attachment1

Guiding Principles for Adverse Event Grading Standards in Clinical Trials of Prophylactic Vaccines

1. Introduction

Preventive vaccines (hereinafter referred to as vaccines) refer to preventive biological products used for human immunization to prevent and control the occurrence and spread of diseases, including immunization program vaccines and non-immunization program vaccines. Vaccine clinical trials

should strictly abide by the "Drug Administration Law of the People's Republic of China" and "Vaccine Administration Law of the People's Republic of China", implement the relevant provisions of the "Drug Registration Management Measures", and comply with the "Good Clinical Practice for Drugs" (GCP), "Vaccine Clinical Trials" "Testing Technology Guiding Principles" and "Vaccine Clinical Trial Quality Management Guiding Principles (Trial)" and other relevant requirements. Since vaccines are usually used on healthy people, mostly healthy children or infants, healthy subjects are generally selected for each stage of clinical trials. Therefore, in clinical trials of vaccines, safety considerations and risk control requirements should be considered. Higher than therapeutic drugs, we implement the strictest management system and adhere to risk management and full-process control. This guideline is an adverse event grading standard developed for vaccine clinical trials. It aims to scientifically monitor and evaluate vaccine-related adverse reactions

through reasonable analysis and determination of the causal relationship between adverse events and vaccination, and to minimize the risk of adverse events in healthy subjects. Risks in clinical trials and risks to vaccine users. This guiding principle is drafted based on current regulations and industry standard systems as well as the current level of understanding. The grading standards and basis used refer to the regulations issued by overseas regulatory agencies.

Similar guiding principles and industry guidelines are formulated based on my country's clinical practice experience and will be updated in a timely manner as relevant regulations and standards are continuously improved and

the level of scientific

knowledge increases. 2. Scope of application This guideline is applicable to the graded assessment of the severity (i.e. intensity) of adverse events occurring in vaccine clinical trials. Since the subjects of vaccine clinical trials may be adults, teenagers, children or infants, the severity of clinical symptoms, signs and abnormal laboratory test indicators in the trial should be evaluated based on the physiological characteristics of people of different age groups. The grading evaluation criteria can also be used as emergency unblinding criteria specified in vaccine clinical trial design and as a reference for whether to suspend/terminate clinical trials. At the same time, the unified adverse event grading standards provided by this guideline also facilitate the comparison of safety data in

the same clinical trial

or between different clinical trials. 3. Basic content The grading indicators for adverse events in vaccine clinical trials provided in this guideline include two parts: the first part is clinical observation indicators (i.e., symptoms and signs, including adverse events at the vaccination site, vital signs, and adverse events at non-vaccination sites); The second part is laboratory test indicators (blood biochemistry, blood routine, urine routine, etc.). When conducting clinical trials, appropriate observation indicators can be selected from the adverse event classification table in this guideline for safety monitoring and evaluation based on the characteristics of the vaccine,

the characteristics of the subject population, and the degree of disease hazards. This guidance does not cover all safety indicators that need to be observed in vaccine clinical trials. For new vaccines, new monitoring indicators may need to be added based on safety tips from preclinical toxicology studies of vaccines or experience with similar products. The basis for the grading standards for the new indicators should be clear and expl

Grading standards used in clinical trials due to differences in observation or detection methods

If the grading standards are inconsistent with those in this guideline, and the grading standards need to be re-established, sufficient evidence should be provided and explained in the clinical trial plan. The observation indicators for children and infants included in this guideline are limited. When applying, it can be supplemented accordingly based on the safety assessment requirements of the candidate vaccine. (1) Adverse event grading table

In the monitoring of adverse events in vaccine safety studies, clinical symptoms and signs need to be considered together with corresponding laboratory testing indicators, and comprehensive causal analysis and evaluation should be conducted to obtain reliable conclusions.

