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# A critical view of harmonization of regulatory requirements for Generic Drug approval submissions in ASEAN countries

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## Abstract

To ensure quality, efficacy, and safety of drugs is the prime objective of any country and respective drug regulatory authority. Countries have their own regulatory setup to ensure the proper execution of drug regulatory guidelines in their country. There are several regional organization in world, ASEAN is one of them. It is Association of Southeast nations. ASEAN is very well representing its countries on global platform. The step of harmonization of drug regulatory guidelines by ASEAN is seen as major step taken by an Asian regional organization.

ASEAN is an emerging market and every country has its own needs. As research and development sector is only developed in Singapore in ASEAN region so, generics emerge as a tool for other countries to fulfill UHC goals and Vision 2020 ASEAN. Every country has the different procedure for generic drug registration application approval. To clearly understand the procedure of generic drug registration application approval process we have gone through various guidelines and literature. There are 10 members in ASEAN i.e. Singapore, Malaysia, Thailand, Indonesia, Philippines, Brunei Darussalam, Laos PDR, Myanmar, Vietnam, and Cambodia. Each one's generic drug approval process, requirements and effects on pharmaceutical trade after implementation of ACTD is explained in this research work. This research work also includes the statistical analysis and suggestions on how other countries and regional organization follow the model of ASEAN for drug regulatory harmonization procedure.

**Keywords:** ASEAN, Regulatory affairs, ACTD, UHC, Vision 2020 ASEAN, CTD, Generic drug approval, ACTR.

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## 1. Introduction

Generic drugs in the global market are a new emerging trend (1). Various pharmaceutical industries are involved in manufacturing and export of generic drugs. If we go with the English dictionary meaning of generic drugs then the word generic is defined as "Not protected by trademark registration; non-proprietary or any product, as a food, drug or cosmetic that can be sold without a brand name". If we summarise the definition it may be considered as the salt name of branded drugs or medicines. For example the salt in the Dolo-650 tablet is Paracetamol. As per WHO, " a Generic drug is a pharmaceutical product that is manufactured without a licence from the innovator company and marketed after the expiry date of the patent or other exclusive rights (2)."This definition can be understood by brief review of drug development process:

Nowadays, Generics have been introduced to various countries. The preference is given to generics because of a) low cost and affordability b) more accessible to the patient at each level of the pyramid. In developing countries, it is a difficult job to provide medicine to each patient at the affordable price (3). The High cost of medicine causes unavailability of medicines to the patient which lead to the poor healthcare system in the country. Generic drugs (due to low cost) help developing countries in reducing the national healthcare spending. Treatment of most of the patients is now possible at affordable prices in developing countries. This leads to high demand for generic drugs and high demand come with high responsibility i.e. the responsibility to ensure the quality, efficacy and safety of medicine. To ensure this each country has its own regulatory setup where all functions are enforced and executed by drug regulatory authority of the respective country. Depending upon the nature of

regulatory setup of the countries in the world can be divided into regulated countries (like USA, UK, Japan, Australia etc.) and the semi-regulated countries (like India, ASEAN etc.) (3).

***Overview of ASEAN***

ASEAN (Association of Southeast Asian Nations) was established on 8th August 1967 after signing of the ASEAN declaration in Bangkok, Thailand. The founding countries of ASEAN are Indonesia, Malaysia, Philippines, Singapore and Thailand (4). Now there are 10 countries present as members in ASEAN. These are Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Lao PDR, Myanmar, and Cambodia. These countries are situated at southeast arcs of Asia. In 2016, the total population of ASEAN countries is 636.84 million, which is 8.36% (approx) of world's population. ASEAN countries cover 4.4 Million square kilometre area i.e. 3 % of the total land area of Earth (5). The main objectives behind the regional integration of Southeast Asian countries are:

- To hasten the economic growth, social and cultural development in the region by joint efforts.
- To reinforce the establishment of a prosperous and peaceful community of Southeast Asian nations,
- To promote regional peace and stability by enduring respect for justice and the rule of law in the relationship among countries in the region.

On 24th February 1976, the treaty of amity and cooperation was signed by southeast nations. In this treaty, the relations with each other have been compared and the contracting parties should follow the following principles:

- Mutual respect for the other nation's equality, sovereignty and territorial integrity.
- Non-interference policy should be followed by each country.
- Settling disputes by peaceful ways.
- Effective cooperation should be welcomed among countries.

Ensuring access to the essential medical facilities is the main objective of every health system in the world. Health is the main part for the progress of the country. In the underdeveloped and developing countries, people still live without basic health facilities. Not only the availability of health facilities should be the aim but also the quality of the facilities provided must be assured.

Taking the check on quality assurance of medicine, as an important point, it is necessary that every country has an effective drug regulatory set up that ensures Quality, Safety and Efficacy of the medicine (6). These regulatory authorities are known as NMRA (National Medicine Regulatory Authority). But, in many countries, their respective NMRAs have the shortage of resources and capacity. These NMRAs are unable to meet regulatory tasks. It acts as a prime factor for regional integration in case of drug regulatory guidelines. This is because regulatory cooperation and harmonization ensure the availability of high quality medicines at each level of the pyramid. This is the reason behind harmonization of drug regulatory guidelines in ASEAN countries. In ASEAN there are countries like Singapore which is also considered as best development model country nowadays and a strong economy (Table 1). While on another hand there are countries like Cambodia, Myanmar which are not properly developed and also counted as poor economies. The harmonization of drug regulatory guidelines gives benefit to economies like Myanmar, Cambodia in ASEAN (7). The other goals for harmonization of guidelines by ASEAN countries are as follows:

- To create common regulations for pharmaceutical products in the region
- To cut the trade barriers among members
- To ensure quality and efficacy of pharmaceutical product in the ASEAN market.

**Table 1** South East Asian countries in accordance with their GDP/capita and their population (2, 5).

| Sr. No. | Name of the country | Capital | Population (in crore) (as per 2016 census by World Bank) | GDP/Capita (in USD) |
|---|---|---|---|---|
| 1. | Singapore | Singapore | 0.561 | 52,960.71 |
| 2. | Brunei | Bandar Seri Begawan | 0.0423 | 26,938.50 |
| 3. | Malaysia | Kuala Lumpur | 3.12 | 9,502.57 |
| 4. | Thailand | Bangkok | 6.89 | 5,907.91 |
| 5. | Indonesia | Jakarta | 26.11 | 3,570.29 |
| 6. | Philippines | Manila | 10.33 | 2,951.07 |
| 7. | Laos PDR | Vientiane | 0.676 | 2,353.15 |
| 8. | Vietnam | Hanoi | 9.27 | 2,185.69 |
| 9. | Myanmar | Naypyidaw | 5.29 | 1,275.02 |
| 10. | Cambodia | Phnom Penh | 1.58 | 1,261.91 |

