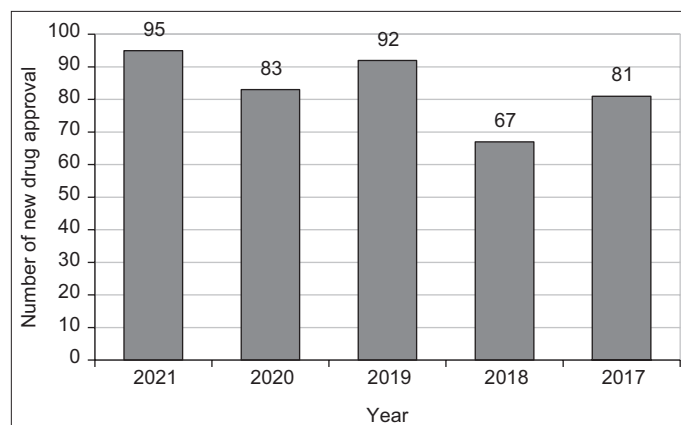
Figure 1: Annual new drug approval in Singapore in the last 5 years
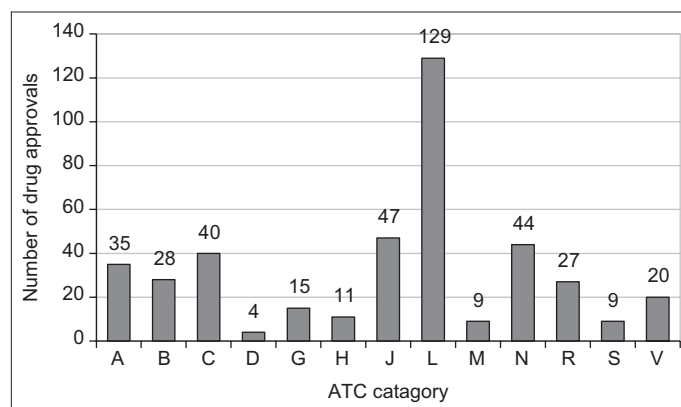
Figure 2: ATC Classification of new drug approval in the last 5 years. ATC Group: (a) Alimentary tract and metabolism; (b) Blood and blood forming organs; (c) Cardiovascular system; (d) Dermatologicals; (g) Genitourinary system and sex hormones; (h) Systemic hormonal preparations, excluding sex hormones and insulins; (j) Anti-infective for systemic use; (l) Anti-neoplastic and immunomodulating agents; (m) Musculo-skeletal system; (n) Nervous system; (p) Anti-parasitic products, insecticides and repellents; (r) Respiratory system; (s) Sensory organs; (v) Various
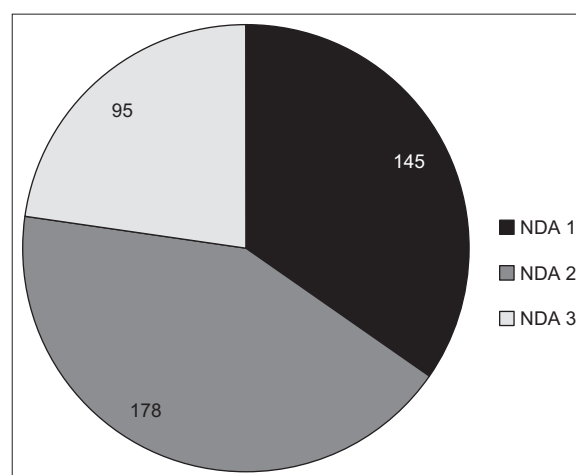
Figure 3: Classification of new drug approval according to NDA category

We found upwards trend of annual new drug approval with each year in this study except during COVID-19 pandemic which

