#2_S6

Title	**Considerations for Nonclinical Studies of Biopharmaceuticals (in terms of assessment for Coronavirus Vaccines Nonclinical studies)** **생물의약품 비임상시험 시 고려사항(코로나19 백신 비임상 자료 심사 관련)**
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Summary	General contents of ICH guideline S6(R1) will be explained, and the assessment of nonclinical studies for Coronavirus vaccines will be explained. ICH S6(R1)에 대한 전반적인 내용에 대한 교육을 진행하고, 코로나19 백신 비임상 자료 평가에 대해서 설명한다.

Consideration for Nonclinical Studies of Biopharmaceuticals

(ICH guideline S5(R1)

5th Nov 2020

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National Institute of Food and Drug Safety Evaluation

Outline

Biopharmaceuticals

Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals S6(R1) (ICH guideline)

Coronavirus vaccine

Assessment for Coronavirus Vaccine nonclinical study

Biopharmaceuticals

Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals S6(R1) (ICH guideline)

Contents

ICH S6(R1)

ICH S6(R1)

1. Introduction

▶ Objectives

The primary goals of preclinical safety evaluation are to identify

(1) initial safe dose & subsequent dose escalation schemes in human

(2) potential target organs

(3) safety parameters for clinical monitoring

▶ Scope

biotechnology-derived pharmaceuticals

(exception) antibiotics, allergenic extracts, heparin, vitamins, DNA vaccines, cellular & gene therapies ...

ICH S6(R1)

2. Specification of the Test Material

▶ Safety concern may arise from

- impurities : purification process
- contaminants : host cell contaminants (bacteria, yeast, virus etc))

→ allergic reactions & other immunopathological effects

▶ Comparability : change manufacturing process, formulation

- based on biochemical & biological characterization, nonclinical & clinical

ICH S6(R1)

3. Preclinical Safety Testing

- Major considerations
  - animal species, age, physiological state
  - dose, administration route, regimen
  - stability
  - GLP compliance (toxicity? pharmacology?)

ICH S6(R1)

3. Preclinical Safety Testing

▶ Biological Activity/Pharmacodynamics

- Biological activity may be evaluated using *in vitro* assays
- *In vitro* cell lines(mammalian cells) can be used to
  · predict *in vivo* activity
  · assess relative sensitivity of various species (including human)
-(monoclonal Ab) antigenic specificity, complement binding, and any unintentional reactivity and/or cytotoxicity towards human tissues

ICH S6(R1)

3. Preclinical Safety Testing

▶ Animal Species/Model Selection

- Relevant animal species

(e.g., mAb) express the desired epitope &
demonstrate a similar tissue cross-reactivity profile
→ evaluate toxicity arising from the binding to the epitope &
any unintentional tissue cross-reactivity

- two relevant species (normally)

But, in certain justified cases one relevant species may suffice
(e.g.) only one relevant species, well known biological activity

- No relevant species exists

→ transgenic animals expressing the human receptor or
homologous proteins should be considered

- Animal models (similar to human disease)

ICH S6(R1)

3. Preclinical Safety Testing

▶ Number/Gender of Animals

- Small sample size

→ failure to observe toxic events due to observed frequency alone

- Limitation of sample size (in case of NHP*)

→ compensated by increasing the frequency and duration

- Both genders should generally be used or justification given for specific omissions

*NHP: Non-human primates

ICH S6(R1)

3. Preclinical Safety Testing

▶ Administration/Dose Selection

- Route and frequency of administration

→ based on proposed clinical use (as close as possible)

- Consideration to

· pharmacokinetics and bioavailability of the product

· volume which can be safely and humanely administered

· effects of volume, concentration, formulation, and site of administration

ICH S6(R1)

3. Preclinical Safety Testing

▶ Administration/Dose Selection

- Dose level

→ selected to provide information on a dose-response relationship (including a toxic dose and a NOAEL*)

- In case of little to no toxicity product

→ a scientific justification of the rationale for the dose selection & projected multiples of human exposure should be provided

- Justification of high dose selection

→ expected pharmacological/physiological effects, availability of suitable test material, and the intended clinical use.

