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COMPARATIVE STUDY OF REGULATORY REQUIREMENTS FOR MULTISOURCE GENERIC DRUGS IN ASEAN COUNTRIES

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INTRODUCTION
Regulatory Affairs department is growing within companies and is constantly evolving and growing and is the one which is least impacted during the Acquisition and Merger and also during recession. Global harmonization in standards has led to consistent approach in regulatory submissions and hence its review. Systematic formulation development acts as a back bone for any dossier preparation in export registration. There are different requirements in different countries for registration. It is difficult for any company to develop product for each region. Therefore, we need to consider majority of requirements during technical data submission which will help in export registration. Regions, but all are national registrations in these countries. Enormous diversity of regulatory requirements is there. However, harmonization occurs as clusters e.g. ASEAN, Gulf Council etc.

A generic drug (generic drugs/Products, short: generics) is defined as "a drug product that is comparable to reference (brand) listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use."

Generic drugs are usually sold for significantly lower prices than their branded equivalents. Reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents. Companies incur fewer costs in creating generic drugs and are therefore able to maintain profitability at a lower price. The prices are low enough for users in many less-prosperous countries to afford them.

Dossieris afile document submitted based on the requirement of the drug approval process. It is a comprehensive scientific document used obtained world I de licensing approval of a drug by diverse health authorities. Its creations processing, compilation & dispatch to the field by a regula tory affairs department, is dependent upon many interrelated activities the filling process in thee merging markets will be depends upon the region. In the Asean region A-CTD filling after compilation1copy of the dossier will be submitted to the regulatory authorities for the registration of the drug product.

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. Therefore, the aim of the pharmaceutical industry is to identify and develop a generic drug product which can be tailor made to meet the diverse market requirements. As per global market trend, it is estimated that approximately $150 billion worth of drugs will be off-patented during the period 2010 to 2017, which will serve as a platform for pharmaceutical companies to develop generic drugs.[1] The pharmaceutical industry in India has shown a remarkable growth which in turn has risen the economy of India.[2] After the introduction of the product patent regime in India, there was a need for pharmaceutical companies both in India and abroad to explore newer markets. Indian pharma majors are entering new markets with global ambitions, mergers and acquisitions are in focus with a reason to enter new market. For sustained growth over the next few decades, firms have to concentrate on generic drug products. "Diseases that cannot be cured, diseases that have to be managed, provide great opportunities for generic drugs." Government has the responsibility to protect their citizens. It is the responsibility of national governments to establish regulatory authorities with strong guidelines for quality assurance and drug regulations in the respective territories. Somewhat parallel with the ongoing harmonization and movement toward creating a common market for medicines inside the EU, the need for wider harmonization was felt by officials from Japan, EU, and US during International Conference of Drug Regulatory Authorities (ICDRA) organized by world health organization (WHO). The informal discussions had led to a need of the harmonization of requirements relating to the new innovative drugs and also subsequently paved the wayto the establishment of

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan and the United States with observers from WHO, EFTA, and Canada. Efforts to harmonize various elements of drug regulatory activities have been initiated by various inter-governmental organizations at regional and inter-regional level in the past decade. The driving force behind these efforts has been the increase in global trade in pharmaceutical products and growth in the complexity of technical regulations related to drug efficacy, safety, and quality.

The regulatory requirements of various countries of the world vary from each other. Therefore, it is challenging for the companies to develop a single drug which can be simultaneously submitted in all the countries for approval. The regulatory strategy for product development is essentially to be established before commencement of developmental work in order to avoid major surprises after submission of the application. The role of the regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country. It not only includes the process of regulating and monitoring the drugs but also the process of manufacturing, distribution, and promotion of it. One of the primary challenges for regulatory authority is to ensure that the pharmaceutical products are developed as per the regulatory requirement of that country.

Theregistrationprocedureisdifferentineveryregion.somewillfollowtheICHguidelines, WHOguidelines for the registration of the drug product. But some region have the country specific guidelines for the registration of the FPP. Drug regulatory affairs in pharma industries have mandated two types of dossier namely CTD (Common Technical Dossier) and ACTD (Asean Common Technical Dossier). Regulated pharma markets (eg.USA, Europe) markets require submission of dossier in CTD format which has to provide clinical trial and bioequivalence studies. Asagainstthis, semi-regulatedpharmamarkets(SouthEastAsian)requireACTD format which does not require exhaustive details like CTD. All of these guidelines will Be considered the safety, quality and efficacy of the FP product. This process involves the assessment comparision of regulatory requirements for multisource generic products in ASEAN countries during product development.

The Association of Southeast Asian Nations(ASEAN)
ASEAN-Introduction

The ASEAN was established on 8 August 1967 in Bangkok by the five original member countries (Indonesia, Malaysia, Philippines, Singapore and Thailand). Meanwhile five additional countries (Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia) joined ASEAN.

In 1999 a harmonization initiative was started among the 10 ASEAN countries. One aim of this harmonization should be to harmonize quality guidelines that are valid for all countries involved. Another focus lies in the technical co-operation. Therefore the ACCSQ PPWG was established. The objective of the ACCSQ PPWG is the development of "harmonization schemes of pharmaceuticals' regulations of the ASEAN member countries to complement and facilitate the objective of ASEAN Free Trade Area (AFTA), particularly, the elimination of technical barriers to trade posed by these regulations, without compromising on drug quality, safety and efficacy."

The strategy of the ACCSQ PPWG is the "exchange of information on the existing pharmaceutical requirements and regulation implemented by each ASEAN member countries, to study the harmonized procedures and regulatory systems implemented in the ICH region, development of common technical dossiers with a view of arriving at MRAs (Mutual Recognition Arrangements).