During the implementation of clinical trials, in addition to recording and reporting with reference to the adverse event types listed in the following table, detailed information on adverse events of concern should also be recorded as much as possible. 1. Clinical observation indicators (Tables 1 to 3)

Table 1. Grading table of adverse events at the vaccination site (local)

Symptoms/Signs	Level 1	level 2	Level 3	level 4
Pain, tenderness (optional; tenderness is used for subjects who cannot express pain autonomously)				
pain	Does not affect or slightly affects physical activity	Affecting physical activities, affecting daily life, loss of basic self-care ability, or hospitalization		
tenderness	Contact or contact resistance refuse, shrink back	Crying after contact or touching, but can soothe	Continuous crying that cannot be comforted	Requires emergency room or hospitalization
Induration*, swelling (optional use)** #				
>14 years old	Diameter 2.5ÿ<5 cm Or area 6.25ÿÿ 25 cm2 and does not affect	Diameter 5ÿ<10 cm or Area 25ÿ<100 cm2 or affect daily life	Diameter ÿ10 cm or area ÿ100 cm2 or ulcerated or Secondary infection or phlebitis	abscess, exfoliative dermatitis, dermal or deep tissue necrosis

	Or slightly affect daily life Life		or sterile abscess or wound Oral drainage or serious impact daily life	
ÿ14 years old	Diameterÿ2.5cm	Diameter ÿ 2.5cm, and area <50% of the inoculated limb (solution Anatomical site of vaccination On a limb, such as the upper arm or thigh leg)	Area ÿ inoculated limb 50% or ulceration or secondary Infection or phlebitis or trauma Oral drainage	abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*, redness (optional)** #				
>14 years old	Diameter 2.5ÿ<5 cm Or area 6.25ÿÿ 25 cm2 and does not affect Or slightly affect daily life Life	Diameter 5ÿ<10 cm or Area 25ÿ<100 cm2 or affect daily life	Diameter ÿ10 cm or area ÿ100 cm2 or ulceration or Secondary infection or phlebitis or sterile abscess or wound Oral drainage or serious impact daily life	abscess, exfoliative dermatitis, dermal or deep tissue necrosis
ÿ14 years old	Diameterÿ2.5cm	Diameter ÿ2.5cm and area <50% of the inoculated limb (referring to anatomically connected The limb where the seed part is located is as above arm or thigh)	Area ÿ inoculated limb 50% or ulceration or secondary Infection or phlebitis or trauma Oral drainage	abscess, exfoliative dermatitis, dermal or deep tissue necrosis

other				
itching	Itching at the vaccination site, since OK or 48h after processing internal relief	Itching at the vaccination site, where No relief within 48 hours after treatment	affect daily life	THAT
cellulitis	THAT	Need for non-injectable Treatment (such as oral antimicrobial Antibacterial, antifungal, antiviral drug-like treatment)	Requires intravenous injection Treatment (such as intravenous antimicrobial Antibacterial, antifungal, disease resistant toxic drug treatment)	Sepsis, or tissue necrosis, etc.

Note: *In addition to directly measuring the diameter for grading evaluation, the progress of the measurement results should also be recorded.

**Maximum measured diameter or area should be used.

#The evaluation and grading of induration, swelling, rash and redness should be based on functional grade and actual measurement results, and higher graded indicators should be selected.

Table 2. Vital signs grading table

physical signs	Level 1	level 2	Level 3	level 4
Fever* [axillary temperature (ÿ)]				
>14 years old	37.3ÿÿ38.0	38.0ÿÿ38.5	38.5ÿ<39.5 ÿ39.5, lasting for more than 3 days	
ÿ14 years old	37.5ÿÿ38.0	38.0ÿÿ39.5	ÿ39.5	ÿ39.5, lasting more than 5 days
ECG PR interval prolongation or atrioventricular block (optional)				
>16 years old	PR interval 0.21~ <0.25 seconds	PR intervalÿ0.25 seconds or 2nd degree atrioventricular block Type I	2nd degree atrioventricular block II ventricular intermittent ÿ3 seconds	complete atrioventricular block