*NOAEL: no observed adverse effect level

ICH S6(R1)

3. Preclinical Safety Testing

▶ Immunogenicity

- Measurement of Abs

→ repeated dose toxicity studies in order to aid in the interpretation of these studies

- Characterization of Ab response

(e.g., titer, number of responding animals, neutralising or non-neutralising)

- Correlation between appearance & pharmacological and/or toxicological changes

ICH S6(R1)

4. Specific Considerations

- Safety Pharmacology
  - Find out functional effects on the major physiological systems (cardiovascular, respiratory, central nervous systems)
  - Investigate the potential for undesirable pharmacological activity in appropriate animal models
  - Separate studies or Incorporated in the design of toxicity studies

ICH S6(R1)

4. Specific Considerations

▶ Exposure Assessment

⊙ Pharmacokinetics and Toxicokinetics

- Single/multiple dose PK, toxicokinetics, tissue distribution studies
- Differences in PK among animal species

→ Impact on the predictiveness, assessment of dose response relationships

- Utilise preparations : intended for toxicity testing and clinical use,
- Administration route : relevant to the anticipated clinical studies
- Systemic exposure monitoring (during the toxicity studies)
- Radiolabeled proteins : Activity, biological properties equivalent between radiolabeled and unlabeled

ICH S6(R1)

4. Specific Considerations

▶ Exposure Assessment

⊙ Assays

- One validated method, generally
- Same for animals and humans. ideally

⊙ Metabolism

- Classical biotransformation studies(like drugs) are not needed

  * metabolic pathways are generally understood

ICH S6(R1)

4. Specific Considerations

- Single Dose Toxicity Studies
  - Relationship of dose to systemic and/or local toxicity
  - Information on dose- response relationships
  - Safety pharmacology parameters should be considered

ICH S6(R1)

4. Specific Considerations

▶ Repeated Dose Toxicity Studies

- Route, dosing regimen should reflect clinical use(or exposure)
- Set recovery period, group

→ monitored until reversibility is demonstrated

ICH S6(R1)

4. Specific Considerations

- Immunotoxicity Studies
  - Assessment of potential immunogenicity
  - Evaluated humoral & cell-mediated immunity
  - simple injection trauma and/or specific toxic effects caused by the vehicle may also result in toxic changes at the injection site
  - Screening, mechanistic studies may require
  - Routine or standard testing batteries not recommended

ICH S6(R1)

4. Specific Considerations

▶ Reproductive Performance and Developmental Toxicity Studies

- Dependent on product, clinical indication, intended patient population
- Specific design based on

→ species specificity, immunogenicity, biological activity and/or a long elimination half-life

▶ Genotoxicity Studies

- Generally not needed

→ not expected interact directly with DNA or other chromosomal material

- cause for concern about the product should be performed

(e.g., organic linker molecule in a conjugated protein product)

ICH S6(R1)

4. Specific Considerations

▶ Carcinogenicity Studies

- Generally not needed
- Product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (growth factors, immunosuppressive agents…)
- Studies are needed

→ Potential proliferation of transformed cells and clonal expansion (receptor expression in various malignant and normal human cells)

ICH S6(R1)

4. Specific Considerations

- Local Tolerance Studies
  - Should be evaluated
  - In certain justified cases,
    the testing of representative formulations may be acceptable
  - Can be evaluated in single or repeated dose toxicity studies