From August 2003 – December 2004 each ASEAN country should implement a trial implementation period for the ASEAN requirements (like ATCD and ACTR). The full implementation of the ASEAN requirements was originally planned for January 1st, 2005. The period for the ASEAN requirements was extended to December 31st, 2008 as it was not possible for the ASEAN countries to implement the ACTD until January 1st, 2005.

The full implementation of ACTD for new products was planned to be done in the ASEAN countries at different points in time between 2005 and 2008, which are summarized attached:

- Singapore and Malaysia by December 2005.
- Thailand by December 2006.
- Indonesia and Vietnam by December 2007.
- Philippines, Cambodia, Laos and Brunei by December 2008.

As the full implementation of the ASEAN requirements (like ACTD and ACTR) in the ASEAN countries is not yet finalized, a prolongation/transition period was done. There is an interim period agreed wherein ACTD and national formats allowed in most of the ASEAN countries, whereas in some countries like Singapore ICH CTD is accepted.

The full implementation of ACTD for new products was expected by 31 December 2008 whereas the full implementation for currently registered products is expected to be done until 01 January 2012. According to information received from the ASEAN countries (January 2009) some of the ASEAN countries still accept the CTD-format for MAAs of NCEs and NBEs whereas for RENs and VARs only the ACTD-format is accepted by ASEAN countries. According to the information of the "forum institute seminar on October 21st and 22nd in Cologne" the full implementation of ACTD became

mandatory by end of 2008 for MAAs and already registered products have to be transferred to ACTD until 2012.

All regulatory agencies in these 10 countries have a relatively weak infrastructure and limited resources. The agencies are structured differently and standards of scientific guidelines are not well established. A big problem of the agencies is the lack of consistency and the lack of transparency especially regarding the evaluation of dossier. To solve these problems they are constantly improving with more dialogues with the industry.

In all ASEAN countries a Certificate of a Pharmaceutical Product (CPP) from the reference country is required and builds the basis of the drug approval as the DRAs don't have the possibilities, capacities and scientific know-how to make a full evaluation of the submitted dossier (especially with regard to preclinical and clinical data).

Advantages of ACTD (ASEAN Common Technical Dossier)

- One dossier can be used for the application of registration of pharmaceutical for human use for whole region, rather than filling individual application for different countries.
- Significantly reduce the time and resources used for compiling an application.
- Transparency in the regulatory authorities of member countries.
- Transparency in the structure of regulatory framework to be follows for single filling.
- Faster review and approval process those are more transparent.
- Reduced costs for industry, as the format is less expensive for dossier preparation.
- Improved access to medicines in all countries.
- Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.
- Single filling, single monitoring, improved public trust in the Approved medicines.

ASEAN- Introduction to Respective Regulatory authorities

SINGAPORE: Health Science Authority

The Health Sciences Authority (HSA) is a multidisciplinary agency in health sciences expertise. Their core capabilities encompass administering the national regulatory frameworks for pharmaceuticals, complementary medicines, medical devices and other health products; the running of the national blood bank and provision of transfusion medicine services; and the provision of forensic medicine expertise, investigative forensic and analytical science services.

THAILAND: **Thai FDA**

The regulation of pharmaceutical products in Thailand began in 1909 when the adulteration of drug products and narcotic substances was prohibited. There had been practically no control of drugs before 1909. The first legislation promulgated in 1922 was the Harmful and Habit-forming Drugs Act. However, the duties for manufacturing and dispensing medicines were not assigned to pharmacists until 1929.

CAMBODIA: Department Of Drug, Food and Cosmetics

Department of Drugs, Food and Cosmetics is responsible for:

1. Organizing and implementing the national policy on drug, food and cosmetics works.
2. Organizing articles to manage the control of products selling at market and to control the uses of drug and medical instruments.

LAO PEOPLE'S DEMOCRATIC REPUBLIC: **Ministry Of Health - Food and Drug Department (FDD)**

The main responsibility of the drug regulatory agency is to ensure that all products subject to its control and being made available to the general public conforms to acceptable standards of quality, safety and efficacy. Drug product registration enables the regulatory authority to assess the benefits of a product and to control and regulate its distribution.

INDONESIA: **National Agency of Drug and Food Control.**

The main agency responsible for regulating pharmaceuticals/drugs in Indonesia is the National Agency of Drug and Food Control (NA-DFC).

Main Functions

1. Assessment and organization national policy in food and drug evaluation field.
2. The Implementation of a specific policy in food and drug evaluation field.
3. Coordination of functional activities in the implementing of NA-DFC duties.
4. Monitoring and providing guidance and development on the activities of government agencies in food and drug evaluation field.

PHILIPPINES: **Bureau of Food and Drug Administration**

a) Develops plans policies, programs and strategies for regulating processed foods, drugs and other related products.
b) Formulates rules, regulations and standards for licensing and accreditation of processed foods, drugs and other related products.
c) Conducts licensing and accreditation of processed foods, drugs and other related products.
d) Provides technical, consultative and advisory services to and develops capability of field offices on licensing and enforcement of laws, rules and regulations pertaining to processed foods, drugs and other related products.

e) Monitors, evaluates and ensures compliance of manufacturers, distributors, advertisers and retailers of processed foods, drugs and other related products to health rules and regulations and standards of quality. Advises the Secretary and Undersecretary of Health on matters pertaining to regulation of processed foods, drugs and other related products.

MALAYSIA: National Pharmaceutical Control Bureau (NPCB)

The National Pharmaceutical Control Bureau (NPCB), formerly known as the National Pharmaceutical Control Laboratory, was set up in October 1978 under the quality control activity of Pharmacy and Supply Programme. This institution was established to implement quality control on pharmaceutical products. The infrastructure and facilities were designed to meet the requirements for testing and quality control activities.

In 1996, NPCB was given an international recognition by the World Health Organization (WHO) as a "WHO Collaborating Centre for Regulatory Control of Pharmaceuticals". This recognition is an acknowledgement from WHO for NPCB's contribution in the field of regulatory affairs.