ÿ16 years old	1st degree atrioventricular block (PR interval>Same as Age and type of people normal value)	2nd degree atrioventricular block I mold	2nd degree atrioventricular block II ventricular intermittent ÿ3 seconds	complete atrioventricular block
physical signs	**Level 1**	**level 2**	**Level 3**	**level 4**
heart rate				
Tachycardia (beats/minute)	101ÿ115	116ÿ130	ÿ130 Arrhythmia requiring emergency department or hospitalization	
Bradycardia (times/minute)	50ÿ54	45ÿ49	ÿ45	Arrhythmia requiring emergency room visit or hospitalization
blood pressure				
High blood pressure (mmHg)				
ÿ18 years old	Systolic blood pressure: 140ÿÿ 160 or diastolic blood pressure: 90ÿÿ100	Systolic blood pressure: ÿ160~ <180 or diastolic blood pressure: ÿ100ÿÿ110	Systolic blood pressure: ÿ180 Or diastolic blood pressure: ÿ110	Emergence of previously undiagnosed threats Life complications (e.g. malignant hypertension) or hospitalization
<18 years old	Systolic blood pressureÿ120ÿ <152 or diastolic blood pressure ÿ80ÿÿ95	Systolic blood pressure ÿ152ÿÿ 178 or diastolic blood pressure ÿ95ÿÿ109	Systolic blood pressure ÿ178 or Diastolic blood pressure ÿ109	Emergence of previously undiagnosed threats Life complications (e.g. malignant hypertension) or hospitalization
Hypotension (systolic blood pressure) (mmHg) 85ÿ<89		80ÿÿ85	ÿ80	Shock or hospitalization
Respiration rate (times/minute)	17ÿ20	21ÿ25	ÿ25	Need tracheal intubation

Note: *Axillary temperature is usually used in China, and converted to oral and rectal temperatures when necessary. Usually, oral temperature = axillary temperature + 0.2ÿ;

Rectal temperature = axillary temperature + (0.3~0.5ÿ). When persistent high fever occurs, the cause of the high fever should be determined as soon as possible.

Table 3. Non-vaccination site (systemic) adverse event grading table

Organ system symptoms/signs	Level 1	level 2	Level 3	level 4
gastrointestinal system				
diarrhea	Mild or transient, 3~ 4 times/day, stool characteristics Abnormal, or mild diarrhea Lasts less than 1 week	Moderate or persistent, 5 to 7 times/day, different stool characteristics Often, or diarrhea >1 week	>7 times/day, fecal abnormal, or hemorrhagic Diarrhea, orthostatic hypoemia pressure, electrolyte imbalance, Requires intravenous infusion >2L	Hypotensive shock requires Hospitalization
constipate*	Stool softeners are needed to and dietary adjustments	Need laxative medication	Stubborn constipation requires manual removal Pass or use an enema	Toxic megacolon or intestinal infarction block
hard to swallow	Mild discomfort when swallowing	Restricted diet	Eating and talking are very popular restricted; unable to eat solid food food	Cannot eat liquid food; need require intravenous nutrition
anorexia	Appetite decreases but does not decrease less food intake	Decreased appetite, food intake Decrease, but not significantly in weight reduce	Decreased appetite and weight Obvious reduction	Intervention is needed (such as gastric tube feeding, parenteral camp keep)
Vomit	1~2 times/24 hours and no influence activities	3~5 times/24 hours or live limited movement	>6 times in 24 hours or Need intravenous fluids	Needed due to hypotensive shock Inpatient or other access nutrition
nausea	Transient (<24 hours) or intermittent and ingesting food Things are basically normal	persistent nausea leading to food Reduced intake (24 to 48 hours hour)	Persistent nausea leads to several Almost no food intake (ÿ 48 hours) or need to rest	Threatening life (such as hypotensive shock)

