Dedicated to public health

COMPARISON BETWEEN ASEAN AND ICH CTDS

Singapore
Wednesday 27th March 2019

Advanced Training Workshop:
Building a CTD for registration of vaccines globally
27th–28thMarch 2019, Singapore

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ASEAN

Organization membership

 Brunei

 Cambodia

 Indonesia

 Laos

 Malaysia

 Myanmar

 Philippines

 Singapore

 Thailand

 Viêt Nam

ASEAN CTD (ACTD)

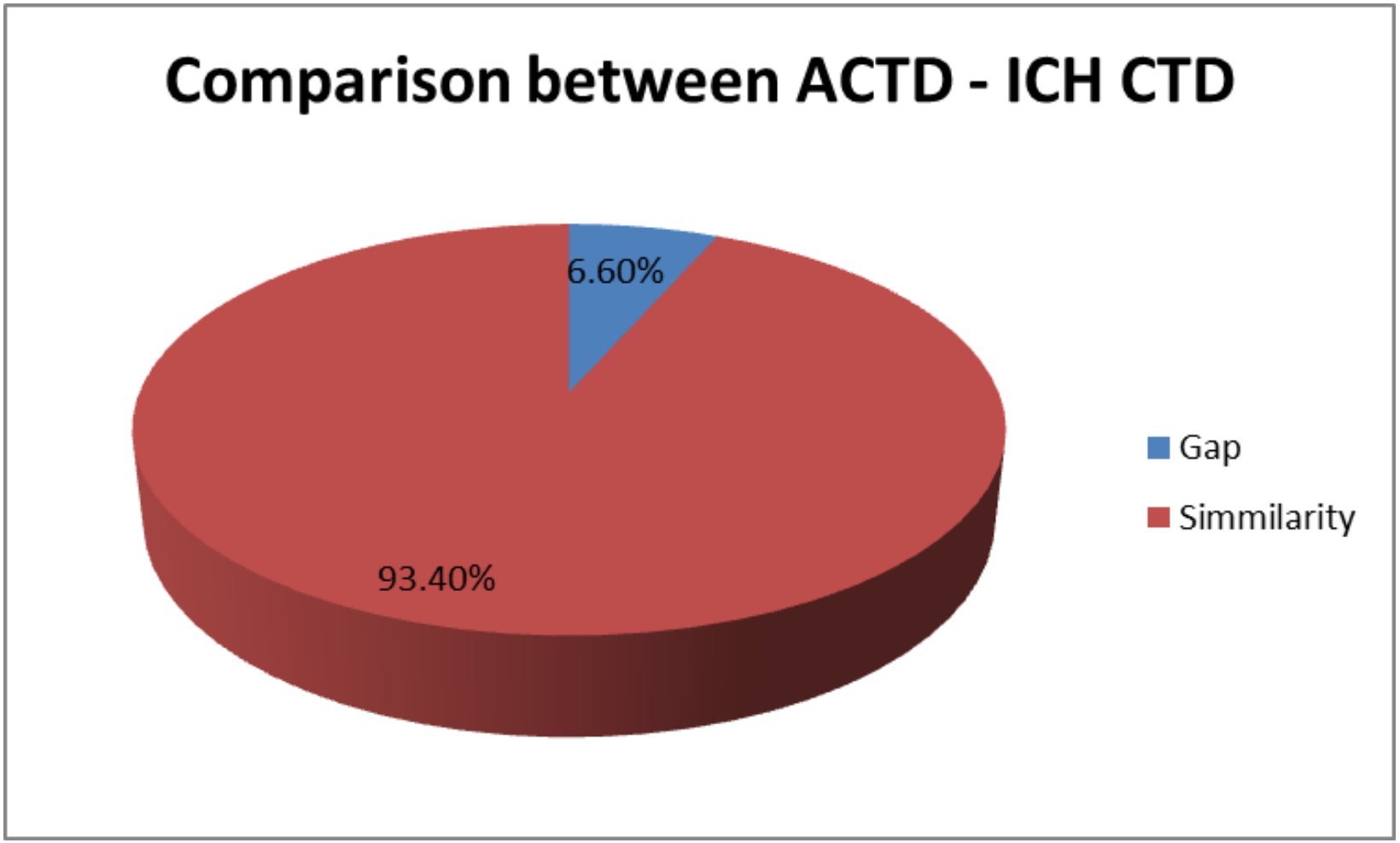
- Established in Jakarta (ASEAN Secretariat), **December 2016**
- Guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be **submitted to ASEAN regulatory authorities** for the registration of pharmaceuticals for human use.
- This guideline merely demonstrates an appropriate write-up format for acquired data. However, **applicants can modify**, if needed, to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results upon pharmaceutical registration.