Vision

To be a world renowned regulatory authority for medicinal products and cosmetics**.**

Mission

To safeguard the nation's health through scientific excellence in the regulatory control of medicinal products and cosmetics.

Objective

To ensure that therapeutic substances approved for the local market are safe, effective and of quality and also to ensure that cosmetic products approved are safe and of quality.

BRUNEI: **Ministry of Health**

The Ministry of Health is the main agency responsible for direct or indirect delivery of health care, health care information and all health care-related services in Negara Brunei Darussalam and is headed by The Minister of Health. There are three major groups of service provider in MOH organization structure

- Ministry proper/central.
- Health services.
- Medical services.

VIETNAM: **Drug Administration of Vietnam**

Under Vietnam's Ministry of Health, the Drug Administration of Vietnam (DAV) is responsible for the regulation of pharmaceuticals. The DAV evaluates pharmaceutical applications for their compliance with the2005 Pharmaceutical Law and issues licenses accordingly. Imported pharmaceuticals, however, require a separate import permit in addition to product approval. For a small fraction of pharmaceuticals, the DAV will also perform product sample analysis.

MYANMAR: Food and Drug Administration

The Myanmar (Burma) government enacted the National Drug Law (‘the ND Law’) in 1992. The basic purpose of the ND Law is to control and systematically regulate the manufacture, import, exports, storage, distribution and sale of drugs. The ND Law is administered by the Ministry of Health (‘the MOH’).The MOH is composed of a total of 14 departments and institutes.

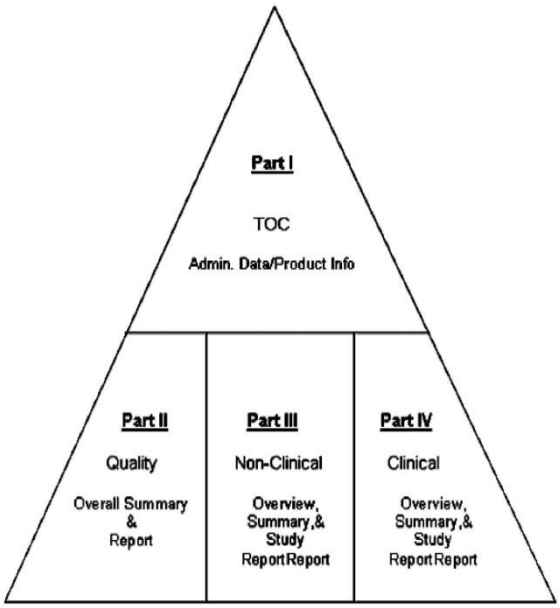
ASEANHARMONISE GUIDELINES FOR GENERIC FILLING

- ASEAN Guidance on ACTD
- ASEAN Guideline for Validation of Analytical Procedures.
- ASEAN Guideline on Process Validation.
- ASEAN Guideline for the Conduct of Bio availability and Bio equivalence Studies.
- ASEAN Guideline for Drug Product Stability Study.

Guideline	Basis	Present Scenario
ASEAN harmonized Product ACTD	Based on ICH CTD	Approved & Implemented
Analytical Validation	Based on ICH Q2A & Q2B	Approved & Implemented
Bioavailability/Bioequivalence	Based on EU directives	Approved & Implemented
GMP Standard	Based on ICH Q7A	
Process Validation	Based on EU directives	Approved & Implemented
Stability Studies	Based on ICH guidelines(Q1A,Q1B,Q1C,Q1D,Q1E,Q1F)	Approved & Implemented
Post Market Surveillance	Based on E2B guideline	Approved & Implemented

ACTD

The ASEAN Common Technical Document is organized into four parts as follows:



A-CTD have beenorganizeinto4 modules or parts

Part 1Administrative & prescribing information
Section A: Introduction
Section B: Overall ASEAN common technical dossier table of contents
Section C: Documents required for registration (for example, applications, labelling, product data sheet, Prescribing information).

Part2 Quality document
Section A: Table of contents.
Section B: Quality overall summery.
Section C: Body of data.

Part 3 Non-Clinical Overview
Section A: Table of contents.
Section B: Non clinical over view.
Section C: Non clinical written and tabulated summaries.
Section D: non clinical study reports.

The document of this part is not required for generic products, minor variation products and some major variation products. For ASEAN member countries, the study reports of this part may be required for NCE.

Part 4: Clinical study report
Section A: Table of contents.
Section B: Clinical overview.
Section C: Clinical summery.

1. Summary of Bio pharmaceutics and associated analytical methods.
2. Summary of clinical pharmacology studies.
3. Summary of clinical efficacy.
4. Summary of clinical safety.
5. Synopses of individual studies.

Section D: Tabular listing of all clinical studies.
Section E: Clinical study reports.
Section F: List of key literature studies.

The document of this part is not required for generic products, minor variation products and some major variation products. For ASEAN member countries, the study reports of this part may be required for NCE.

Part: 1 Administrative & prescribing information
Section A: Introduction.
Section B: Overall ASEAN common technical dossier table of contents.
Section C: Documents required for registration (for example, applications, labelling, product data sheet, Prescribing information).

Part 2 Quality document
Section A: Table of contents.
Section B: Quality overall summery.
Section C: Body of data.

S DRUG SUBSTANCE
S 1 General Information
S 1.1 Nomenclature
International non–proprietary name (INN).
Compendial name if relevant.
Registry number of chemical abstract service (CAS).
Laboratory code (if applicable).
Chemical name(s).

S 1.2 Structural formula
The structural, includingrelativeandabsolutestereochemistry, themolecularformula, andtherelative molecular mass should be provided.

S 1.3 General Properties
A list should be provided of physico chemical and other relevant properties of the drug substance.
Reference ICH Guidelines: Q6A

S 2 Manufacture
S 2.1 Manufacturer(s)
Name and full addresses including the city and country of the manufacturer of active ingredient.