**2. ASEAN: A new emerging market for Generic Drugs**

ASEAN region is both a scope for interesting study as well as full of potential market viz-a-viz pharmaceutical industry. The region proudly represents Asia on the global map. It is envy for both the developed as well as developing powers. Not only is the region politically stable but economically friendly. The developed market

(with respect to ASEAN members) may have led the harmonization procedure for drug regulatory guidelines which redefining the game. The region, unlike EU, has both general as well as country-specific guidelines as of now. This will allow some member to cope with the transition phase smoothly. The ICH guidelines were and will be of great help to ASEAN countries. Now drug registration in ASEAN countries act as a transparent lock which can only be unlocked by the key of knowledge. A better understanding of all the country's' requirements will emerge as a winner. The first initiative of regional integration takes place in 1967 when ASEAN emerges. The idea of interregional cooperation into trade was first initiated in 1992 with AFTA (ASEAN Free Trade Area). The purpose was economic development and to enhance competitiveness as a consequence of efficiency. The second initiative was taken in 1999 which gave PPWG to harmonise and streamline drug regulatory guidelines along with ICH which results in the formation of ACTD and ACTR (8).

Every member if ASEAN is unique both in terms of political setup as well as economic setup. The uneven distribution of income clearly indicates that every country is to be treated differently. The prize of ignorance and empathy could be the very existence of ASEAN as a powerful organization. ASEAN is an emerging market and every country has its own needs. As research and development sector is only developed in Singapore in ASEAN region so, generics emerge as a tool for other countries to fulfill UHC goals and Vision 2020 ASEAN. Every country has the different procedure for generic drug registration application approval. To clearly understand the procedure of generic drug registration application approval process we have gone through various guidelines and literature.

ASEAN countries together are considered as new emerging market for generic drugs (9). Many pharmaceutical countries show their interest in ASEAN pharmaceutical market because of the increasing demands for generic drugs in the market. The reasons behind considering ASEAN as new emerging market for generic drugs can be following:

- Among ASEAN member countries, the countries like Indonesia, Myanmar, and Cambodia which are developing countries. It results in an increase in pressure on healthcare setup of the country to provide better health facility at the affordable price.
- ASEAN countries have approximately 636 million populations which are about 8.36% of world population. This significant number in terms of population always considered as good market. And so is the view of pharmaceutical companies involve in generic drug manufacturing.
- In the current situation, there is lack of infrastructure and other resources in ASEAN countries for Research and Development (EXCEPT Singapore and Thailand). Research and development sector demands so much capital investment in case of new drug development.
- Branded drugs or patented products are costly if compared with generic drugs. If we considered the expenditure per 0capita (Table 2) in the ASEAN countries, generic drugs would be the best option for providing quality healthcare at affordable prices.
- The life expectancy in ASEAN countries is more than 66 years (Table 2). To increase the life expectancy of the people and to maintain the health of the people better healthcare is needed. Old age comes with many non-communicable diseases like diabetes, heart problems, Alzheimer's disease, etc. These diseases are not curable. So to provide the quality life to the patient generic drugs would be the best option.
- Most of the ASEAN countries have more than 10% of total population below poverty line which trigger the need of affordable prices (Table 3).

**Table 2** Showing Gross Domestic Product (GDP), Medical expenditure per capita and Life expectancy of ASEAN countries (2, 5).

| Sr. No. | Name of the country | GDP (in Crore USD) 2016 | Medical expenditure per capita (as in 2014) | Life expectancy (in 2015) |
|---|---|---|---|---|
| 1. | Singapore | 29,696.57 | 2750 | 82.60 |
| 2. | Brunei | 1,140.03 | 1778 | 79.04 |
| 3. | Malaysia | 29,635.91 | 423.43 | 74.88 |
| 4. | Thailand | 40,683.97 | 227.52 | 74.60 |
| 5. | Indonesia | 93,225.92 | 99.41 | 69.07 |
| 6. | Philippines | 30,490.54 | 135 | 68.41 |
| 7. | Laos PDR | 1,590.34 | 32.57 | 66.54 |
| 8. | Vietnam | 20,261.59 | 142 | 75.78 |
| 9. | Myanmar | 6,742.96 | 20.29 | 66.04 |
| 10. | Cambodia | 2,001.67 | 61.28 | 68.66 |