ORGANIZATION Of THE DOSSIER

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

- Part I. Introduction, Table of Contents, Administrative Data and Product Information
- Part II. Quality Document
- Part III. Non-clinical Document
- Part IV. Clinical Document

COMPARISON OF ASEAN – ICH CTD



GAP

There is one point mentioned in ACTD, but not mentioned in ICH CTH

ASEAN COMMON TECHNICAL DOSSIER (ACTD)				
Part	**Name**	**Section**	**Name**	**Contents**
Part II.	Quality Document	Section C	P 9 Product Interchangeability	This requirement applies to Major Variation and Generic. 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 refer to ASEAN (proposed) Bioavailability and Bioequivalence requirement, Guideline for Bioavailability and Bioequivalence Studies or WHO Manual for Drug Regulatory Authority. (Reference: - WHO, Regulatory Support Series No 5, ”Bioequivalence Studies in Humans.”- ASEAN Guideline on Bioequivalence Study)

GAP

There are 17 points mentioned in ICH CTD, but not mentioned in ACTH

INTERNATIONAL COUNCIL FOR HARMONISATION-ICH CTD				
Module	**Title**	**Sub Module**	**Title**	**Contents**
Module 2	Common Technical Document Summaries	2.3.A	APPENDICES	
Module 2	Common Technical Document Summaries	2.3.A.1	Facilities and Equipment (name, manufacturer)	Biotech: A summary of facility information described under 3.2.A.1 should be included.
Module 2	Common Technical Document Summaries	2.3.A.2	Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)	A discussion on measures implemented to control endogenous and adventitious agents in production should be included. A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.
Module 2	Common Technical Document Summaries	2.3.A.3	Excipients	
Module 2	Common Technical Document Summaries	2.3.R	REGIONAL INFORMATION	A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.
Module 2	Common Technical Document Summaries	2.6.4.2	Methods of Analysis	This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.
Module 3	Quality	3.2.P.3.1	Manufacturer(s) (name, dosage form)	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided
Module 3	Quality	3.2.P.4.3	Validation of Analytical Procedures (name, dosage form)	Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.
Module 3	Quality	3.2.P.4.4	Justification of Specifications (name, dosage form)	Justification for the proposed excipient specifications should be provided, where appropriate.

GAP

INTERNATIONAL COUNCIL FOR HARMONISATION-ICH CTD				
Module	**Title**	**Sub Module**	**Title**	**Contents**
Module 3	Quality	3.2.A	APPENDICES	
Module 3	Quality	3.2.A.1	Facilities and Equipment (name, manufacturer)	A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product. Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included. A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate. Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.
Module 3	Quality	3.2.A.2	Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)	Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.
Module 3	Quality	3.2.A.3	Excipients	
Module 3	Quality	3.2.R	Regional Information	The section titles of Part 3.2.R (Regional Information) represent examples of typical topics of information that are not common to all ICH regions. Hence, the information to be provided in these sections should be based on the relevant regional guidelines.
Module 4	Nonclinical Study Reports	4.2.3.7.3	Mechanistic studies (if not included elsewhere)	
Module 5	Clinical Study Reports	5.3.3.3	Intrinsic Factor PK Study Reports	Reports of PK studies to assess effects of intrinsic factors, should be placed in this section
Module 5	Clinical Study Reports	5.3.3.4	Extrinsic Factor PK Study Reports	Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

Total GAP

- *There is one point mentioned in ACTD, but not mentioned in ICH CTH*
- *There are 17 points mentioned in ICH CTD, but not mentioned in ACTH*
- *Total GAP = 18 points*
- *Total points in ICH = 273 points*
- *Gap % = ((1+17)/273)*100% = 6.6%*