			pulse rehydration	
Organ system symptoms/signs	**Level 1**	**level 2**	**Level 3**	**level 4**
Musculoskeletal and connective tissue				
muscle ache (non-vaccination site)	Does not affect daily activities.	Slightly affects daily activities.	Severe muscle pain, severe Severe impact on daily activities	Emergency room or hospitalization
arthritis	Mild pain with inflammation symptoms, erythema, or joint swelling swelling; but does not impede function	Moderate pain with inflammation, erythema or joint swelling; obstruction hinders functionality, but does not affect daily life Regular activities	severe pain with inflammation symptoms, erythema, or joint swelling Bloating; affecting daily activities	permanent and/or incapacitating joint damage
joint pain	Mild pain, no hindrance Function	Moderate pain; pain relief required drugs and/or pain that interferes with function Yes, but does not affect daily life move	Severe pain; need to stop Analgesics and/or pain effects daily activities	disabling pain
nervous system				
Headache	Does not affect daily activities, No treatment required	Transient, minor impact Normal activities may require treatment or intervene	Seriously affects daily life Movement, need treatment or dryness pre	Refractory, requiring emergency room or hospitalization
Fainting	Near syncope, no loss Consciousness (e.g. aura)	Loss of consciousness, but no need to enter perform treatment	Loss of consciousness, need to carry out treatment or hospitalization	THAT

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new onset convulsions				
ÿ18 years old	THAT	THAT	1 to 3 convulsions	Prolonged and multiple seizures (e.g. status convulsant) or difficult to control (e.g. stubborn epilepsy)
<18 years old	Seizure duration <5 minutes, and convulsive seizures Post-operation status <24 hours	The duration of convulsion is ÿ5ÿ <20 minutes, and convulsions Postictal state <24 hours hour	Seizure duration ÿ20 minutes or after a convulsive attack Status>24 hours	Prolonged and multiple seizures (e.g. status convulsant) or difficult to control (e.g. stubborn epilepsy)
respiratory system				
cough	Transient, persistent cough that does not require treatment, treatment is effective		Paroxysmal cough, no treatment legal control	Emergency room or hospitalization
acute bronchospasm	Transient; no treatment required; FEV1% is 70%ÿ 80%	Treatment required; bronchiectasis Tonic treatment returns to normal; FEV1% is 50%ÿ70%	bronchodilator therapy cannot return to normal; FEV1% is 25%ÿ 50% or persistent concave intercostal space trap	Cyanosis; FEV1%<25%; or require intubation
Difficulty breathing	Difficulty breathing during exercise	Difficulty breathing during normal activity	Difficulty breathing during rest	Difficulty breathing, need oxygen treatment treatment, hospitalization or assisted breathing

Organ System Symptoms/Signs Grade 1		level 2	Level 3	level 4
Skin and subcutaneous tissue				
Itching at non-inoculation sites (no skin damage)	Slightly itchy, does not affect or Slightly affects daily life	Itching affects daily life	Itching that makes it impossible to carry out the day daily life	THAT
Abnormalities of skin and mucous membranes	erythema/itch/color Change	Diffuse rash/maculopapular rash/ dryness/flaking	Blisters/oozing/desquamation/ulceration ulcer	Exfoliative dermatitis involves mucous membranes, Or erythema multiforme, or suspected Stevens-Johnsons Comprehensive disease
mental system				
Insomnia*	Mild difficulty falling asleep, no Impact or minor impact day daily life	Moderate difficulty falling asleep, affecting daily life	Severe difficulty falling asleep, severe seriously affects daily life, Requires medical treatment or hospitalization	THAT
irritate or inhibit	Mildly irritated or mildly depressed system	Irritability or lethargy	Unable to soothe or have low responsiveness Down	THAT
mental disorder (including anxiety, depression, Mania and insanity) Detailed symptoms should be reported	Mild symptoms, no need for medical treatment diagnosis or behavior does not affect or Slightly affects daily life	If you have clinical symptoms, seek medical advice if necessary. diagnosis or behavior that affects daily life live	Requires hospitalization or disability unable to support daily life live	Have a tendency to harm yourself or others tendency or acute insanity or Loss of basic self-care ability
immune system				
Acute allergic reaction** Localized urticaria (watery localized urticaria requiring treatment of generalized urticaria or vasoanaphylactic shock or life-threatening				

	blisters), no treatment required or mild angioedema, No treatment required		Sexual edema needs treatment or is mild bronchospasm	Bronchospasm or larynx Head edema
other				
fatigue, weakness	Does not affect daily activities.	Influence normal daily activities.	Seriously affects daily life Can't move, can't work	Emergency room or hospitalization
Pain at non-inoculation site# (Specify location when reporting)	Mild pain, no impact Or slightly affect daily life live	Pain affects daily life	Pain prevents daily activities Life	disabling pain, loss of basic self-care ability