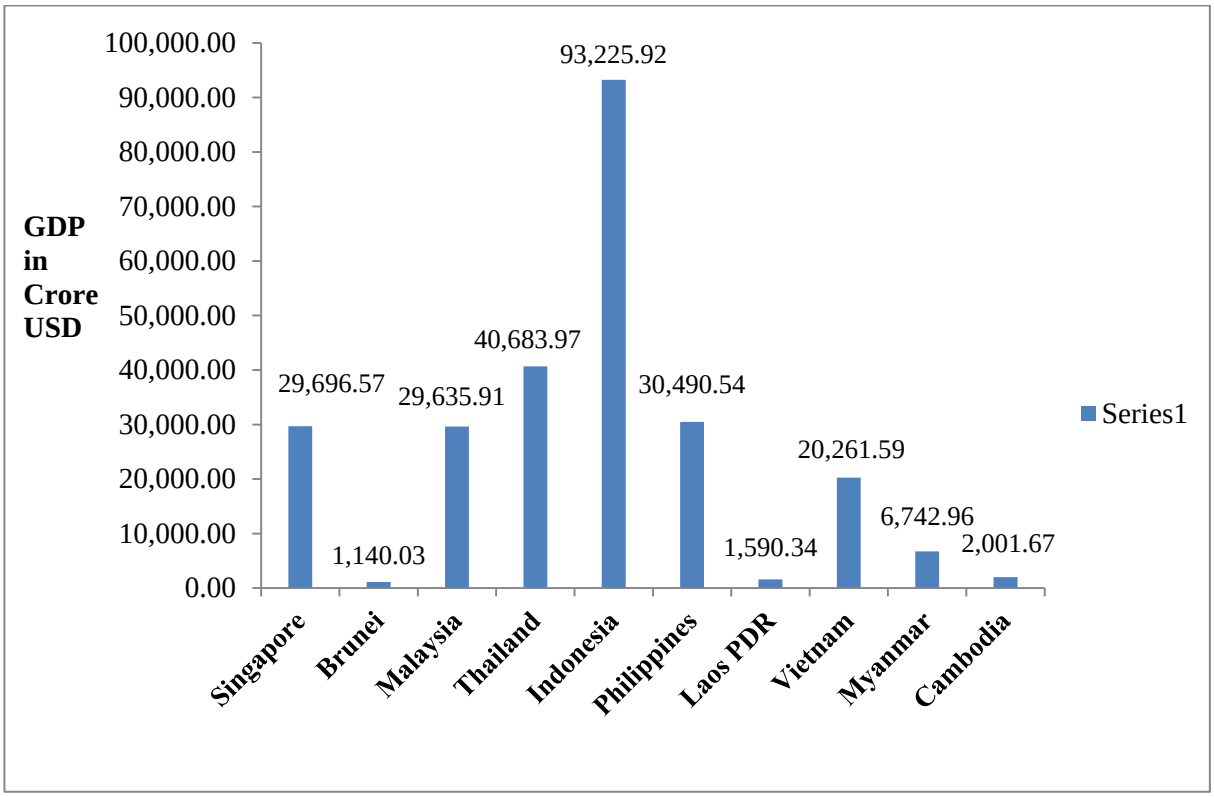



**Figure 1.** Showing GDP of ASEAN countries: Indonesia has highest GDP and brunei has lowest GDP in ASEAN region.

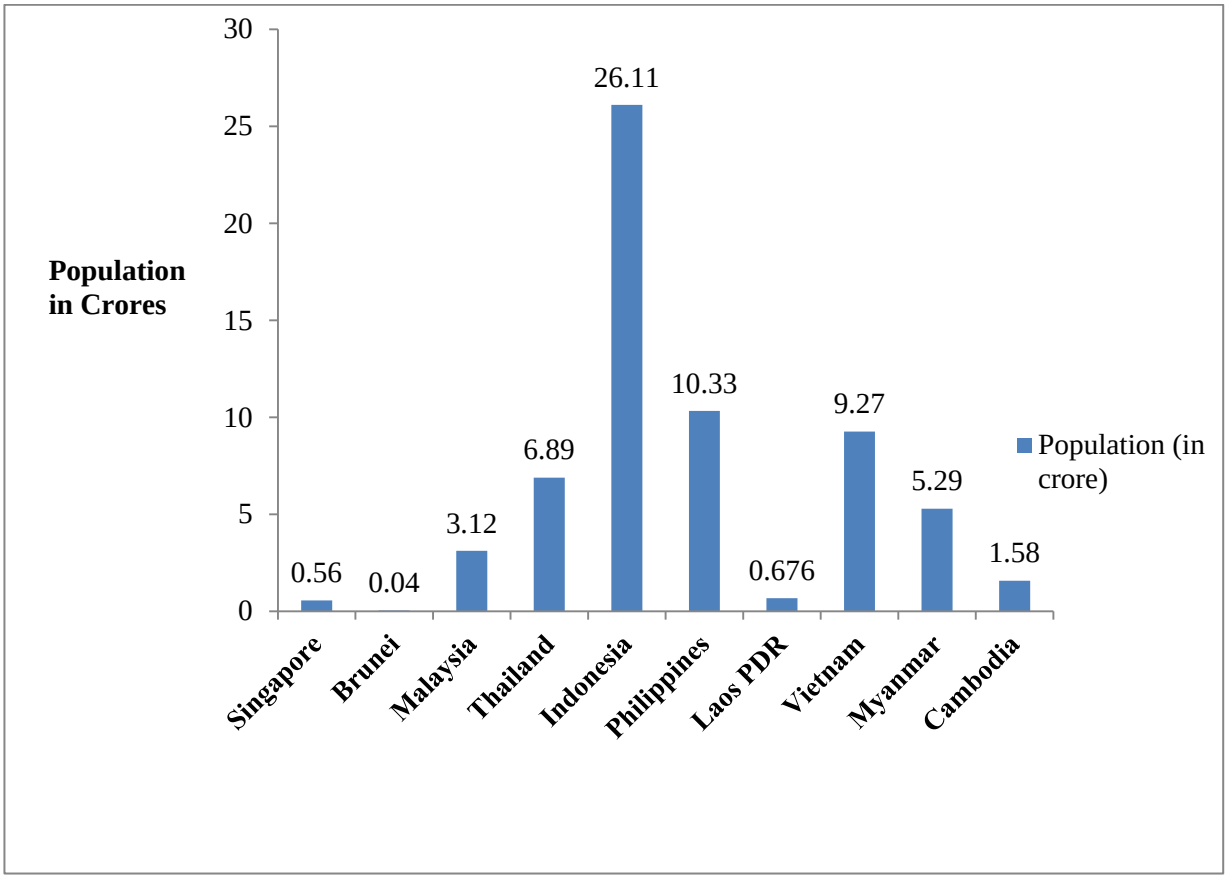



**Figure 2.** Showing population of ASEAN countries: Indonesia has highest population and Brunei has lowest population in ASEAN region.

**Table 3** Showing socioeconomic conditions of ASEAN countries giving reference to certain factors like HDI, IMR and population below poverty line. HDI (human development index is a composite statistic that includes life expectancy, education, per capita income indicators, and ranks 188 countries into four tiers of human development (2, 5).

| Sr. No. | Name of the country | Human Development Index (HDI) (Rank) among 188 countries as per Human Development Report 2016 | Infant Mortality Rate (IMR) deaths/ 1000 live births | Population below Poverty Line (In % of population) |
|---|---|---|---|---|
| 1. | Singapore | 5 | 2.4 | N/A |
| 2. | Brunei | 30 | 7.7 | N/A |
| 3. | Malaysia | 59 | 12.5 | 0.6 |
| 4. | Thailand | 87 | 9.2 | 7.2 |
| 5. | Indonesia | 113 | 22.7 | 11.2 |
| 6. | Philippines | 116 | 21.4 | 22.0 |
| 7. | Laos PDR | 138 | 49.9 | 24.0 |
| 8. | Vietnam | 115 | 17.3 | 7.0 |
| 9. | Myanmar | 145 | 35.8 | - |
| 10. | Cambodia | 143 | 47.4 | 13.5 |

***Brief overview of health transition in ASEAN countries***

Diseases are the major factors that decide the medicine. Southeast Asia consists of 10 independent countries located on the off-shores and arcs of Asia. Major factors that affects the disease trend of the region depends upon various factors like population, its distribution (Table 4) and climate of the region. Occurrence of diseases depends upon the age. For example the younger population is more susceptible to communicable diseases while the elder population is susceptible to non-communicable diseases.