Implementation of ACTD vs ICH CTD in ASEAN Countries

ASEAN regulatory authorities

Indonesia

No	Product Name	Country	Certificate No.	Date of Registration	Status
1	ANTI VENIN SERUM	Indonesia	GKL8502903743A1	28/04/2015	valid
2	ANTI DIPHTHERIA SERUM 20.000 UI	Indonesia	GKL8502903443A1	08/03/2016	valid
3	ANTI TETANUS SERUM 1.500 UI	Indonesia	GKL8502903542A1	08/03/2016	valid
4	ANTI TETANUS SERUM 20.000 UI	Indonesia	GKL8502903543C1	08/03/2016	valid
5	BIOADS (ANTI DIPHTHERIA SERUM)	Indonesia	DKL1102906743A1	21/06/2016	valid
6	BIOSAT 1.5 (ANTI TETANUS SERUM)	Indonesia	DKL1102906643A1	21/06/2016	valid
7	BIOSAT 20 (ANTI TETANUS SERUM)	Indonesia	DKL1102906643B1	21/06/2016	valid
8	BIOSAVE (ANTI VENIN SERUM)	Indonesia	DKL1102906543A1	21/06/2016	valid
9	BIO-TT (TT VACCINE)	Indonesia	DKL0202905843A1	28/04/2015	valid
10	BIVALENT ORAL POLIOMYELITIS VACCINE TYPES 1 & 3	Indonesia	GKL1502907036A1	11/05/2015	valid
11		Indonesia	GKL1502907036A1	10/08/2015	valid
12	MEASLES VACCINE	Indonesia	GKL9302900544A1	28/04/2015	valid
13		Indonesia	GKL9302900544B1	28/04/2015	valid
14	DT VACCINE	Indonesia	GKL8502901643A1	21/12/2015	valid
15	DTP VACCINE	Indonesia	GKL8502901743A1	03/03/2015	valid
16	DTP-HB 5 VACCINE	Indonesia	GKL0302906043A1	04/12/2013	valid
17	DTP-HB 10 VACCINE	Indonesia	GKL0302906043B1	24/10/2016	valid
18	FLUBIO (INFLUENZA VACCINE)	Indonesia	DKL0902906343A1	22/01/2015	valid
19		Indonesia	DKL0902906343A1	22/01/2015	valid

ASEAN regulatory authorities

Indonesia

No	Product Name	Country	Certificate No.	Date of Registration	Status
20	HEPATITIS B VACCINE	Indonesia	GKL9802905543A1	18/05/2017	valid
21		Indonesia	GKL9802905543A1	28/04/2016	valid
22		Indonesia	GKL9802905543A1	28/04/2016	valid
23		Indonesia	DKL0302905943A1	10/07/2017	valid
24	MONOVALENT ORAL POLIOMYELITIS VACCINE TYPE 1	Indonesia	GKL0502906136A1	20/11/2015	valid
25	POLIOMYELITIS ORAL VACCINE	Indonesia	GKL9402905436A1	04/08/2015	valid
26		Indonesia	GKL9402905436A1	18/09/2015	valid
27		Indonesia	GKL9402905436A1	18/09/2015	valid
28	ADSORBED Td Vaccine	Indonesia	GKL0802901643B1	14/11/2013	valid
29		Indonesia	GKL0802901643B1	01/04/2014	valid
30		Indonesia	GKL0802901643B2	25/11/2014	valid
31	TT VACCINE	Indonesia	GKL8502901443A1	31/05/2013	valid
32	BIO Td	Indonesia	DKL1302906843A1	04/01/2018	valid
33	BCG VACCINE (FREEZED DRIED)	Indonesia	GKL85029000444A1	05/12/2013	valid
34		Indonesia	GKL85029000444A1	05/12/2013	valid
35	Pentabio (DTP-HB-HIB)	Indonesia	DKL1302906943A1	14/11/2013	valid
36		Indonesia	DKL1302906943A1	14/06/2013	valid
37		Indonesia	DKL1302906943A1	21/12/2015	valid
38	DTP-HB-Hib	Indonesia	GKL1502907143A1	04/01/2016	valid