S 2.2 Description of Manufacturing Process and Process Controls
The description of the drug substances manufacturing process represents theapplicant's commitment for the manufacture of drug substances. The following information should be provided to adequately describe the manufacturing process and process controls:

A schematic flow diagram of the synthetic process (es) should be provided that includes molecular formulae, weights and yields, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereo chemistry and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process that provides quantities of rawmaterials, solvent, catalysts and reagent reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time etc.

Alternative process should be explained and described with the same level of details as the primary process.

Reprocessing steps should be identified and justified.

S 2.3 Control of Materials
Material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials(including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes)meet standards appropriate for their intended use(including the clearance or control of adventitious agents) should be provide as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.
Reference ICH Guidelines:Q6A

S 2.4 Controls of critical steps and intermediates
Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process. Reference ICH Guidelines: Q6A.

S 2.5 Process Validation and/or Evaluation
Process validation or evaluation studies for aseptic processing and sterilization.

S 2.6 Manufacturing Process Developments
Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing non-clinical, clinical scale-up, pilot and if available, production scale batches.
Reference ICH Guidelines: Q3A.

S 2.5 Reference Standards or Materials
Quality information of Reference standard or material used for testing of substance should be provided.
Reference ICH Guidelines: Q6A.

S 2.6 Container Closure System
A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component, and each specifications. The specifications should include description and identification(and critical dimensions with drawings where appropriate).

Non- compendia methods (withvalidations) should be included where appropriate.

Fornon-functional secondary packaging components (e.g.those that donot provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 3 Characterizations
S 3.1 Elucidations of Structure and Characteristics
Confirmation of structure based on e.g.synthetic route and spectral analysis. Information on the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorph should also be included.
Reference ICH Guidelines: Q6A.

S 3.2 Impurities
Information on impurities should be provided.
Reference ICH guidelines: Q3A,Q3C, and Q6A.

S 4 Control of Drug Substance
Specification and justification of specification(s). Summary of analytical procedure and validation.

S 4.1Specification
Detailed specification, tests and acceptance criteria for the drug substance should be provided. Compendia specifications are adequate. Indicate clearly whether the drug substance is purchased based on specification with a certificate of analysis, or tested by applicant.
Reference ICH Guidelines Q6A.

S 4.2 Analytical Procedures
The analytical procedure used for testing the drug substance should be provided insufficient detail to enable reproducible testing by another laboratory.
Reference ICH Guidelines: Q2A.

S 4.3 Validation of Analytical procedures
S 4.4 Batch Analyses
Description of batches and results of batch analyses should be provided.
Reference ICH Guidelines: Q3A, Q3C and Q6A.

S 4.5 Justification of Specification
Justification for the drug substance specification should be provided.
Reference ICH Guidelines: Q6A.

S 5 Reference standards or materials
S 6 container closure systems
S 7 Stability Summary and Conclusion
The types of studies conducted, proto colsused, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.
Reference ICH Guidelines: Q1A(R2),Q1B.

S 7.1 Post-approval Stability Protocol and Stability Commitment
The post-approval stability protocol and stability commitment should be provided.
Reference ICHGuidelines: Q1A(R2).

S 7.2 Stability Data
Results of the stability studies (e.g.forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included. Manufacturer stability data or equivalent information for generic drug.
Reference ICH Guidelines: Q1A(R2),Q1B,Q2A,Q2B.

PDRUGPRODUCT
P1 Description and Composition
A description of the drug product and its composition should be provided. The information provided should include, forexample:
Description of the dosage form;
Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, ifany) the function of the components, and a reference to their quality standards (e.g.,compendial monographs or manufacturer's specifications).

Description of accompanying reconstitution diluent(s); and Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.
Reference ICH Guidelines: Q6A.

P 2.0 Pharmaceutical Development
P 2.1 Informationon Development Studies
The section of Pharmaceutical Development presents information and data on the development studies conducted to establish that the dosageform, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug productquality. Supportive data and result from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application.
Reference ICH Guidelines: Q8(R2).

P 2.2 Component of Drug Product
P 2.2.1 Active Ingredients
The compatibility of the drug substances with excipients listed in Item2.1shouldbediscussed. Additionally, key physicochemical characteristics (e.g. Water content, solubility, particlesize distribution, poly morphic or solid state form) of the drug substance, which may influence the performance of the drug product should be discussed. For generic drug Literature data is sufficient.

P 2.2.2 Excipients
The choice of excipients listed in ItemP1, their concentration and characteristics which influence the drug product performance should be discussed relative to their respective function.

P 2.3 Finished Product
P 2.3.1 Formulation Development
A brief summary describing the development of the drug product should be provided, taking in to consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e.Composition) described in ItemP1 and P2should be discussed. Results from comparative in vitro studies (e.g.dissolution) or comparative invivo studies (e.g., bioequivalence)should be discussed when appropriate.

P 2.3.2 Overages
Any overages in the formulation(s) described in ItemP1 should be justified.

P 2.3.3 Physico chemical and Biological Properties
Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, re dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

P 2.4 Manufacturing Process Development
The selection and optimization of the manufacturing process described in Item P3.2, in particularits critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in ItemP3. 2that can influence the performance ofthe product should be discussed.

P 2.5 Container Closure System
The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion

should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials ofc onstruction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes
Where appropriate, the microbiological attributes of the dosage form should be discussed including the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility
The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

P 3 Manufacture
P 3.1 Batch Formula
The formula with name and quantities of all ingredients (active and otherwise) including substance(s)which are removed in the course of manufacture should be included:
The actual quantities (g,kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must stated. A description of all stages involved in the manufacture of the dosage form is required.

P 3.2 Manufacturing Process and Process Control
A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture.

For sterile product the description includes preparation and sterilization of components (i.e.Containers, closures, etc.).