Coronavirus Vaccine

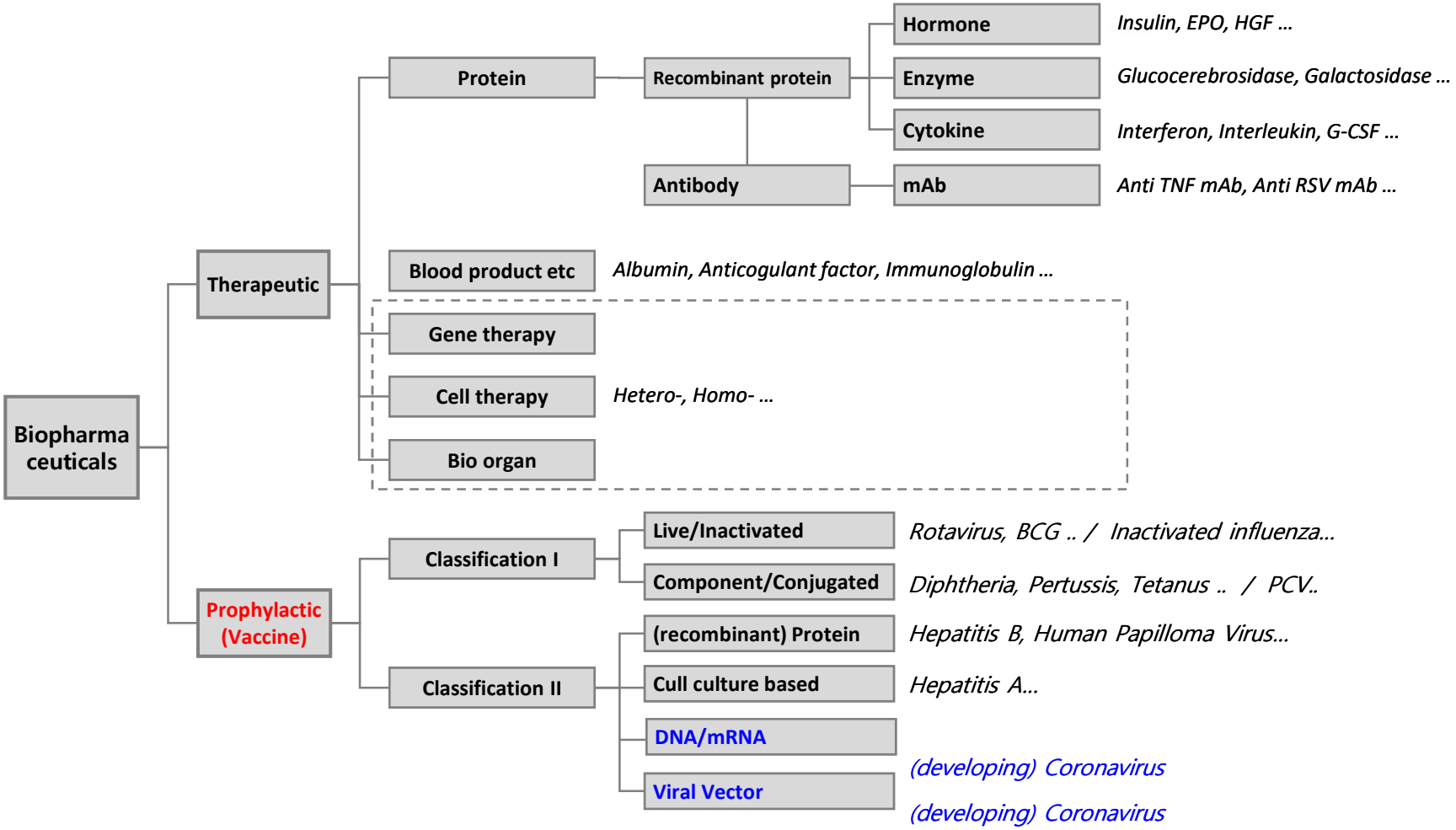
Assessment for Coronavirus Vaccine nonclinical study

Contents

Coronavirus Vaccine

Assessment for Coronavirus Vaccine nonclinical study

Biopharmaceuticals & Vaccines



Assessment for Coronavirus Vaccine nonclinical study

Definition of Vaccine

▶ Definition of Vaccine

- A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.