ASEAN regulatory authorities

Indonesia

- Registration Process in Indonesia based on Indonesian NRA regulation No. 24, 2017, on the subject of drug registration procedure
  (Peraturan Kepala Badan Pengawas Obat dan Makanan RI No. 24 Tahun 2017 Tentang Kriteria dan Tata Laksana Registrasi Obat)
- **ASEAN CTD** and **ICH CTD** format are accepted

ASEAN regulatory authorities

Thailand

No	Product name	Countries	Date of registration (initial)	Certificate No	Status*)
1	Bio TT Vaccine	Thailand	11-Jun-04	1C 106/47	Valid
2	TT Vaccine 10 ds	Thailand	01-Nop-03	1C 236/46	Valid
3	Bio Td Vaccine	Thailand	24-Feb-16	2C 1/59 (B)	Valid
4	Adsorbed Td Vaccine 1 ds	Thailand	07-Jul-14	2C 4/55 (B)	Valid
5	Adsorbed Td vaccine 10 ds	Thailand	13-Des-12	2C 4/55 (B)	Valid
6	DT vaccine 10 ds	Thailand	11-Jun-04	2C 29/47	Valid
7	DTP vaccine 10 ds	Thailand	30-Sep-04	2C 63/47	Valid
8	DTP-HB vaccine 10 ds	Thailand	03-Feb-06	2C 57129/56 (NB)	Valid
9	mOPV1 vaccine 20 ds	Thailand	18-Okt-07	1C 267/50	Valid
10	bOPV types 1 dan 3 20 ds	Thailand	21-Mar-16	2C 2/59 (B)	Valid
11	Measles vaccine 10 ds	Thailand	22-Jun-06	1C 173/49	Valid
12	OPV 10 ds	Thailand	20-May-05	2C 36/48	Valid
13	OPV 20 ds	Thailand	27-Mar-06	2C 20/49	Valid
14	Pentabio 1, 5 and 10 ds	Thailand	17-Jan-2018	2C 2/61 (NBC)	Valid

*) Valid as long as import license provided

ASEAN regulatory authorities

Thailand

Name of countries				
Thailand	Adsorbed Td vaccine 10 ds	ACTD Td 10 DS/2009 I/CTD/ICH/Td/July 2013	ASEAN CTD ICH CTD	18-Mei-2009 21-Feb-2014
	bOPV types 1 dan 3 20 ds	CTD bOPV (I-CTD-ICH/bOPV/November 2013)	ICH CTD	24-Des-2013
	Pentabio 1, 5 and 10 ds	I/CTD-ICH/PENTABIO/APRIL 2014)	ICH CTD	24-Apr-2014

Note:
ASEAN CTD was accepted. However, Thai FDA tend to request ICH CTD in the recent years.

ASEAN regulatory authorities

Malaysia

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	TT Vaccine 10 ds	Malaysia	05-Agust-04	MAL20041042A	Valid
2	DT vaccine 10 ds	Malaysia	05-Agust-04	MAL20041069A	Valid
3	DTP vaccine 10 ds	Malaysia	5-Agust-04	MAL20041068A	Valid
4	Measles vaccine 10 ds	Malaysia	27-Mei-04	MAL20040877A	Valid
5	OPV 10 ds	Malaysia	09-Sep-04	MAL20041126A	Valid
6	OPV 20 ds	Malaysia	09-Sep-04	MAL20041126A	Valid
7	Bio TT Vaccine	Malaysia	28-Jan-16	-	In process registration
8	Pentabio Vaccine 1, 5, 10 ds	Malaysia	31-Des-15	-	In process registration
9	bOPV types 1 and 3 20 ds	Malaysia	15-Des-15	-	In process registration
10	bOPV types 1 and 3 10 ds	Malaysia	15-Des-15	-	In process registration
11	Adsorbed Td vaccine 10 ds	Malaysia	28-Jan-16	-	In process registration

