The ASEAN Common Technical Requirement on Nonclinical Data (Safety) for Pharmaceutical Registration

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS									
			NCE	BIOLOGICS	RT	S/P	IND	VACCINE				
								NV	NC	CV/ EV	IND	S/P
M3	1. Pharmacology	- Studies designed to examine effects other than the primary therapeutic effect of a drug substance.										
	1.1. Primary Pharmacodynamics / Immunogenicity study	- Studies are done to identify the mode of action and/or effects of a substance in relation to its desired therapeutic target.	✓	✓	-	-	-	✓	✓	-	❖	-
	1.2. Secondary Pharmacodynamics	- Studies are done to identify the mode of action and/or effects of a substance not related to its therapeutic target.	✓	✓	-	-	-	-	-	-	-	-
S7A S6	1.3. Safety Pharmacology	- Studies focus on identifying adverse drug reactions on physiological functions. - Core battery includes the assessment of effects on the vital functions, such as cardiovascular, central nervous and respiratory systems, and these should be evaluated prior to human exposure. - These evaluations may be conducted as addition to toxicity studies or as separate studies.	✓	✓	-	-	-	❖	-	-	-	-
	1.4. Pharmacodynamic Drug Interactions	- If they have been performed, pharmacodynamic drug interaction studies should be briefly summarized in this section.	✓	✓	-	-	-	❖	❖	-	-	-
S3B S3A	2. Pharmacokinetics	- PK data form the basis for prediction of therapeutic doses and suitable dosage regimen.										
	2.1. Absorption	- Extent and rate of absorption, in-vivo and in situ studies - Kinetic parameters, bioequivalence and or bioavailability (serum/ plasma/ blood PK studies)	✓	❖	❖	❖	-	-	-	-	-	-
	2.2. Distribution	- Tissue distribution studies - Protein binding and distribution in blood cells - Placental transfer studies	✓	❖	❖	❖	-	❖	❖	❖	-	❖
	2.3. Metabolism (inter-species comparison)	- Chemical structure and quantities of metabolites in biological samples - Possible metabolic pathways - Pre- systemic metabolism (GI/ Hepatic First-Pass Effects)	✓	❖	❖	❖	-	-	-	-	-	-

		- In vitro metabolism including P450 studies - Enzyme induction and inhibition										
	2.4. Excretion	- Route and extent of excretion - Excretion in milk	✓	❖	❖	❖	-	-	-	-	-	-
	2.5. Pharmacokinetic Drug Interaction (Nonclinical)	- If they have been performed, nonclinical pharmacokinetic drug interaction studies (in-vitro and/ or in-vivo) should be briefly summarized in this section.	✓	-	-	-	-	-	-	-	-	-
	2.6. Other Pharmacokinetic Studies	- If studies have been performed in nonclinical models of disease (eg. Renally impaired animals), should be summarized in this section.	✓	-	❖	-	-	-	-	-	-	-
S4	3. Toxicology	- The scope of the toxicologic evaluation should be described in relation to the proposesd clinical use.										
	3.1. Single Dose Toxicity	- The single dose data should be briefly summarized, in order by species, by route. - It should be evaluated in two mammalian species prior to the first human exposure. - A dose escalation study is considered an acceptable alternative to the single dose design.	✓	✓	-	-	-	❖	❖	❖	-	-
S4A	3.2. Repeat Dose Toxicity	- Studies should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g. nature and severity of target organ toxicity, dose (exposure)/ respon relationships, no observe adverse effect levels (NOEL)) - It is performed on rodents and non-rodents with a study duration of 6 months and 9 months respectively. Particular for vaccine at least one animal species with at least one additional vaccination (n+1) relative to the clinical trial. - Studies are related to the duration, therapeutic indication and scale of the proposed clinical trial of the pharmaceutical.	✓	✓	-	-	-	✓	❖	❖ *)	-	-
S2A S2B	3.3. Genotoxicity	- Brief summaries of in vitro and in vivo tests designed to detect compounds which induce genetic damage directly or indirectly by various mechanisms: ▪ In vitro tests include tests for the detection of bacterial mutagens ▪ In vivo tests include tests for the detection of clastogens (either by chromosomal aberrations or micronuclei polychromatic erythrocytes)	✓	-	-	-	-	❖	❖	❖	-	-