P 3.3 Controls of Critical Steps and Intermediates
Critical steps
Tests and acceptance criteria should be provided(with justification, including experimental data) performed at the critical steps identified P3.3of the manufacturing process, to ensure that the process is controlled.

Intermediates
Information on the quality and control of intermediates isolated during the process should be provided.
Reference ICH Guidelines: Q2Aand Q6A

P 3.4 Process Validations and/or Evaluation
Description, documentation and result of the validation studies should be provided from critical steps or critical assays used in the manufacturing process. (e.g. Validation of the sterilization process or aseptic processing or filling).
Reference:Q6A or Asean guidelines for Process validation

P 4 Control of Excipients
P 4.1 Specification
The specification for the excipients should be provided.

P 4.2 Analytical Procedures
Theanalyticalprocedureusedforthetestingofcriticalexcipients.e.substanceswhich affectstabilityandbioavailabilityoffinishedproduct (e.g.preservative, buffer components, dissolution enhancer)should be provided.
Reference ICH Guidelines: NCE: Q2AandQ5A.

P 4.3 Excipients of Human and Animal Origin
For excipients of human or animal origin, provide information of sources (e.ggelatin, enzyme, etc), specifications, description, viral safety data) regarding adventitious agents (e.g., TSE, viruses, mycoplasma).
Reference ICH Guidelines: NCE:Q5A,Q5D;

P 4.4 *Novel* Excipients
For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (non clinicalor clinical) should be provided.

P 5 Control of Finished Product
Specification and justification of the specification, summary of the analytical procedure and validation and characterization of impurities.

P 5.1 Specification
The specification for the finished product should be provided.
Reference: ICH Guidelines: NCE:Q6A;

P 5.2 Analytical Procedures.
The analytical procedures use for the testing the finished product should be provided.
Reference ICH Guidelines: NCE:Q2A.

P 5.3 Validation of Analytical Procedures
Analytical validation information, including experimental data for the analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines: NCE: Q2 A and Q2B.
Reference: ASEAN Guideline

P 5.4 Batch analyses
Description (including size, origin and use) and test result of all relevant batches e.g pre-clinical, clinical pilot, scale-up and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines: NCE:Q3A,Q3C and Q6A

P 5.5 Characterization of Impurities
Information on the characterization of impurities should be provided, if not previously provided inItem1.3.2 Impurities.
Reference ICH Guidelines: NCE :Q3Band Q6A

P 5.6 Justification of Specification
Justification for the proposed finished product should beprovided
Reference ICH Guidelines: NCE:Q3B andQ6A

P 6 Reference Standards or Materials
Requirement: Quality information and tabulated presentation of Reference standard or materials used for testing of drug product should be included.

P 7 Container closure system
A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g.those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located inP2.

P 8 Product Stability
Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life, that toxic decomposition products are not produced insignificant amount during this period and thatpotency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion.
AllcriteriaunderICHGuidelinesareacceptablewiththeexception of *realtime* storageconditionswhich should be 30^0C, 70% RH. Provision of moisture protection of the packaging should be taken into consideration.

P 9 Product Interchange ability
The type of studies conducted, protocol used and the result of the studies should be presented in the study report. Type of studies conducted should referto ASEAN (proposed) Bioavailability and Bioequivalence requirement, Guideline for Bioavailability and Bioequivalence Studies or WHOM annual for Drug Regulatory Authority.

REFERENCE
WHO, Regulatory Support Series No5,"Bioequivalence StudiesinHumans."
Section D: Key Literature References.
Key literature references should be provided, if applicable.

Part 3 Non –clinical study report
Section A: Table of contents
Section B: Non clinical over view
Section C: Non clinical written and tabulated summaries
Section D: non clinical study reports

The document of this part is not required for generic products, minor variation products and some major variation products. for ASEAN member countries, the study reports of this part may be required for NCE

Part 4- clinical study report
Section A: Table of contents
Section B: Clinical overview
Section C: Clinical summery

1. Summary of Biopharmaceutics and associated analytical methods
2. Summary of clinical pharmacology studies
3. Summary of clinical efficacy
4. Summary of clinical safety
5. Synopses of individual studies

Section D: Tabular listing of all clinical studies.
Section E: Clinical study reports.
Section F: List of key literature studies.

The document of this part is not required for generic products, minor variation products and some major variation products. For ASEAN member countries, the study reports of this part may be required for NCE.

COMPARISION OF SPECIFIC REQUIREMENTS FOR ASEAN COUNTRIES

PART - I	**A ADMINISTRATIVE DATA**		**Requirements for phillippiens**	**Requirements for myanmar**	**Requirements for cambodia**
Section A:	INTRODUCTION		Yes	Yes	Yes
Section B:	TABLE OF CONTENTS		Yes	Yes	Yes
Section C:	ADMINISTRATIVE DATA AND PRODUCT INFORMATION		Yes	Yes	Yes
	1	Letter of Authorization	Yes	Yes	
	2	Product name	Yes	Yes	Should be on brand name
	3	Certificates	Yes	Yes	Yes
		3.1 Manufacturing License	Yes	Yes	Yes
		3.2.Certificate of Pharmaceutical product	COPP should be provide with Excipientscomposition, pharmacopoeia status and attachment of annexure	Yes	Should be on brand name & Country specific
		3.3 Site master File of Manufacturer	Yes	Yes	Yes
	4	Labeling	Yes	Yes	Yes
	5	Product Information	Yes	Yes	Yes
		5.1 Package insert	Yes	Yes	Yes
		5.2 Summary of Product Characteristics	Yes	For NCE/Biotech	Not required for generic products
		5.3 Patient Information Leaflet	Yes	Over the counter products	Not required for generic products