*source: CDC homepage

Assessment for Coronavirus Vaccine nonclinical study

General Characteristic of Vaccine

▶ General Characteristic of Vaccine

- Complexity of Manufacturing process

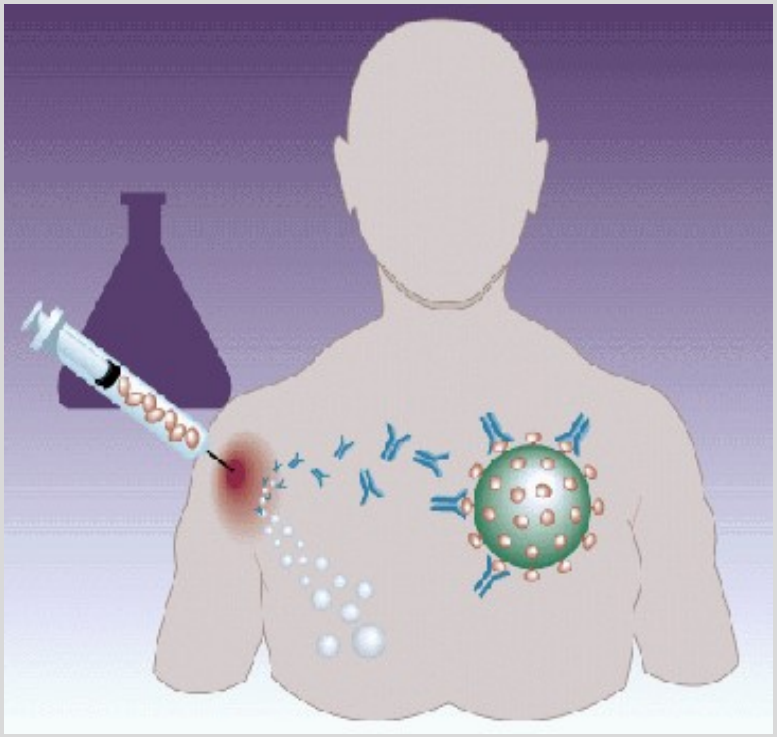
→ Important to manage contaminants, impurities

- Sensitivity to surrounding conditions(temp', light, humidity…)
- (usually) targeted Healthy person, Prophylactic purpose
- Not administered IntraVenously (IM, SC, ID)(not systemic but local)
- Mass vaccination in a short period