Note: FEV1% refers to forced expiratory volume in one second (FEV1)/forced vital capacity (FVC)

*For constipation and insomnia, attention should be paid to changes before and after vaccination.

**Refers to Type I hypersensitivity reaction.

#Refers to pain at non-vaccination sites except muscle pain, joint pain, and headache.

2. Laboratory testing indicators (Tables 4 to 6) Since

laboratory testing indicators are used as reference standards for safety evaluation, in addition to being based on industry-recognized scientific standards, it is also necessary to consider the updates of currently used clinical testing technologies and testing methods. In the design of clinical trial plans, the selection of monitoring indicators and standards must be based on sufficient basis, that is, they should comply with the prescribed or recognized normal value ranges of physiological and biochemical indicators to prove their rationality and feasibility. The following relevant indicators are for reference only.

For values between the upper limit (ULN) or the lower limit (LLN) of the reference range and Class 1 Laboratory test values between adverse events are not reported as adverse events.

Table 4. Blood biochemical index grading table

Detection Indicator	Level 1	level 2	Level 3	level 4
liver function (ALT, AST elevated)	1.25ÿÿ2.5 ×ULN	2.5ÿÿ5.0×ULN	5.0ÿÿ10×ULN	ÿ10×ULN

Elevated total bilirubin (mg/dL; µmol/L)				
>28 days old	1.1ÿÿ1.6×ULN 1.6ÿÿ2.6×ULN		2.6ÿ5.0×ULN	ÿ5.0×ULN
7ÿÿ28 days old (breastfeeding)	5ÿÿ10 85.5ÿÿ171	10ÿÿ20 171ÿÿ342	20ÿÿ25 342ÿÿ427.5	ÿ25 ÿ427.5
7ÿÿ28 days old (not breastfeeding)	1.1ÿÿ1.6×ULN 1.6ÿÿ2.6×ULN		2.6ÿ5.0×ULN	ÿ5.0×ULN
72 hoursÿ<7 days old	11ÿÿ16 188.1ÿÿ273.6	16ÿÿ18 273.6ÿÿ307.8	18ÿÿ24 307.8ÿÿ410.4	ÿ24 ÿ410.4
48ÿ<72 hours	8.5ÿÿ13 145.5ÿÿ222.3	13ÿÿ15 222.3ÿÿ256.5	15ÿÿ22 256.5ÿÿ376.2	ÿ22 ÿ376.2
24ÿ<48 hours	5ÿÿ8 85.5ÿÿ136.8	8ÿÿ12 136.8ÿÿ205.2	12ÿÿ19 205.2ÿÿ324.9	ÿ19 ÿ324.9
<24 hours	4ÿÿ7 68.4ÿÿ119.7	7ÿÿ10 119.7ÿÿ171	10ÿÿ17 171ÿÿ290.7	ÿ17 ÿ290.7
Pancreatin (amylase, lipase) 1.1ÿ<1.5×ULN 1.5ÿ<3.0×ULN			3.0ÿÿ5.0×ULN	ÿ5.0×ULN
Creatine phosphokinase (CPK)	1.25ÿÿ 1.5×ULN	1.5ÿÿ3.0×ULN	3.0ÿÿ10×ULN	ÿ10×ULN
Hypernatremia (Na, mmol/L) 146ÿ<150		150ÿÿ154	154ÿÿ160	ÿ160
Hyponatremia (Na, mmol/L) 130ÿ<135		125ÿÿ130	121ÿÿ125	ÿ120
Hyperkalemia (K, mmol/L) 5.6ÿ<6.0		6.0ÿÿ6.5	6.5ÿÿ7.0	ÿ7.0
Hypokalemia (K, mmol/L) 3.0ÿ<3.4		2.5ÿÿ3.0	2.0ÿÿ2.5	ÿ2.0