Table 1: New drug approvals in NDA 1 category in Singapore in last 5 years

Few common conditions/disease	New drug approval in last 5 years
Common Cancer	
ALL	Pegaspargase, Inotuzumab Ozogamicin, Ponatinib Hcl
AML	Gemtuzumab ozogamicin, Gilteritinib, Midostaurin
CLL	Ponatinib Hcl, Venetoclax
Refractory B cell lymphoma	Polatuzumab vedotin
Breast cancer	Trastuzumab deruxtecan, Tucatinib, Talazoparib tosylate, Alpelisib , Neratinib maleate , Abemaciclib, Ribociclib
Non-small cell lung cancer	Tepotinib, Capmatinib, Lurbinectedin, Entrectinib, Dacomitinib monohydrate, Lorlatinib , Brigatinib, Durvalumab, Atezolizumab, Necitumumab, Alectinib
Multiple myeloma	Thalidomide, Carfilzomib, Ixazomib
Renal cell carcinoma (RCC)	Cabozantinib
Mantle cell lymphoma	Zanubrutinib, Acalabrutinib
Prostate cancer	Darolutamide milled, Apalutamide
Gastric cancer	Trastuzumab deruxtecan
Solid tumors	Larotrectinib
Urothelial carcinoma	Erdafitinib
Merkel cell lymphoma (MCC)	Avelumab
Colorectal Cancer (CRC)	Tipiracil hydrochloride + trifluridine
Malignant Glioma	Aminolevulinic acid
Malignant Melanoma	Cobimetinib, Trametinib
Common infections	
HIV 1	Doravirine, Elvitegravir+Cobicistat+Emtricitabine+Tenofovir Alafenamide Fumarate
Compleacated intra-abdominal infection (C IAI), UTI, Ventilator associated pneumonia (VAP)	Eravacycline, Avibactam sodium, Ceftazidime pentahydrate, Bictegravir sodium+emtricitabine+tenofovir alafenamide fumarate, Ceftolozane+Tazobactam
HCV	Sofosbuvir+Velpatasvir Voxilaprevir, Glecaprevir+Pibrentasvir, Elbasvir+razoprevir, Sofosbuvir+Velpatasvir
Aspergilosis, Mucormycosis	Isavuconazonium sulfate
Cytomegalo virus infection (CMV)	Letermovir
SARS-CoV-2	Tozinameran, Remdesivir
HZ, PHN	[Antigen] Recombinant Varicella Zoster Virus glycoprotein E (gE)
Influenza	Pandemic Influenza Virus Type A, inactivated and disrupted , Baloxavir marboxil
Botulism	Botulism antitoxin (equine) serotypes A, B, C, D, E, F, G
Menigococcal disease	MnB rLP2086 subfamily A, 120μg/ml, MnB rLP2086 subfamily B, 120μg/ml
Common Fungal Infection	Bifonazole
Tuberculosis with HIV	Rifapentine
Common CNS disorders	
Depression	Esketamine, Brexpiprazole
Schizophrenia	Brexpiprazole, Cariprazine
Tardive Diskinesia	Valbenazine ditosylate
Prophylaxysis of Migraine	Eptinezumab, Fremanezumab, Galcanezumab, Erenumab
Insomnia	Lemborexant
Lennox-Gastaut syndrome (LGS)	Rufinamide
Neuromyelitis optica spectrum disorders (NMOSD)	Satralizumab
Spinal Muscular atrophy (SMA)	Risdiplam
Neurofibromatosis	Selumetinib
Multiple sclerosis	Ofatumumab, Siponimod, Cladribine
Post-surgical pain	Dinalbuphine sebacate
ADHD	Lisdexamfetamine dimesylate

(Contd...)