S.No	**INDEX**		**Regulatory Requirements for Malaysia**	**Regulatory Requirements for Indonesia**
PART – I				
Section A : Administrative data and product information				
	A1	Name of the product	Yes	Yes
	A2.	Name and Strength of active ingredients	Yes	Yes
	A3.	Product Description	Yes	Yes
	A4	A4.1 Pharmaco dynamics	Yes	Yes
		A4.2 Pharmacokinetics	Yes	Yes
	A5	Indications	Yes	Yes
	A6	Recommended dose	Yes	Yes
	A7	Mode of administration	Yes	Yes
	A8	Contraindication	Yes	Yes
	A9	Warnings and precautions	Yes	Yes
	A10	Interaction with other medicaments	Yes	Yes
	A11	Pregnancy and lactation	Yes	Yes
	A12	Side effects 7 -7- 8 - 8	Yes	Yes
	A13	Symptoms and treatment of overdose	Yes	Yes
	A14	Storage conditions	Yes	Yes
	A15	Shelf life	Yes	Yes
	A16	Therapeutic code	Yes	Yes
SectionB:	**Product formula**			
	B1.1	Batch manufacturing formula	Batch formula should match with Drug product section "P.3.1 Batch Formula"	Batch formula should match with Drug product section "P.3.1 Batch Formula"
	B1.2	Attachment of batch formula documentation	Yes	Yes
Section C:	**Particulars of packing**			

	C1	Pack size	Yes	Yes
	C2	Immediate container type	Yes	Yes
	C3	Barcode/Serial No.	Yes	Yes
	C4	Recommended distributor price	Yes	Yes
	C5	Recommended retail price	Yes	Yes
Section D :	**Label (Mockup) for intermediate container, outer carton and proposed package insert**			
	D1	Label (Mockup) for intermediate container	Mockup's in pdf format. Details of Name of API, strength, Batch no., Expiry date & Name/logo of manufacturer should be present on each Tablet/Capsule.	Mockup's in pdf format. It includes name & address of importer (MAH), batch coading& Reg. number details, store below 30ºC and keep out of reach of children in English & Indonesian language.
	D2	Label (Mockup) for outer carton	On carton we have to include Marketing Authorization holder name, Store below 30ºC, Route of administration: Oral. The terms controlled medicine and keep out of reach of children in Malaysian language.	On carton specific matter is same as to foil. Also we have to include customer logo.
	D3	Proposed package insert	Yes	Yes
Section E:	**Supplementary documentation**			
	E1.1	Product owner	Yes	Yes
	E1.2	Letter of authorization from product owner	Yes	Yes
	E2.1	Letter of appointment of contract manufacturer	Yes	Yes
	E2.2	Letter of acceptance of contract manufacturer	Yes	Yes
	E3	Is the active substance patented in Malaysia	Yes	Yes
	E4	Certificate of pharmaceutical product (CPP)	Country specific	Country specific & Should be legalized with Indonesia embassy.
	E5	Certificate of free sale (CFS)	Yes	Not required
	E6	Certificate of good manufacturing practice (GMP)	Yes	Should be legalized with Indonesia embassy.
	E7	Summary of product characteristics (product data sheet)	Yes	Yes
	E8	Patient information leaflet (PIL)	Yes	Yes
	E9	Attachment of protocol analysis	Yes	Yes
	E10	Attachment of analysis validations	Yes	Yes
	E11	Attachment of certificate of analysis	Yes	Yes
	E12	Other supporting documentation	Yes	Yes
	E13	Manufacturer	Yes	Yes
	E13.1	Importer	Yes	Yes
	E14	Other manufacturer involved (if any)	Yes	Yes
	E15	Storage address (if any)	Yes	Yes

Regulatory requirements for Singapore

PART - I Administrative data and product information			**Specific requirements.**
Section A			
PART - I	1.1	Comprehensive Table of contents	
	1.2	Introduction	
		Provide a concise and precise summary of the application	
		Justify the lack of certain documents and deviation(s) from guidelines	
	1.3	PRISM Application form	(it should be agreed by HAS)
		Section 1: Company Particulars	
		Section 2: Applicant particulars	
		Section 3: Applicant details	
		3.1 Type of application	
		3.2 Type of product	
		3.3 Reference product	
		3.4 Product intended for export	
		3.5 Type of dossier	
		3.6 Type of format	
		Section 4: Product information	
		4.1 Product Name	
		4.2 Product formula	
		4.3 Ingredients derived from human blood or animal sources	
		4.4 ATC code	
		4.5 Dosage form	
		4.6 Route of administration	
		4.7 Packaging, shelf life and storage condition	
		4.8 Forensic classification	
		4.9 Registration status in other countries	
		4.10 Product owner	
		Section 5: Manufacturer's particulars	
		Section 6: Batch released details	
		Section 7: Supporting documents	
	1.4	Labeling and PI/PIL	(not only manufacturer address, require product owner address)
		1.4.1 Outer/Carton Labels	(not only manufacturer address, require product owner address)
		1.4.2 Inner/Blister Labels	(not only manufacturer address, require product owner address)
		1.4.3 Package Insert (PI)	Revised date, shelf life
		1.4.4 Patient Information Leaflet (PIL)	
	1.5	Approved SmPC/PI/PIL	
	1.7	Description of batch numbering system	
	1.10	Authorization Letters	
		1.10.1 authorizations Letter from Product Owner to the Applicant firm	
		1.10.2 authorization Letter from Product Owner to the Manufacturer(s)	
		1.10.3 authorization Letter from Product Owner to the Batch Releaser	
	1.11	Certification	
	1.12	Patent Declaration form	
	1.13	Declaration on rejection, withdrawal and deferral	specific
	1.15	Registration status in other countries as separate attachment in PRISM under "supporting attachments"	With date, month and stage.