Assessment for Coronavirus Vaccine nonclinical study

Understanding of Vaccine

How Vaccine Works



Component of Vaccine

Antigen + **Formulation & Delivery**

Virus/
Protein /
Plasmid DNA

Vaccine vehicle
Adjuvant/conjugate

Recruit immune cell
Electroporation

Specificity

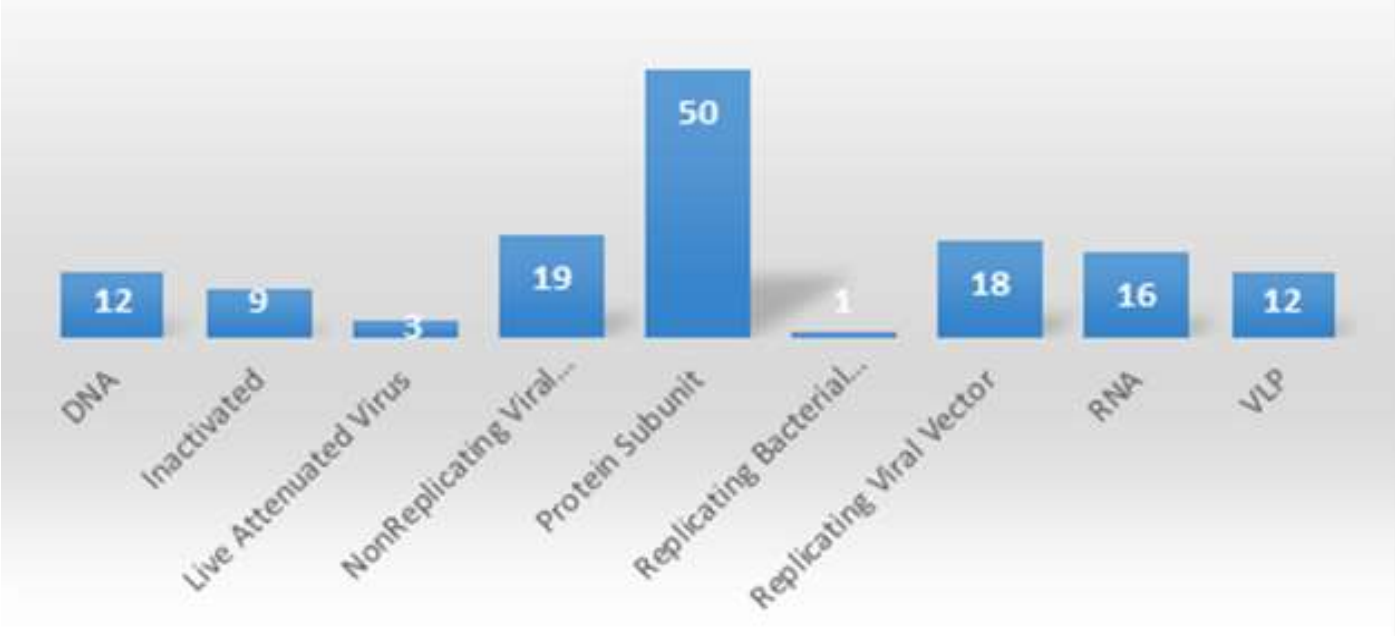
Composition
Duration

EFFICACY & SAFETY

Assessment for Coronavirus Vaccine nonclinical study

COVID19 Vaccines

▶ Candidate vaccines

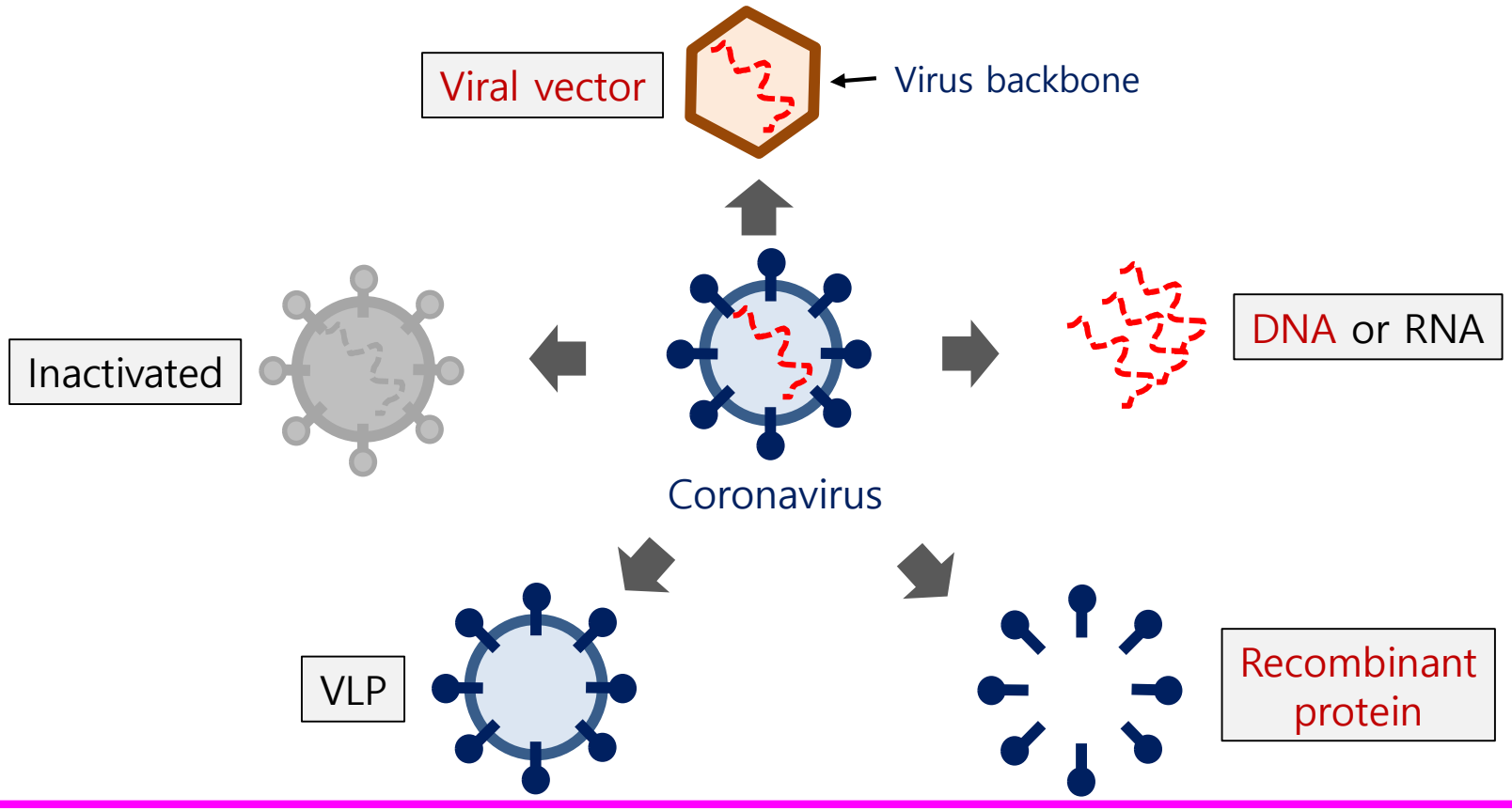


*source: WHO COVID 19 Landscape(25th Aug)