**Table 4** Showing population distributions of ASEAN countries as per age groups (10).

| Sr. No. | Name of country | % Population in accordance with age group (in years) | | | | |
|---|---|---|---|---|---|---|
| | | **0-4** | **5-19** | **20-54** | **55-64** | **65** |
| 1. | Singapore | **4.8** | **16.5** | 52.3 | **14.0** | **12.4** |
| 2. | Brunei | 7.9 | 24.2 | **56.3** | 7.4 | 4.3 |
| 3. | Malaysia | 8.3 | 25.3 | 52.8 | 7.5 | 6.0 |
| 4. | Thailand | 5.7 | 19.0 | 52.1 | 12.2 | 11.0 |
| 5. | Indonesia | 9.3 | 26.5 | 51.3 | 7.7 | 5.3 |
| 6. | Philippines | **11.0** | 30.3 | **47.2** | **6.5** | 4.9 |
| 7. | Laos PDR | 10.5 | **32.3** | 47.6 | 5.3 | **4.2** |
| 8. | Vietnam | 8.3 | 22.4 | 51.7 | 9.7 | 8.0 |
| 9. | Myanmar | 9.3 | 28.2 | 48.9 | 7.7 | 5.9 |
| 10. | Cambodia | 10 | 28.7 | 49.7 | 6.5 | 5.1 |
| **TOTAL** | ASEAN | 9 | 25.8 | 50.6 | 8.2 | 6.4 |

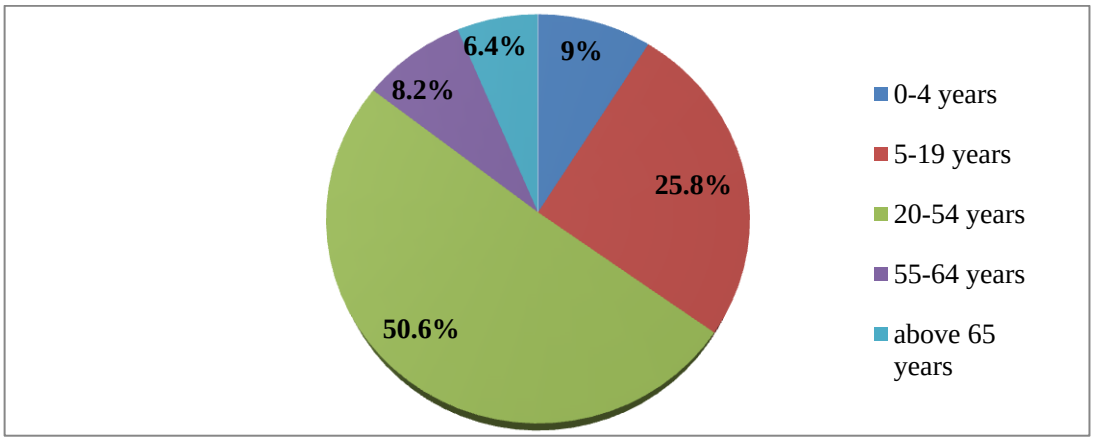



**Figure 3.** Showing distribution of age group in ASEAN region.

- Singapore has the lowest people in age group 0-4 years and age group 5-19 years, while on the other hand it has the highest percentage of population in age group 55-64 years and above 65 years.
- Brunei has the highest percentage of people in age group 20-54 years.
- Philippines have the highest percent of the population in age group 0-4 years and the lowest percentage of population in age groups 20-54 years and 55-64 years.
- Laos PDR has the highest percentage of population in age group 5-19 years and lowest percentage of people in age group above 65 years.

Countries with the high aged population have a higher risk of non-communicable diseases. Countries with the high young population have a high the risk of communicable disease. In ASEAN countries malaria and tuberculosis are also prevalent. These types of risks of the disease can be one of the factors for increasing importance of Generic medicine in ASEAN region.

***Pharmaceutical establishments in ASEAN countries***

If we go through the number of pharmaceutical establishments, we can observe through the data in Table 5 that on an average the pharmaceutical industries are only 0.3% of total industries established. It can be an inducing factors for import of medicine from other countries especially the generic medicine.

**Table 5** Pharmaceutical establishments in ASEAN countries and % of pharmaceutical establishments with respect to total industries established (1, 10).

| Sr. No. | Name of country | Number of pharmaceutical establishments | % of total industries established |
|---|---|---|---|
| 1. | Singapore | 51 | 0.6 |
| 2. | Brunei | Data not available | |
| 3. | Malaysia | 371 | 0.8 |
| 4. | Thailand | 395 | 0.40 |
| 5. | Indonesia | 272 | 0.10 |
| 6. | Philippines | 117 | 0.50 |
| 7. | Laos PDR | Data not available | |
| 8. | Vietnam | 442 | 0.70 |
| 9. | Myanmar | 84 | 0.20 |
| 10. | Cambodia | 10 | 0.01 |

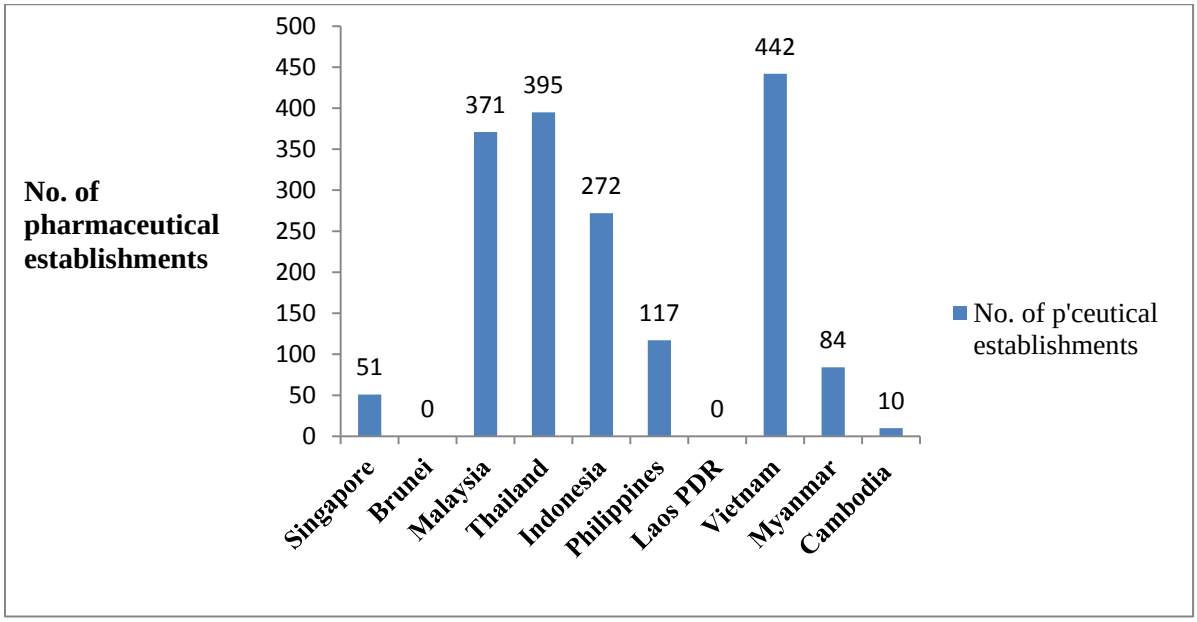



**Figure 4.** Showing number of Pharmaceutical establishments in ASEAN region: Vietnam has highest no of Pharmaceutical establishments and Brunei and Laos PDR has no Pharmaceutical establishments.