Regulatory Requirements for Vietnam

PART - I	**ADMINISTRATIVE DATA**	**Remarks**
Section A:	INTRODUCTION	
Section B:	TABLE OF CONTENTS	
Section C:	DOCUMENTS REQUIRED FOR REGISTRATION	
	• Application forms	We have to provide form4 & Form 2A for Vietnam.
	• Labeling and pack insert	SPC have to provide Vietnam
	• Product data sheet	It is a special format for two pages to typing
	• Product Description	These section have to provide for Vietnam. It is a special requirement for Vietnam.
	• Pharmacodynamics & Pharmacokinetics	
	• Indication / Usage	
	• Dose / Use Instruction	
	• Recommended Dose & Route of Administration	
	• Contraindication	
	• Warnings and Precaution	
	• Drug Interaction	
	• Side Effects / Adverse Reactions	
	• Pregnancy and Lactation	
	• Signs and Symptoms of Overdose and Treatment	
	• Storage Conditions	

DRUG LABELLING REQUIREMENTS FOR ASEAN

Effective pharmaceuticals have been directly responsible for major gains in health around the world and better improvement is possible only if prescriber of products have the information they need to use drug products safely and effectively. Appropriate drug labelling is the norm in this context that provides comprehensive and concise statement of a drug's quality, Safety and Efficacy.

Although ASEAN is a group, there are no harmonise labelling guidelines for them. However each country has its own labelling requirements.

MALAYSIA

S. No	**Information that is to be included**	**Unit Carton**	**Strips/Blisters**	**Inner Labels**
1.	Product Name	Yes	Yes	Yes
2.	Dosage form	Yes	NA	Yes
3.	Name and Strength of Active Substance(s)	Yes	Yes	Yes
4.	Batch No.	Yes	Yes	Yes
5.	Manufacturing Date	Yes	NA	Yes
6.	Expiration Date	Yes	Yes	Yes
7.	Route of Administration	Yes	NA	Yes
8.	Storage Condition	Yes	NA	Yes
9.	Country's Registration Number	Yes	NA	Yes
10.	Name & Address of Marketing Authorization (Product License) Holder/Product Owner	Yes	Name or Logo of Manufacturer/Product owner	Yes
11.	Name and Address of Manufacturer	Yes	NA	Yes
12.	Special warning, declaration of sources of ingredients from animal origin etc.	Yes	NA	Yes
13.	Pack size	Yes	NA	Yes
14.	Security Labelling Hologram	Yes	NA	Yes

PHILIPPINES

There is no separate Drug labelling requirements given for Philippines for Carton, Blister/ Strips and for Inner label. The mandatory Drug Labelling requirements given under Harmonization scheme are as follows:

a) Name of the product (Generic name alone or with Brand name, as the case may be)

b) Dosage form and strength
c) Pharmacologic category
d) Name and complete address of manufacturer and trader, when applicable
e) Net content
f) Formulation
g) Indication(s)
h) Contraindication(s), precaution(s), warning(s)
i) Mode of administration/directions for use
j) Batch and lot number
k) Expiry/expiration date and date of manufacture
l) Registration number
m) Storage conditions
n) For Prescription products, Foods, drugs and devices and Cosmetic Act prohibits dispensing without prescription.

SINGAPORE

S. No	Information that is to be included	Unit Carton	Strips/Blisters	Inner Labels
1.	Product Name	Yes	Yes	Yes
2.	Dosage form	Yes	NA	Yes
3.	Name and Strength of Active Substance(s)	Yes	Yes	Yes
4.	Batch No.	Yes	Yes	Yes
5.	Manufacturing Date	Yes	NA	Yes
6.	Expiration Date	Yes	Yes	Yes
7.	Route of Administration	Yes	NA	Yes
8.	Storage Condition	Yes	NA	Yes
9.	Country's Registration Number	Yes	NA	Yes
10.	Name & Address of Product License Owner	Yes	Name or Logo of Manufacturer/Product owner	Yes
11.	Name and Address of Manufacturer	Yes	NA	Yes
12.	Warnings(if applicable)	Yes	NA	Yes
13.	Pack size	Yes	NA	Yes
14.	Special Warnings(if Applicable)	Yes	NA	Yes

INDONESIA

S. No	Information that is to be included	Unit Carton	Strips/Blisters	Inner Labels
1.	Product Name	Yes	Yes	Yes
2.	Dosage form	Yes	Yes	
3.	Package size	Yes	Yes	
4.	a)Name & strength of API Generic name should appear under the brand name, size for brand name is 80% min.	Yes	Yes	Yes
5.	Imported Drugs: Name of Applicant & Manufacturer Address of Applicant & Manufacturer	Yes Yes	Yes Yes	Yes NA
6.	Name of Manufacturer and Address of Manufacturer			
7.	Registration No.	Yes	Yes	Yes
8.	Batch No.	Yes	Yes	Yes
9.	Date of Production	Yes	NA	
10.	Expiration Date	Yes	Yes	Yes
11.	Indication	Yes	If Required	NA
12.	Posology	Yes	If Required	NA
13.	Contraindication	If Required	If Required	NA
14.	Adverse Reactions	If Required	If Required	NA
15.	Drug Interaction	If Required	If Required	NA
16.	Warnings and Precaution	If Required	If Required	NA
17.	Storage Condition	Yes	Yes	NA
18.	Specific information in accordance with valid provisions (if any) e.g. Source of Porcine Alcohol content Specific information on ceiling price	Yes	Yes	NA
19.	Warning for limited over the counter drug (OTC)	Yes	Yes	NA
20.	Specific round mark of prescription drug /OTC / limited OTC	Yes	Yes	NA

THAILAND

Printed packaging material, including package inserts, must be submitted for approval. The following information must appear on the package label.