ASEAN regulatory authorities

Malaysia

Name of countries	DOSSIER	FORMAT	Year of submission
Malaysia	I-CTD-ACTD-bOPV-OCTOBER 2015(bOPV 20 ds)	ASEAN CTD	2015
	I/CTD-ICH/PENTABIO/APRIL 2014)	ICH CTD	2015
	II-CTD-ACTD-Td-NOVEMBER 2015	ASEAN CTD	2016
	I-CTD-ACTD-TT-OCTOBER 2013	ASEAN CTD	2016
	I-CTD-ACTD-bOPV 10-JANUARY 2016 (Bopv 10)	ASEAN CTD	2016

Note:
ASEAN and ICH CTD are accepted by Malaysia Authority

Việt Nam

ASEAN regulatory authorities

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	Diphtheria Bulk (DAM)	Vietnam	29-Des-09	QLVX-0284-09	Renewal
2	Tetanus Bulk (TAM)	Vietnam	24-Nop-08	QLVX-0146-08	Renewal
3	Pertussis Bulk (PFB)	Vietnam	29-Des-09	QLVX-0285-09	Renewal
4	Bio TT Vaccine	Vietnam	24-Nop-08	QLVX-0145-08	Renewal

Viêt Nam

ASEAN regulatory authorities

Name of countries	DOSSIER	FORMAT	Year of submission
Vietnam	PSF Bulk DTP/May 2006	PSF	≤ 2008
	ACTD BIO TT/2010	ASEAN CTD	2008

Note:
ASEAN CTD and any other format are accepted

ASEAN regulatory authorities

Philippines

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	Bio TT Vaccine	Philippines	25-Nop-08	BR-663	Valid
2	DTP-HB vaccine 10 ds	Philippines	25-Nop-08	BR-662	Renewal
3	OPV 10 ds	Philippines	20-Feb-12	BR-847	Expired
4	-	Philippines	23-Mei-17	CDRR-NCR-DI/W-1872	GMP certification-Valid
5	Adsorbed Td vaccine 10 ds	Philippines	04-Des-13	-	In process registration

ASEAN regulatory authorities

Philippines

Name of countries	DOSSIER	FORMAT	Year of submission
Philippine	ACTD Measles 10 DS/2009	ASEAN CTD	2009
	ACTD OPV/2009	ASEAN CTD	2009
	I/CTD-ACTD/Td/November 2013	ASEAN CTD	2013

Note:
Philippines accepts ASEAN CTD.
Although Bio Farma is having no experience using ICH CTD in registration process to Philippines, it is most likely that ICH CTD might also be accepted

ASEAN regulatory authorities

Myanmar

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	Bio TT Vaccine	Myanmar	28-Agust-06	1108 A 8909	Renewal
2	Adsorbed Td Vaccine 1 ds	Myanmar	16-Jun-16	2106AA9638	Valid
3	Tetanus Toxoid bulk (PTT)	Myanmar	22-Des-17	-	In process registration
4	bOPV types 1 and 3 10 ds	Myanmar	30-Jun-16	-	In process registration
5	Adsorbed Td vaccine 10 ds	Myanmar	29-Mei-15	-	In process registration

ASEAN regulatory authorities

Myanmar

Name of countries	DOSSIER	FORMAT	Year of submission
Myanmar	I/CTD-ACTD/Td/November 2013	ASEAN CTD	2013
	I-CTD-ACTD-bOPV 10-JANUARY 2016 (Bopv 10)	ASEAN CTD	2016
	I/CTD-ICH/PTT/DECEMBER 2017	ICH CTD	2017

Note:
Myanmar accepts ASEAN and ICH CTD

Laos

ASEAN regulatory authorities

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	Bio TT Vaccine	Laos	27-Jun-07	06 I 2932/07	Renewal
2	Adsorbed Td vaccine 1 ds	Laos	04-Des-13	-	In process registration
3	bOPV types 1 and 3 20 ds	Laos	24-Mar-17	-	In process registration
4	bOPV types 1 and 3 10 ds	Laos	24-Mar-17	-	In process registration
5	Adsorbed Td vaccine 10 ds	Laos	04-Des-13	-	In process registration

Laos

ASEAN regulatory authorities

Name of countries	DOSSIER	FORMAT	Year of submission
Laos	I/CTD-ACTD/Td/November 2013	ASEAN CTD	2013