**3. Overview of ACTD and CTD** (11, 12)

***ACTD (ASEAN Common Technical Document)***

The harmonization of the guidelines by ASEAN countries was done in 1999. From 2005 to 2008 all 10 member countries of ASEAN accept ACTD as the common technical document to submit drug registration application to the concerned drug regulatory body. It is a guideline agreed upon ICH-CTD. There are four parts in ACTD (Figure 5):

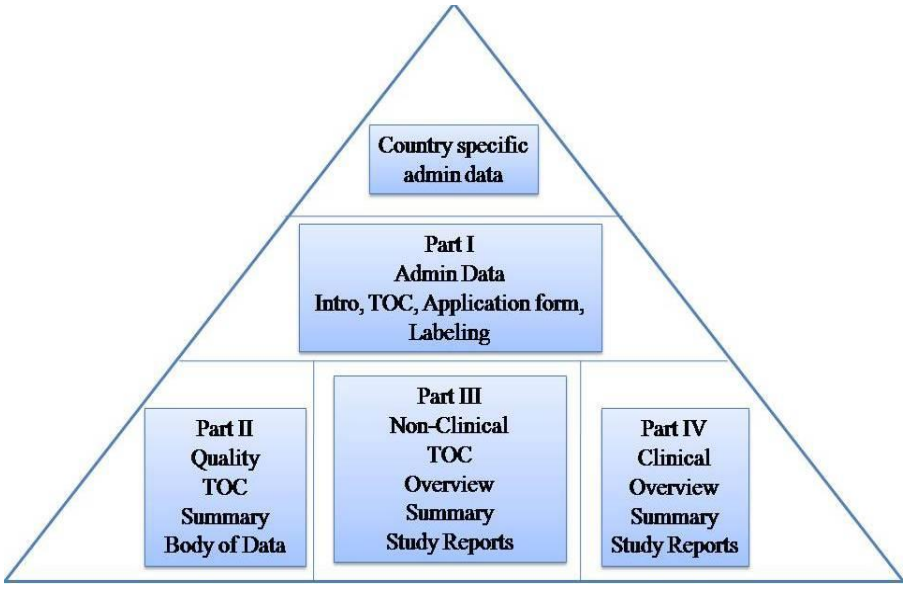



**Figure 5.** ACTD triangle showing parts of ACTD

- **Part I:** Table of Content Administrative Information and Prescribing Information
- **Part II:** Quality Document
- **Part III:** Nonclinical Document
- **Part IV:** Clinical Document

***CTD (Common Technical Document)***

CTD was first agreed in November 2000 in San Diego, USA. It was developed by the efforts of EMEA, Food &Drug Administration (FDA), the ministry of health and family welfare Japan. CTD is mainly maintained by ICH (International Conference on Harmonization of technical requirement for registration of pharmaceuticals for human use). CTD is a single document basically contains each and every detail related with quality, safety, efficacy of drug product. It was first used by Europe, Japan and USA. Nowadays, many countries of the world are following CTD for drug registration purposes. As per FDA CTD is "An information package of clinical, non-clinical, manufacturing, technical data in the same format and with the same content, that would be submitted for registering new drugs in all three ICH regions i.e.; US, European Union and Japan." **There are 5 modules in CTD. These are (Figure 6):**

- **Module-I:** Administrative prescribing information.
- **Module-II:** Overview & summary of modules 3-5.
- **Module-III:** Quality (Pharmaceutical documentation).
- **Module-IV:** Safety toxicology studies (Non-clinical Study Reports)
- **Module-V:** Efficacy clinical studies (Clinical Study Reports)

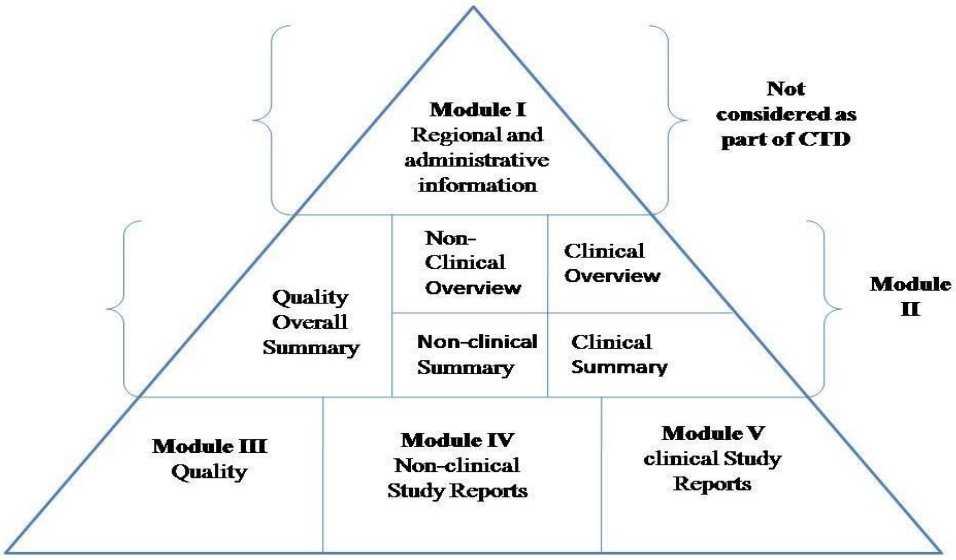



**Figure 6.** CTD triangle showing modules of CTD

***Comparison between CTD and ACTD:*** However, ACTD and ICH CTD are fundamentally similar but there are some notable differences between them. These are as follows:

**Table 6** Difference between ACTD and ICH CTD

| CONTENT | ICH CTD | ACTD |
|---|---|---|
| Administrative documents and product information | Module 1 | Part1 |
| Common Technical Document overview and summaries | Module 2 | Part 2, 3, 4 |
| Quality documents | Module 3 | Part 2 |
| Nonclinical documents | Module 4 | Part 3 |
| Clinical documents | Module 5 | Part 4 |

ACCSQ-PPWG (ASEAN Consultative Committee for Standards and Quality- Pharmaceutical Product Working Group) (13)

After the formation of ACCSQ i.e. ASEAN Consultative Committee on Standards and Quality in 1992, ACCSQ takes an important initiative of formation of ACCSQ-PPWG in 1999. The formation of ACCSQ-PPWG takes place to fulfill the following objectives:

- To develop harmonization schemes of pharmaceutical regulation of the ASEAN member countries so as to facilitate the objective of ASEAN Free Trade Area (AFTA).
- To eliminate the technical barriers to trade posed by the regulations but it will be achieved without compromising drug quality, efficacy, and safety.

PPWG has a large scope. It covered New Chemical Entities (NCEs), Biotechnological products, major and minor variation products and generics as well. The main steps taken by PPWG were:

- Harmonization of technical guidelines and regulatory requirements applicable to ASEAN pharmaceutical industry.
- Development of common technical requirements (achieved as ACTR) for ASEAN region.
- Development of common technical document (ACTD) for ASEAN region.
- Simplification of existing technical guidelines of the pharmaceutical industry.