Hypercalcemia (Ca, mmol/L)				
ÿ7 days old	2.65ÿÿ2.88	2.88ÿÿ3.13	3.13ÿÿ3.38	ÿ3.38
<7 days old	2.88ÿÿ3.10	3.10ÿÿ3.23	3.23ÿÿ3.38	ÿ3.38
Hypocalcemia (Ca, mmol/L)				
ÿ7 days old	1.95ÿÿ2.10	1.75ÿÿ1.95	1.53ÿÿ1.75	ÿ1.53
<7 days old	1.63ÿÿ1.88	1.50ÿÿ1.63	1.38ÿÿ1.50	ÿ1.38
Hyperglycemia (Glu, mmol/L)				
Hunger	6.11ÿÿ6.95	6.95ÿÿ13.89	13.89ÿÿ27.75	ÿ27.75
non-hungry	6.44ÿÿ8.89	8.89ÿÿ13.89	13.89ÿÿ27.75	ÿ27.75
Hypoglycemia (Glu, mmol/L)				
ÿ1 month old	3.05ÿÿ3.55	2.22ÿÿ3.05	1.67ÿÿ2.22	ÿ1.67
<1 month old	2.78ÿÿ3.00	2.22ÿÿ2.78	1.67ÿÿ2.22	ÿ1.67

Note: ULN refers to the upper limit of the normal value range.

Table 5. Routine blood test grading table

Testing indicators/grading	Level 1	level 2	Level 3	level 4
Elevated white blood cells (WBC, 109 /L)	11~ÿ13	13ÿÿ15	15ÿÿ30	ÿ30
Low white blood cells (WBC, 109 /L)				
>7 days old	2.000ÿ2.499	1.500ÿ1.999	1.000ÿ1.499	ÿ1.000
ÿ7 days old	5.500ÿ6.999	4.000ÿ5.499	2.500ÿ3.999	ÿ2.500
lymphopenia	0.75ÿ1.00	0.5ÿ0.749	0.25ÿ0.49	ÿ0.25

ÿLYÿ109 /Lÿ				
Neutropenia (ANC, 109 /L)				
>7 days old	0.800ÿ1.000	0.600ÿ0.799	0.400ÿ0.599	ÿ0.400
2 to 7 days old	1.250ÿ1.500	1.000ÿ1.249	0.750ÿ0.999	ÿ0.750
ÿ1 day old	4.000ÿ5.000	3.000ÿ3.999	1.500ÿ2.999	ÿ1.500
Eosinophils (Eos, 109 /L)	0.65ÿ1.5	1.51ÿ5.0	ÿ5.0	High eosinophils cell syndrome
Thrombocytopenia (PLT, 109 /L)				
>12 years old	125ÿ140	100ÿ124	25ÿ99	ÿ25
ÿ3 months oldÿÿ12 years old	THAT	50ÿ75	25ÿ49	ÿ25
Low hemoglobin (g/dL)				
ÿ13 years old male	10.0ÿ10.9	9.0ÿÿ10.0	7.0ÿÿ9.0	ÿ7.0
ÿ13 years old female	9.5ÿ10.4	8.5ÿÿ9.5	6.5ÿÿ8.5	ÿ6.5
57 days old ~ <13 years old (boys and girls)	9.5ÿ10.4	8.5ÿÿ9.5	6.5ÿÿ8.5	ÿ6.5
36 days old ~ 56 days old (boys and girls)	8.5ÿ9.6	7.0ÿÿ8.5	6.0ÿÿ7.0	ÿ6.0
22 days old ~ 35 days old (boys and girls)	9.5ÿ11.0	8.0ÿÿ9.5	6.7ÿÿ8.0	ÿ6.7
8 days old ~ 21 days old	11.0ÿ13.0	9.0ÿÿ11.0	8.0ÿÿ9.0	ÿ8.0