Note:
Laos accepts ASEAN CTD.
Although Bio Farma is having no experience using ICH CTD in registration process to Laos, it is most likely that ICH CTD might also be accepted

ASEAN regulatory authorities

Cambodia

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	Bio TT Vaccine	Cambodia	15-Jan-07	039/07	Valid

ASEAN regulatory authorities

Cambodia

Name of countries	DOSSIER	FORMAT	Year of submission
Cambodia	ACTD BIO TT/2010	ASEAN CTD	2012

Note:
Cambodia accepts ASEAN CTD.
Although Bio Farma is having no experience using ICH CTD in registration process to Cambodia, it is most likely that ICH CTD might also be accepted

ASEAN regulatory authorities

Singapore

No	Product name	Countries	Date of registration (initial)	Certificate No	Status
1	TT Vaccine 10 ds	Singapore	8-Jul-2015	x	Process was terminated

ASEAN regulatory authorities

Singapore

Name of countries	DOSSIER	FORMAT	Year of submission
Singapore	I-CTD-ACTD-TT-OCTOBER 2013	ASEAN CTD	2015

Note:
Format was not an issue. Insufficient clinical studies was highlighted.

We, Novem Healthcare Pte Ltd, having principal place of business at Solstice Business Center, 23 New Industrial Road #03-08 Singapore 536209, hereby state that TT (TT 10ds vaccine from PT. Bio Farma (Persero), at Jalan Pasteur No. 28 Bandung 40161-Indonesia) registration in Singapore is no longer continued. Based on the reasons found during pre-registration consultation process with the Health Sciences Authority, Therapeutic Products Branch, Singapore, the available clinical studies are insufficient to support vaccines registration and hence the dossier could not be accepted for registration in Singapore.

Brunei

ASEAN regulatory authorities

- Bio Farma is currently not having registered product in Brunei.

ASEAN CTD for Non ASEAN Countries

- ASEAN CTD also accepted in Non ASEAN countries.
- Bio Farma registered bOPV 10 doses and 20 doses to **Ghana** and approved on 2 October 2017 using ASEAN CTD
- Bio Farma registered bOPV 20 doses, mOPV 1 20 doses, OPV 10 and 20 doses to **Nigeria**, approved on 7 August 2012 (bOPV and OPV) and 31 May 2007 (mOPV 1) using ASEAN CTD

ASEAN CTD for Non ASEAN Countries

- Bio Farma registered DTP-HB 10 and TT vaccine in **Egypt**, approved on 24 June 2015 and 17 June 2015 respectively, using ASEAN CTD

Conclusion

- **Format** is not always be an issue in submitting registration.
- The most challenging part in registration is having **different references** in particular subject. For example: for stability study, NRA might refer to general pharmaceutical product which consider humidity as environmental factor, in addition to temperature; whereas in vaccine, temperature should be the only environment factor considered.

WHO TRS 962 Annex 3 Guidelines for stability evaluation of vaccines, page 179, it is mentioned that "*Among the environmental factors considered to influence pharmaceuticals, the only one that affects characteristics of all vaccines over time is temperature. The impact of humidity is not relevant for the vast majority of vaccines due to their liquid formulation, and the protective nature of the packaging, providing that the closure system of the vial or ampoule is appropriate*".

Conclusion

- Other issue might also arise during registration is the **incomplete data for old product.** Example: Having no data in pre-clinical and limited data in clinical study. Bio Farma had experience with Singapore authority in TT Vaccine registration and the process was terminated due to insufficient clinical studies.

We, Novem Healthcare Pte Ltd, having principal place of business at Solstice Business Center, 23 New Industrial Road #03-08 Singapore 536209, hereby state that TT (TT 10ds vaccine from PT. Bio Farma (Persero), at Jalan Pasteur No. 28 Bandung 40161-Indonesia) registration in Singapore is no longer continued. Based on the reasons found during pre-registration consultation process with the Health Sciences Authority, Therapeutic Products Branch, Singapore, the available clinical studies are insufficient to support vaccines registration and hence the dossier could not be accepted for registration in Singapore.

wonderful
indonesia