The Scope of PPWG:

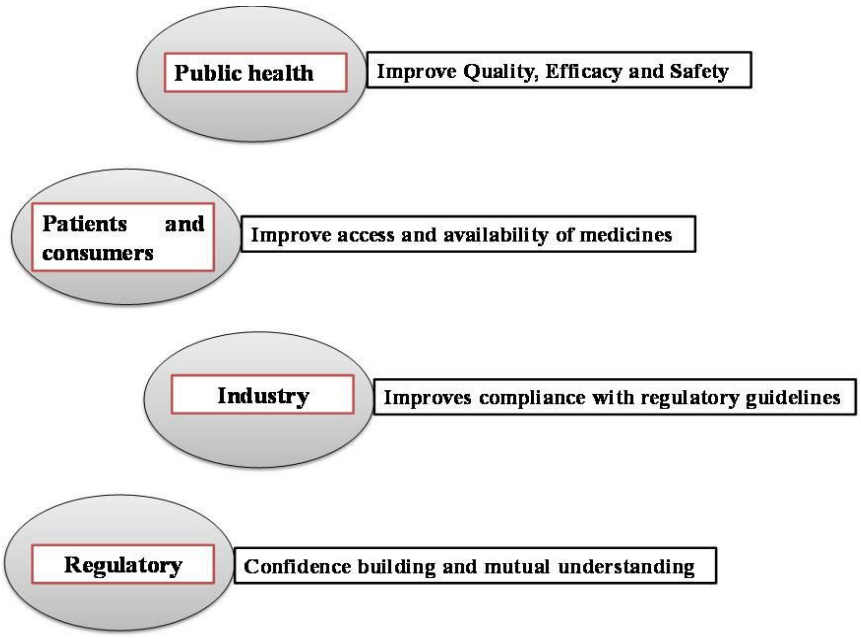



**Figure 7.** Impact of the steps of PPWG (Harmonization)

## 4. Benefits of harmonization of drug regulatory guidelines on drug approval process in ASEAN

### *Single guidelines to be followed*

The main aim of harmonization procedure is to streamline the regulatory guidelines and simplify them so that these can be easily understandable. By the harmonization procedure, all 10 countries in ASEAN now have common simplified guidelines. The two regulatory extremes (Singapore and Brunei) of ASEAN are following the same guidelines.

### *A Common technical format for registration*

Applicants have to submit drug dossier to get their product registered in any country. There is a specific requirement of any country to be fulfilled while preparing the dossier. It becomes very complex task for the manufacturer to prepare the different dossier for different countries for single drug. Drug regulatory harmonization

procedure introduce single format which is to be submitted while filing registration application. Likewise, ASEAN harmonization procedure introduces ACTD. Every member country accepts ACTD format for drug registration.

***Technical cooperation***

Different countries have been bestowed with different resources and technologies. Some are better on the technological front while some are gifted with better human resources. This difference can both be taken as a challenge as well as a potential for equilibrium. The harmonization procedure enables the countries to help each other technologically as well as on resources front. In ASEAN region Singapore and Malaysia are doing their best in research and development sector while on the other hand Laos, Cambodia, Myanmar, and Vietnam suffer from lack of technology. Through regional integration and drug harmonization procedure, equilibrium will be achieved through mutual help and coordination.

***The Strong economies are supporting poor economies***

To make any regulation effective capital is the first and important requirement. In ASEAN countries there are poor economies like Laos, Cambodia, Vietnam and Myanmar while, on the other hand, there are strong economies also like Singapore, Malaysia, Brunei, Indonesia. ASEAN unite them and strong economies solve the problem (related to capital investment) of poor economic countries.

***Resources fulfillment***

Regional integration and drug harmonization procedure enable transfer of not only technology but also skilled labor, services, and other resources from one country to another country.

***Effective representation at the global level***

Regionally integrated countries have a different position at the global level. Regional organization will be considered as the more powerful organization rather than a single country. By regional integration, such organization can present their point of view related with an issue at the global level which will be appreciated by another world.

***Attracts more investors in the country***

Harmonization procedure introduces stability in the regulatory environment which attracts the foreign investors in the country for manufacturing or registration of drugs.

***Emerging of a cross country approach from a country focused approach***

Harmonization procedures aim is to improve and simplify the drug regulatory guidelines and this will be done by a shifting country focused approach to the cross country approach. Enormous financial, as well as technical expertise is required for accessing the quality of medicine before approving it for the market. Regional initiatives resulting from harmonization procedures enables pooling of resources from each other and this makes a shift from a country focused approach to the cross country approach.

***The Requirement for strong governance will be fulfilled***

Medical regulations are very complex. With increasing globalisation and the technical advancements in the field of pharmaceuticals, it becomes difficult for NMRAs to effectively carry out their functions. This leads to weak governance. By regional integration and drug regulatory harmonization procedures, the governance will become strong because of establishments of governing authorities at regional level. Collaborative regional initiatives help in solving this problem.

***Growth in the pharmaceutical industry***

By integration and regional cooperation, the local pharmaceutical market grows which results in the growth of pharmaceutical industry. After the regional integration ASEAN countries show immense growth in the pharmaceutical sector. Even Vietnam's market is growing at the rate of 16%.

***Export among countries of a regional organization increases***

Regional integration results in the reduction or complete elimination of trade barriers among the members of the regional organization which results in an increase in the import and export among these countries. The technical cooperation among country increases domestic production which enables the country for export of finished product on one hand and import of technology on the other hand.

***Helps in achieving UHC***

Medicines are the inevitable part of health care system. The main goal of UHC is to provide the best health care system to the people. Medicines are the major carrier for achieving UHC goal. Not only the availability of medicine is an issue but also the availability of quality medicine is an issue. Through Harmonization of guidelines, technical support will be achieved. It helps in assessing the quality of medicine. Hence improves the quality of medicine in market ad achieving UHC goals.

***Improvement in Health Status of weak countries***

There is an improvement in health status after regional integration of Southeast Asian countries. Health indicators like medical expenditure per capita/ life expectancy, infant mortality rate speaks for themselves. HDI scores also have significant improvement in poor economies like Cambodia, Laos, Myanmar, and Vietnam.