Table 1: (*Continued*)	
Few common conditions/disease	**New drug approval in last 5 years**
Parkinson's disease (PD)	Rasagiline
Common respiratory system disease	
Chronic obstructive pulmonary disease (COPD)	Revefenacin, Erdosteine, Aclidinium
Asthma	Erdosteine, Benralizumab, Mepolizumab
Common CVS diseases	
Dyslipidemia	Inclisiran sodium, Pitavastatin, Evolocumab, Alirocumab
CHF	Vericiguat, Finerenone
Myocardial Infarction	Finerenone
Essential Hypertension	Fimasartan Potassium
Pulmonary Arterial Hypertension (PAH)	Selexipag
Amyloidosis	Tafamidis meglumine
Erectile dysfunction	Avafanil
Hyperkalemia	Sodium zirconium cyclosilicate
Hyprnatremia	Tolvaptan
Common Blood diseases	
Methemoglobinemia	Methylthioninium chloride trihydrate (methylene blue)
Hemophilia A	Turoctocog Alfa, Rurioctocog alfa pegol [Antihemophilic Factor (Recombinant), PEGylated], Lonoctocog alfa , Emicizumab
Non valvular atrial fibrillation (NVAF), Deep vein thrombosis (DVT), Pulmonary embolism (PE)	Edoxaban Tosilate
Febrile neutropenia	Lipegfilgrastim
Congenital hypo- or afibrinogenaemia	Human Fibrinogen
Iron deficiency anemia	Ferric Derisomaltose 417 mg/ml (Elementary Iron 100 mg/ml)
Hemophilia B	Albutrepenonacog alfa
Common Hormonal diseases	
Diabetes mellitus	Semaglutide, Ertugliflozin, Insulin Degludec
Osteoporosis	Romosozumab
X- Linked hypophosphetemia (XLH)	Burosumab
Medical termination of pregnancy (MTP)	Mifepristone
Vulvular vaginal atrophy (VVA)	Ospemifene
Controlled ovarian stimulation	Follitropin delta
Secondary Hyperparathyroidism (SHPT)	Etelcalcetide
Common Opthalmic disease	
Glaucoma	Latanoprostene Bunod, Omidenepag Isopropyl, Ripasudil Hydrochloride Hydrate,
Common skin disease	
Plaque psoriasis	Risankizumab, Ixekizumab, Guselkumab, Apremilast
Atopic dermatitis	Dupilimumab
Common GIT Disease	
Hepatic encephalopathy	L-ornithine-L-aspartate
Peptic ulcer, GERD	Vonoprazan
Constipation	Lubiprostone
Morning sickness	Doxylamine Succinate+ Pyridoxine Hydrochloride
Motion sickness	Cyclizine Hydrochloride
Common Inflammatory condition	
Rheumatoid arthritis	Upadacitinib, Sarilumab, Baricitinib
Common diagnostic agents	
Scintigraphy	Sodium pyrophosphate decahydrate
Radiopharmceuticals	Lutetium (177Lu) chloride, Lutetium (177Lu) oxodotreotide, Ioflupane [123I],

(Contd...)

Table 1: (*Continued*)	
Few common conditions/disease	**New drug approval in last 5 years**
PET imaging	Flutemetamol[18F]
Other conditions	
Fabry's disease	Agalsidase alfa
Ttype 1 Gaucher's disease	Velaglucerase alfa
Submental Fat	Deoxycholic acid

NSCLC: Non-small cell lung cancer, SHPT: Secondary Hyperparathyroidism, VVA: Vulvular vaginal atrophy, MTP: Medical termination of pregnancy, XLH: X- Linked hypophosphatemia, NVAF: Non valvular atrial fibrillation, DVT Deep vein thrombosis, PE: Pulmonary embolism, PAH: Pulmonary Arterial Hypertension, COPD: Chronic obstructive pulmonary disease, RCC: Renal cell carcinoma, SMA: Spinal Muscular atrophy NMOSD :Neuromyelitis optica spectrum disorders

has affected new drug approval all over the world significantly. During the pandemic period, majority countries including Singapore had given conditional Emergency Use Authorization to drugs which were useful in COVID management.

Observations from this study showed that maximum numbers of drugs (30.86%) were approved in ATC Class L which contains Anti neoplastic and immunomodulating agents. In one study by Kataria *et al*. (2016) from India showed anti-neoplastic and immunomodulating drug approval rate of 36.26%.[12] Similar other studies mentioned higher anti-cancer drug approvals recently.[13-16]

Maximum anti-cancer drugs approval in last 5 years in Singapore were for breast cancer and NSCLC. Tastuzumab and Tucatinib for breast cancer and Tepotinib and Capmatinib for NSCLC were few example of new anti-caner drug approvals.

Now a day, number of new drugs approval is increasing with each year.[11] Reasons cited by few studies for this trend were:
a. Increase in number of NDA by pharmaceutical companies
b. Significant growth in anti-cancer drugs development in the past decade
c. Faster drug approval by few countries like US, UK in the form of expedited drug review program (fast track review/break through therapy review/priority review/accelerated approval review)[17]
d. Incentive to Orphan drug development by many countries.[11]

Our study is first study of new drug approval pattern in Singapore and generated baseline data. This study analyzed data of last 5 years. Therefore, to know the trend of new drug approval over larger period, further future study with longer duration can be planned. Drug recalls have not been considered for analysis in this study.

CONCLUSION

This was the first study on new drug approval pattern in developed South East Asian country Singapore in last 5 year. In this study, it was found that in Singapore maximum number of new drug approvals was in anti-neoplastic and immunomodulator category. This trend is quite matching with other country such as US and UK. In last 5 years, number of drug approval given for breast cancer, NSCLC was maximum. That shows drug development in anti-cancer drug and immunomodulator is significant. This study provides baseline data for future larger scale studies.

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