Some of the labelling requirements for drugs include:

- Drug name
- Quantity
- Active ingredient(s)
- Lot/batch number
- Manufacturer's name and province
- Date of production
- Drugs classified as Specially-controlled drugs, dangerous drugs or common household drugs should belabeled as such.
- Expiration date
- Where applicable and on a red label: "Ya Antarai (Dangerous Drug)" in Thai, "Special Control" in Thai, "External or Topical Use" in Thai.
- Package inserts also are required and are expected to contain the product name; active ingredients; indications; instructions for use, including warnings, precautions, adverse drug reactions and contraindications; dosage, and storage information.
- All labelling information must be in Thai or English. Thailand also requires that all other information companies intend to send to doctors, such as reminder advertisements or other promotional material, be included with the registration application. Any changes in labels for products already registered must be approved by the government.

BRUNEI DARUSSALAM

S. No.	Information that should be included	Unit Carton	Strips/Blisters	Inner Labels
1.	Product Name(Should be bigger than brand name)	Yes	Yes	Yes
2.	Dosage Form	Yes	-	Yes
3.	Name & Strength of API	Yes	Yes	Yes
4.	Batch No.	Yes	Yes	Yes
5.	Manufacturing Date	Yes	-	Yes
6.	Expiration Date	Yes	Yes	Yes
7.	Route of Administration	Yes	-	Yes
8.	Storage Condition	Yes	-	Yes
9.	Country's Registration Number	Yes	Yes	Yes
10.	Name & Address of Marketing Authorization	Yes	-	-
11.	Name & Address of Manufacturer	Yes	Yes	Yes
12.	Special Labelling(if applicable)	Yes	-	Yes
13.	Warnings	Yes	-	Yes
14.	Pack Size	Yes	-	Yes
15.	Recommended Daily allowance	Yes	-	Yes

VIETNAM

S. No.	Information that should be included	Unit Cartons	Strips/Blisters	Inner Labels
1.	Product Name	Yes	Yes	Yes
2.	Name and Strength of active substances	Yes	Yes	Yes
3.	Expiration date	Yes	Yes	Yes
4.	Name and Address of Manufacturer	Yes	(Only Name)	Yes
5.	Batch No.	Yes	Yes	NA
6.	Indication	Yes	NA	Yes
7.	Contraindication	Yes	-	Yes
8.	Route of Administration	Yes	-	Yes
9.	Adverse reactions	-	-	Yes
10.	Drug Interaction	-	-	Yes
11.	Manufacturing Date	Yes	Yes	NA
12.	Storage Condition	Yes	NA	Yes
13.	Registration number	Yes	NA	Yes
14.	Name and address of Importer	Yes	Yes	Yes
15.	Pack Size	Yes	NA	Yes
16.	Warnings (if applicable)	-	-	Yes
17.	Name and Contents of excipients	-	-	Yes
18.	With Physician Prescription only(for Prescription drugs only)	Yes	-	Yes

MYANMAR

Every drug to be registered in Myanmar must be properly labeled. Labelling language may be written in Myanmar or in English or in both.

Labelling requirement for containers, strip and box:

- Brand name
- Generic name
- Standard name of active ingredients and amount
- Batch number or Lot no.
- Date of manufacture
- Expiry date
- Quantity
- Name and address of manufacturer must be indicated on containers of a drug, such as bottle, package, strip, box, packaging material and in addition to the above mentioned particulars
- The Myanmar drug registration number,
- Method of administration
- Package size
- Storage conditions must be present on packaging material
- For prescription drugs "Drug only with Prescription" must be written.

LAOS

S. No.	Information that should be Included	Unit Cartons	Strips/Blisters	Inner Labels
1.	Product Name	Yes	Yes	Yes
2.	Dosage Form	Yes	Yes	Yes
3.	Name & strength of API	Yes	Yes	Yes
4.	Batch No.	Yes	Yes	Yes
5.	Manufacturing Date	Yes	-	Yes
6.	Expiration Date	Yes	Yes	Yes
7.	Route of Administration	-	-	Yes
8.	Storage Condition	Yes	-	Yes
9.	Country's registration number	Yes	Yes	Yes
10.	Name & Address of Manufacturer	Yes	Yes	Yes
11.	Special Labelling (if applicable)dangerous in Red	Yes	-	Yes
12.	Warnings	Yes	-	Yes
13.	Lao English/English/French	Yes	-	-
14.	Recommended daily Allowance (for Vitamins and Minerals)	-	-	Yes

CAMBODIA

S. No.	Information that should be Included	Unit Cartons	Strips/Blisters	Inner Labels
1.	Product Name(Bigger than Brand Name)	Yes	Yes	Yes
2.	Dosage form	Yes	-	Yes
3.	Name & Strength of API	Yes	Yes	Yes
4.	Batch No.	Yes	Yes	Yes
5.	Manufacturing Date	Yes	-	Yes
6.	ExpirationDate	Yes		Yes
7.	Route of Administration	Yes	-	Yes
8.	Storage Condition	Yes	-	Yes
9.	Country's Registration number	Yes	Yes	Yes
10.	Name & Address of Marketing Authorisation Holder(Full Address)	Yes	Name/Logo or Manufacturer/Product	Yes
11.	Name & Address of Manufacturer(Name, City, Country)	Yes	-	Yes
12.	Special Labelling's (if applicable) e.g., for sterile products etc.	Yes	-	Yes
13.	Warnings(where applicable)	Yes	-	Yes
14.	Pack size	Yes	-	Yes
15.	Recommended daily allowance(especially for Vitamin Products)	Yes	-	Yes

REFERENCE

ICH Guidelines: Q1A(R2),Q1B,Q2A,Q2B andQ5C ASEAN Guideline on *Stability Study*.

Post-approval stability protocol and stability commitment the post-approval stability protocol and stability commitment should be provided.

References ICH Guidelines: NCE, ASEAN Guideline on *Stability Study* Stability Data.

Results of the stability studies should be presented in an appropriate format (e.g.tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

REFERENCE

ASEAN Guideline on Stability Study, ASEAN Guideline on Validation of Analytical Procedure.