We can see that regulatory harmonization is a viable way of improving the regulatory environment in a particular country. The condition and reason for medicinal regulatory harmonization may vary but the aim remains the same i.e. to serve quality product to the people and to

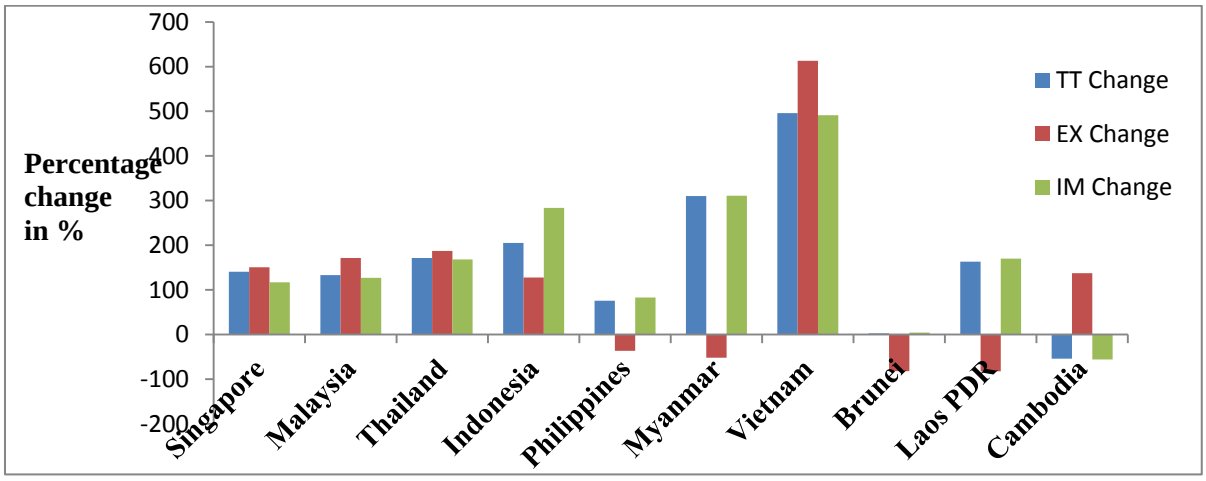
safeguard the interest of pharmaceutical industries as well. Keeping in mind the globalized nature of pharmaceutical markets, a large amount of information, monitoring of complex processes and drug regulatory guidelines and complex review process, the harmonization of drug regulatory guidelines become the need of today that fulfill the requirements of tomorrow. The above-mentioned advantages prove that regulatory harmonization done by regional organizations is a hope, not hype.

***Effect of ASEAN harmonization of guidelines on pharmaceutical market***

Harmonization of regulatory guidelines by ASEAN countries not only affects the drug approval system in ASEAN countries but also affects the pharmaceutical trade in ASEAN countries (with world as well as in ASEAN region). Table 7 mentioned below describes the total trade of ASEAN countries with world (99 countries) and Table 8 Mentioned below describes the total pharmaceutical trade of ASEAN countries within ASEAN region. Comparison of the data is done between before implementation of ACTD and after implementation of ACTD.

**Table 7** Showing total pharmaceutical trade of ASEAN countries within world countries (14, 15)

| Name of country | Total trade (in crores) | | | Export (in crores) | | | Import (in crores) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before implementation of ACTD | After implementation of ACTD (Current) | Percentage growth (%) | Before implementation of ACTD | After implementation of ACTD (Current) | Percentage growth (%) | Before implementation of ACTD | After implementation of ACTD (Current) | Percentage growth (%) |
| Singapore | 3472.04 | 8351.00 | 140.52 | 2433.47 | 6098.85 | 150.62 | 1038.5 | 2252.16 | 116.86 |
| Malaysia | 651.13 | 1516.56 | 132.91 | 86.70 | 235.36 | 171.46 | 564.43 | 1281.20 | 126.99 |
| Thailand | 1020.26 | 2768.55 | 171.35 | 178.28 | 511.86 | 187.11 | 842.00 | 2256.70 | 168.01 |
| Indonesia | 486.08 | 1482.22 | 204.93 | 245.00 | 557.70 | 127.63 | 241.10 | 924.52 | 283.45 |
| Philippines | 626.72 | 1100.91 | 75.66 | 37.64 | 23.80 | -36.76 | 589.08 | 1077.11 | 82.84 |
| Myanmar | 128.20` | 525.90 | 310.21 | 0.23 | 0.11 | -52.17 | 127.97 | 525.80 | 310.87 |
| Vietnam | 532.53 | 3172.89 | 495.81 | 19.93 | 142.15 | 613.24 | 512.60 | 3030.73 | 491.24 |
| Brunei | 62.10 | 63.71 | 2.59 | 1.06 | 0.19 | -82.07 | 61.02 | 63.51 | 4.08 |
| Laos PDR | 8.18 | 21.53 | 163.20 | 0.21 | 0.037 | -82.38 | 7.96 | 21.492 | 170 |
| Cambodia | 99.73 | 45.62 | -54.25 | 0.83 | 1.97 | 137.34 | 98.90 | 43.65 | -55.86 |

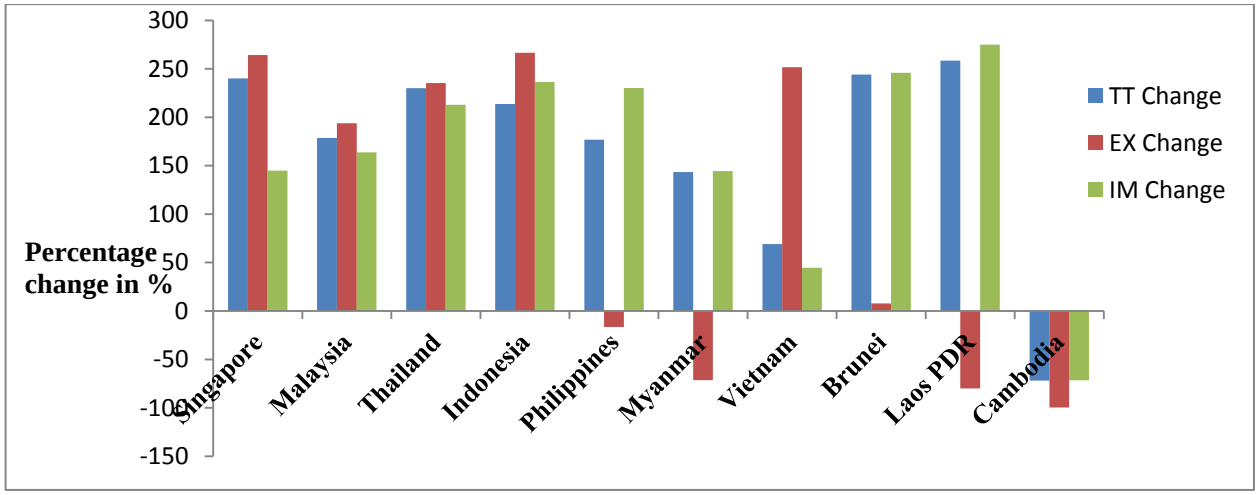



TT* Total Trade, EX* Export, IM* Import

**Figure 8.** Showing comparison of ASEAN countries pharmaceutical trade within world countries w.r.t percentage change in total trade, export and import: The following observations can be made: 1. The total trade in all countries increases, 2. The import in all countries increases, 3. The export in all countries (except Philippines, Myanmar, Brunei, Laos PDR) increases.