S1A S1B S1C S1C (R)	3.4. Carcinogenicity	- Studies are conducted to identify a tumorigenic potential in animals and to assess the relevant risk in humans. - The strategy for testing the carcinogenic potential of a pharmaceutical is developed only after acquisition of information: results of genetic toxicology, intended patient population, clinical dosage regimen, pharmacodynamics in animals and in humans, repeated-dose toxicology studies. No single approach can be expected to predict the carcinogenic potential. - Other factors may also be considered: such as the intended patient population, prior assessment of carcinogenic potential, extent of systemic exposure etc. - A brief rationale should explain why the studies were chosen and the basis for high dose selection. - Individual studies should be summarized and comprises: • one long-term rodent studies, • and either, short / medium term studies (in-vivo rodent test systems) or a long term studies in a second rodent species • Other studies	✓	♦	-	-	-	❖	❖	❖	-	-
S5A S5B (M)	3.5. Reproductive and Develop-mental Toxicity	- Studies are designed to evaluate the effect of the drug on the general reproductive performance of animals starting at implantation and continuing through the weaning period in doses significantly greater than those intended for man or in doses that give greater significantly higher blood and / or other tissue concentration than those achieved in man. - Studies should be conducted in mammalian species, same species and strain as in other toxicological studies, i.e. rats. For embryotoxicity studies, a second mammalian species is required, rabbit being the preferred choice as a non-rodent. - Dosages: choice of high dose should be based on data from all available studies - Route and frequency of administration: similar to the intended route for human usage and usual frequency is once daily or more or less frequent depending on the kinetic profile - Control group: use of vehicle as control group vs test group	✓	✓	-	-	-	❖	❖	❖	-	-
S5A S5B (M)	3.5.1. Fertility and Early Embryonic Development	- Studies are conducted to test for toxic effects/ disturbances resulting from treatment from before mating (males / females) through mating and implantation.	✓	✓	-	-	-	❖	❖	❖	-	-

		- Effects of a potentially toxic substance could be determined by assessment of: maturation of gametes, mating behavior, fertility, preimplantation stages of the embryo, implantation.										
S5A S5B (M)	3.5.2. Embryofetal Development	- Studies conducted to detect adverse drug reactions on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate. - The potential adverse drug reactions to be assessed include: enhanced toxicity relative to that in non-pregnant females, embrypfetal death, altered growth and structural changes - Studies should include: • characterization of the type and incidence of malformations in comparison with the negative and positive controls through detailed skeletal and visceral organ examination • calculation of pregnancy rate, implantation efficiency and fetal viability • evaluation of the effect of treatment or chemical on maternal weight, mortality, behavior, and fetal weight including male/ female ratio	✓	✓	-	-	-	❖	❖	❖	-	-
5SA	3.5.3. Pre-Natal and Post Natal Development including Maternal Function	- The study determines the adverse drug reactions of drugs or chemical on the pregnant/ lactating female and on development of the conceptus and the offspring following exposure of the female from implantation through weaning. Since manifestations of effect induced during this period may be delayed , observations should be continued through sexual maturity. - The potential adverse drug reactions to be assessed shall include: enhanced toxicity relative to that in non-pregnant females, pre- and postnatal death of offspring, altered growth and development, functional deficits in offspring, including behavior, maturation (puberty) and reproduction (F1). - Studies should provide data on: a. labor - as to the presence of dystocia, duration of labor, onset of labor b. gestation - as to duration and weight gain of dams during pregnancy c. litter - as a number of pups (litter size), weight of pups, bursing behavior of pups, physiologic and anatomic	✓	✓	-	-	-	❖	❖	❖	-	-

		parameters (food and water consumption, length, etc.) and effect of cross over nursing of pups - concurrent negative control of animal must be run together with the treated groups (at least 3 dose levels)										
	4. Local Tolerance	- Studies are summarized in order by species, by route and by duration on the following: ▪ Eye irritation test ▪ Dermal toxicity testing	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
	5. Other Toxicity Studies	- Rationale for conducting the studies should be provided - Other studies may include: antigenicity, immunotoxicity, mechanistic studies, dependence, studies on metabolites, impurities and other studies	❖	❖	❖	❖	❖	❖	❖	❖	-	❖
	6. List of Key Literature Reference	List of key references must be submitted	✓	✓	❖	❖	❖	❖	❖	❖	-	❖

The ASEAN Common Technical Requirement on Clinical Data (Efficacy) for Pharmaceutical Registration

No.	PARAMETERS	COMPONENTS	REQUIREMENTS									
			NCE	BIOTECH	RT	S/P	IND	VACCINE				
								NV	NC	CV/ EV	IND	S/P
1	**Bioavalability (BA) and Bioequivalence (BE) Studies**	BA studies evaluate the rate and extent of absorption of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical or in vitro dissolution endpoints, and may be either single dose or multiple dose.										
	a) BA Studies	1) Studies comparing the rate and extent of absorption of a drug substance from a non-intravenous dosage form compared to intravenous injection (Absolute BA study) or compared to that of non-intravenous clear solution dosage form (Relative BA study).	✓	✓	✓	-	-	-	-	-	-	-
		2) Dosage proportionality studies.	✓	✓	✓	-	-	-	-	-	-	-
		3) Food-effect studies.	✓	✓	✓	-	-	-	-	-	-	-
	b) Comparative BA or BE Studies	Studies compare the rate and extent of absorption of the substance from similar drug products (e.g., tablet to tablet, tablet to capsule etc.) Comparative BA or BE studies may include comparison between:										
		1) The drug product used in clinical studies supporting the effectiveness and the to-be-marketed drug if applicable.	✓	✓	✓	✓	-	-	-	-	-	-
		2) The drug product used in clinical studies supporting effectiveness and the drug product used in stability batches if applicable.	✓	✓	✓	✓	-	-	-	-	-	-
		3) Same drug products from different manufacturers if applicable.	✓	✓	✓	✓	-	-	-	-	-	-
2	**Studies Pertinent to Pharmacokinetics Using Human Biomaterials**	To study metabolic pathways relative to drug absorption and elimination and to assess drug-drug interactions with these pathways.										
	a) Plasma Protein Binding Studies	Ex vivo protein binding study.	✓	✓	-	-	-	-	-	-	-	-