Assessment for Coronavirus Vaccine nonclinical study

COVID19 Vaccines

▶ Development status in Korea



Assessment for Coronavirus Vaccine nonclinical study

1. General Consideration

⊙ For accelerate progress,

- nonclinical evaluation based on overall benefit/risk assessment

⊙ Adequate information to characterize product safety

→ may not be necessary to perform nonclinical safety studies prior to FIH clinical trials (parallel progress clinical & nonclinical)

⊙ Route(IM, SC, ID etc), delivery system(EP(DNA vaccine) etc) : based on proposed clinical use

⊙ New adjuvants, ingredients

→ specific nonclinical studies should be considered

Assessment for Coronavirus Vaccine nonclinical study

2. Challenge Test

⊙ Ideally, challenge test perform with several animal species

* Immunologic response can be different depend on animal species

⊙ General Principle

- Relevant animal model (viral infection, clinical symptom onset)
- (nonclinical) Protection be evaluated

wild type coronavirus challenge after immunization

⊙ Recommend ICP assessment

*ICP: immunological correlate of protection

⊙ Animal model for challenge

(e.g.,) hACE-2 transgenic mice, hamster, ferret, NHP etc

Assessment for Coronavirus Vaccine nonclinical study

2. Challenge Test

⊙ Immunogenicity

- total antibody response & functional immunoreaction
  (can be predictable protection, neutralizing Ab etc)
- humoral & cellular immune response

<Test items & Methods>(example)

Test items			Test methods(example)
Immunogenicity test	Humoral	Total Ab	ELISA
		Neutralizing Ab	PRNT
	Cellular	-	
Challenge test after immunization	-	-	Protective effect assessment virus challenge after immunization (comparison viral load & clinical symptom etc)

Assessment for Coronavirus Vaccine nonclinical study

2. Challenge Test

⊙ The most important potential risk of COVID19 vaccine is 'Enhanced disease'

⊙ Even though limitation of nonclinical test, nonclinical studies significant role in prediction of Enhanced disease

Enhanced disease evidences	Test methods(example)
High level of total Ab/neutralizing Ab	ELISA, PRNT
Prominent Th2 cell response (IL-4, IL-5, IL-13, IgG1) / Th1 cell response(IL-12, IFN r, IgG2a)	Cytokine ELISpot, ELISA(IgG1/IgG2a) Intracellular cytokine staining
Increase immune response(post challenge) Test group/placebo group	Hematology (relate to inflammation)
non-expected lung lesions (Test group)	Lung pathology, CT scan

Assessment for Coronavirus Vaccine nonclinical study

3. Safety Pharmacology

See slide #14 (Specific considerations > safety pharmacology)

4. ADME

⊙ Generally not needed

⊙ Product-specific assessment may be needed

- new injection route, adjuvant etc

* ADME: Adsorption Distribution Metabolism Excretion

Assessment for Coronavirus Vaccine nonclinical study

5. Toxicology

⊙ For accelerate progress,

- can be submit unaudited Tox' study report

* include pathology result(recovery), final report submit till next phase CT

⊙ Relevant animal model (viral infection, clinical symptom onset, immune response to candidate vaccine Ag)

* set Enhanced disease parameter

⊙ Administration

- according to animal species & injection site, possible to split injection

⊙ Frequency

-(highly recommended) more than 1 times proposed clinical use

Assessment for Coronavirus Vaccine nonclinical study

5. Toxicology

⊙ Reproductive Performance and Developmental Toxicity Studies

- need to perform before beginning of phase 3 CT

⊙ Genotoxicity / Carcinogenicity Studies

- Generally not needed
- In case of new adjuvant, ingredient etc, may be needed

⊙ Local Tolerance Studies

- Can be evaluated in single or repeated dose toxicity studies

Q & A

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THANK YOU!