**Table 8** Showing total pharmaceutical trade of ASEAN countries within ASEAN countries (14, 15)

| Name of country | Total trade (in crores) | | | Export (in crores) | | | Import (in crores) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before implementation of ACTD | After ACTD Implementation | Percentage change (%) | Before implementation of ACTD | After ACTD Implementation | Percentage change (%) | Before implementation of ACTD | After ACTD Implementation | Percentage change (%) |
| Singapore | 220.50 | 750.09 | 240.17 | 176.14 | 641.52 | 264.21 | 44.33 | 108.57 | 144.91 |
| Malaysia | 97.50 | 271.74 | 178.70 | 48.46 | 142.39 | 193.83 | 49.03 | 129.35 | 163.81 |
| Thailand | 131.51 | 434.02 | 230.02 | 100.53 | 337.05 | 235.27 | 31.00 | 96.98 | 212.83 |
| Indonesia | 107.90 | 338.54 | 213.75 | 84.92 | 311.26 | 266.53 | 22.97 | 77.28 | 236.43 |
| Philippines | 74.94 | 207.46 | 176.83 | 16.22 | 13.54 | -16.52 | 58.71 | 193.91 | 230.28 |
| Myanmar | 47.03 | 114.51 | 143.48 | 0.21 | 0.06 | -71.42 | 46.82 | 114.45 | 144.44 |
| Vietnam | 129.83 | 219.48 | 69.051 | 15.29 | 53.78 | 251.73 | 114.54 | 165.70 | 44.665 |
| Brunei | 16.405 | 56.45 | 244.10 | 0.13 | 0.14 | 7.6923 | 16.28 | 56.31 | 245.88 |
| Laos PDR | 4.04 | 14.48 | 258.41 | 0.20 | 0.04 | -80 | 3.85 | 14.44 | 275.06 |
| **Cambodia** | **38.06** | **10.72** | -71.83 | **0.25** | **0.001** | -99.6 | **37.80** | **10.73** | -71.61 |




TT* Total Trade, EX* Export, IM* Import

**Figure 9.** Showing comparison of ASEAN countries pharmaceutical trade within ASEAN countries w.r.t percentage change in total trade, export and import. Following observations can be made: 1. The total trade in all ASEAN countries (except Cambodia) increases, 2. The import in all ASEAN countries (except Cambodia) increases, 3.The export in all ASEAN countries (except Philippines, Myanmar, Laos PDR, Cambodia) increases.

## 5. Conclusion

By critically viewing the ASEAN guidelines, regulatory harmonization procedure by ASEAN countries and Generic drug approval procedure of ASEAN countries we can conclude that centralized organization for drug regulation like PPWG are doing their work with great efficiency and commitment. It's their effort that each country in ASEAN comes in their way of accepting ACTD as registration dossier format for any type of drug registration. Though ACTD is a common technical document for ASEAN countries, it is fundamentally same as ICH-CTD because the basic aim of both the common technical document is to ensure the quality, safety, and efficacy of drugs. Even ASEAN guidelines are also inspired by ICH guidelines. Harmonization procedure of regulatory guidelines has positive effects on each and every stakeholder be it patient, industry or regulatory organizations of the country. ASEAN countries had faced many challenges and even now are facing e.g. economic problems in some countries, lack of resources, undeveloped research and development centre, certain issues in between ASEAN members etc., but ASEAN countries are setting an example for other countries that despite all challenges these organizations can be successful. The total pharmaceutical trade in ASEAN

region is it with world or with ASEAN countries increases after implementing common technical document for drug registration. Nowadays, ASEAN has its own strong position at the global level. Many drug-related issues like drug trafficking, availability of medicines, better healthcare facilities, counterfeit drugs etc are solving in southeast countries because of their cooperation at drug regulatory level. It was found that different states have different STI performance. Brunei, Cambodia, Lao PDR, Vietnam and Myanmar were "training", Philippines, Thailand, & Indonesia were "catching up", Malaysia is a follower and Singapore is a leader. In terms of progress Brunei Darussalam, Malaysia, Philippines and Thailand showed significant progress. Indonesia, Cambodia, Lao PDR, Myanmar, Vietnam and Singapore show "Slight progress." No ASEAN country shows regression and stagnation. Other regional organization (like gulf countries, African countries, SAARC) can also follow ASEAN model and can provide quality medicines to their people which also helps them in achieving UHC goals. ASEAN highlighted the right path with right direction but to follow it, is based on other countries' discretion.

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**Conflict of interest**

The authors declare that there are no conflicts of interest.

**References**

1. Badjatya J.K. Overview of drug registration requirements for pharmaceuticals in emerging market. Journal of Drug Delivery and Therapeutics. 2013; 3(2): 227-232.
2. WHO | World Health Organization [Internet]. WHO; 2018 [cited 2019 Jan 11]. Available from: http://www.who.int/
3. Handoo S., Khera D., Nandi P., Sahu S., Arora V. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. International Journal of Pharmaceutical Investigation. 2012; 2(3): 1-12.
4. Rodriguez V., Soeparwata A. ASEAN benchmarking in terms of science, technology, and innovation from 1999 to 2009. Scientometrics. 2012; 92(3): 549-73.
5. World Bank | World Bank [Internet]. World Bank; 2019 [cited 2019 Jan 11]. Available from: www.worldbank.org/
6. Pankaj K., Duggal E., Budhwar P., Badjatiya J.K. Marketing authorization of generic drug: global issue and challenges International Journal of Drug Regulatory Affairs. 2013; 1(3): 1-6.
7. APAC Regulations and Approvals Expert Working Group. Identification and Clarification of the differences in Regulatory requirements between Asian Economies. Tokyo, Japan: Asia Partnership Conference of Pharmaceutical Associations (APAC); 2013: 1-118.
8. ASEAN. ACTR., [Internet]. The ASEAN Secretariat: Jakarta; 2016 Dec [cited 2019 Jan 15]. Available from: http://asean.org/storage/2017/03/67.-December-2016-ACTR.pdf
9. Vaseem Akram M., Venketeshwarlu B., Ramaiah M., Nagabhushanam, Nagaarujuna D. Regulatory requirements for the registration of generic solid orals in USA, Singapore, Malaysia, and Thailand. JGTPS. 2014; 5(4):2225-32
10. The ASEAN Secretariat. ASEAN Statistical Yearbook. Jakarta: The ASEAN Secretariat; 2017: 1-280.
11. The ASEAN Secretariat. ACTD. Jakarta: The ASEAN Secretariat; 2016 .p. 4-198.
12. EMEA. CTD. London: EMEA; 2003: 1-26.
13. Health and Healthcare Systems in Southeast Asia - United Nations University [Internet]. Unu.edu 201: Japan; 2012 Apr 5 [cited 2019 Jan 19]. Available from: https://unu.edu/publications/articles/health-and-healthcare-systems-in-southeast-asia.html
14. ASEAN Statista. [Internet]. statista; 2018 [cited 2019 Jan 14]. Available from: https://www.statista.com/statistics/796245/gdp-of-the-asean-countries/.
15. ASEAN [Internet]. ASEAN: Thailand; 2017 [cited 2019 Jan 14]. Available from: https://asean.org/resource/statistics/