	b) Hepatic Metabolism and Drug Interaction Studies	Hepatic metabolism and metabolic drug interaction studies with hepatic tissue.	✓	✓	-	-	-	-	-	-	-	-
	c) Studies Using Other Human Biomaterials, if applicable	Studies with other biomaterials.	✓	✓	✓	-	-	-	-	-	-	-
3	**Human Pharmacokinetic (PK) Studies**											
	a) Healthy subject PK and initial tolerability studies	Studies of PK and initial tolerability in healthy subjects.	✓	✓	✓	♦	-	❖	❖	❖	-	-
	b) Patient PK and initial tolerability studies	Studies of PK and initial tolerability in patients.	✓	✓	✓	♦	-	-	-	-	-	-
	c) Intrinsic factor PK studies	PK studies to assess intrinsic factors such as age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction.	✓	✓	✓	♦	-	-	-	-	-	-
	d) Extrinsic factor PK studies	PK studies to assess extrinsic factors such as drug-drug interactions, diet, smoking, and alcohol use.	✓	✓	✓	♦	-	-	-	-	-	-
	e) Population PK studies	PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials	✓	✓	✓	♦	-	-	-	-	-	-
4	**Human Pharmacodynamic (PD) Studies**											
	a) Healthy subject PD and PK/PD studies	PD and/or PK/PD studies	✓	✓	✓	♦	-	-	-	-	-	-
	b) Patient PD and PK/PD studies	PD and/or PK/PD studies in patients	✓	✓	✓	♦	-	-	-	-	-	-
5	**Efficacy and Safety**											
	a) Controlled clinical studies pertinent to the claimed indication	The controlled clincal studies should be sequenced by type of control: - Placebo control (could include other control group groups, such as an active comparator or other doses) - No-treatment control - Dose-response (without placebo) - Active control (without placebo) - External (historical control, regardless of the control treatment)	✓	✓	✓	✓	✓	-	-	-	-	-
		- To demonstrate the immunogenicity of the relevant active	-	-	-	-	-	✓	✓	✓	✓	✓

		component(s) and the safety profile of a candidate vaccine in the target population. - To define the optimal dose, initial schedule and safety profile of a candidate vaccine before the phase III trials can begin										
	b) Comparative phase III studies (for Vaccine)											
		- Efficacy parameter	-	-	-	-	-	❖#	❖	❖	❖	❖
		- Immunogenicity parameter	-	-	-	-	-	✓	✓	✓	✓	✓
		- Safety parameter	-	-	-	-	-	✓	✓	✓	❖	❖
		- Lot to lot consistency	-	-	-	-	-	❖	❖	❖	-	-
	c) Uncontrolled data	Uncontrolled clinical studies (e.g., open label safety studies or phase 1 study)	✓	✓	✓	✓	✓	❖	❖	❖	❖	❖
	d) Bridging clinical studies (for Vaccine)		-	-	-	-	-	❖	❖	❖	❖	❖
6	**Post Marketing Data (if applicable)**		✓	✓	✓	✓	✓	✓	✓	✓	❖	❖
7	**References**		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

NCE - New chemical entity
Biotech - Biological products
RT - New Route of Administration
S/P - New Strength and Posology
IND - New Indication
NC - New Combination
NV - New/Novel Vaccine, including new adjuvanted vaccine
CV/EV - Conventional Vaccine / Established Vaccine
✓ - Required
- - Not Required
❖ - Where applicable, i.e. change of route of administration due to change in formulation, change of formulation and posology such as immediate release to sustained released) and/or for product with narrow margin of safety or variable kinetics
♦ − Generally inappropriate for Biological products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (eg. Growth factors, immunosuppresive agents, etc.)
*) - Repeated toxicity study may not be needed if no difference in formulation compared to the approved vaccine. Different manufacturer may have different formulation, process and/or composition although the antigen have been established. Hence, the toxicity profile and tolerance may differ with the approved vaccine
- Where Applicable (Note: Vaccine efficacy data is generally required, unless otherwise scientifically justified.)

Notes:

1. As references for requirement, the following WHO Guidelines or their relevant updates are used:
   a. Guidelines on procedures and data requirements for changes to approved vaccines (WHO TRS 993, Annex 4)
   b. Guidelines on procedures and data requirements for changes to approved biotherapeutic products (2017)
   c. WHO Guidelines on nonclinical evaluation of vaccines (WHO TRS 927, annex 1)
   d. Guidelines on clinical evaluation of vaccines: regulatory expections (WHO TRS 1004, Annex 9)
   e. Guidelines on the nonclinical evalution of vaccine adjuvants and adjuvanted vaccines (WHO TRS 987, Annex 2)
2. The term ‘Biologics’ used in this document does not include vaccines with the rationale that vaccines has different characteristics compared with other biological products so that in many cases the requirements are different.