(boys and girls)				
ÿ7 days old (boys and girls)	13.0ÿ14.0	10.0ÿÿ13.0	9.0ÿÿ10.0	ÿ9.0

Table 6. Routine urine examination grading table

Detection Indicator	Level 1	level 2	Level 3	level 4
Urinary protein (PRO) (Urine test paper test)	1+	2+	3+ or higher	THAT
urine sugar (Urine dipstick test)	Trace ~1+ or ÿ250mg	2+ orÿ250ÿ ÿ500mg	ÿ2+ or>500mg	THAT
Red blood cells (microscopic examination) [Number of red blood cells per high-power field (rbc/hpf) (excluding female menstruation)]	6ÿÿ10	ÿ10	Gross hematuria, with or without blood clots; or Cylindrical red blood cells in urine; treatment may be needed	Emergency room or hospitalization

(2) General principles for grading other adverse events

For adverse events not included in the grading table, the intensity will be evaluated according to the following standards:

estimate.

Level 1	level 2	Level 3	level 4	Level 5
Mild: short-term (<48h) Or slight discomfort, does not affect active, no treatment required	moderate: mild or moderate Activities are limited and may require Medical consultation, no need or only need light treatment	Severe: obvious activity Restricted, need to see a doctor and pick up subject to treatment, which may be necessary Hospitalized	Critical: Possibly life-threatening Life, activities seriously affected Limited, need monitoring and treatment	die

Rare adverse events associated with vaccination (i.e. rare adverse reactions) often require

It can only be discovered through large-sample clinical trials or population applications, and sometimes requires further evaluation in post-marketing studies. For vaccines whose main applicable population is healthy people, including infants and young children, the safety requirements are more stringent than those of other drugs. In pre-market clinical trials, the sample size should be expanded as much as possible in order to discover rare diseases related to vaccination. Risk signal. If necessary, clinical trials using safety observation indicators as clinical evaluation endpoints can be conducted, and the minimum sample size must meet the statistical requirements of safety studies.

(3) Relevance evaluation and safety report

Clinical safety monitoring should focus on the evaluation of the correlation between adverse events and experimental vaccines, and special attention should be paid to serious adverse reactions related to vaccination; during the clinical trial process, unexpected serious adverse reactions should be reported in a timely manner in accordance with relevant ICH requirements (SUSAR) and periodic safety reports (DSUR) during research and development.

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Attachment 2

Revision of "Guiding Principles for Adverse Event Grading Standards for Clinical Trials of Prophylactic Vaccines"

1. Background

The "Adverse Reactions in Clinical Trials of Preventive Vaccines" was first formulated and released in 2005. "Guiding Principles of Grading Standards" is specifically designed to address adverse events related to vaccine clinical research. Grading standards developed in response to more scientific monitoring and evaluation of healthy subjects Adverse reactions related to vaccine candidates and minimizing clinical Risks of Experimentation. This guiding principle has been in use for 14 years now and has been instrumental in promoting our China's vaccine clinical trials should be developed scientifically and standardizedly and in line with international standards, especially in WHO played an important role in the evaluation of my country's NRA vaccine regulatory system.

The contents of the 2005 version of the guidelines are applicable to healthy adults and adolescents. For testers, some of the grading indicators for adverse events are not fully applicable to infants and young children; In addition, with the deepening of clinical research practice and understanding of human medicine, and the Advances in laboratory testing technology, especially the Vaccine Administration Law of the People's Republic of China The promulgation and implementation of the Fully draw on the basis of similar guidelines and industry standards issued by foreign regulatory agencies Based on my country's clinical practice experience, the State Food and Drug Administration decided to The 2005 edition of the guiding principles has been revised. The Center for Drug Evaluation has set up a special drafting group. Based on extensive research, based on expert opinions and with reference to the releases of overseas regulatory agencies Similar guiding principles and industry guidelines, combined with my country's clinical practice experience,

A draft for comments will be prepared and publicly solicited on the center's website. Afterwards, in the battle

Based on the summary and analysis of the collective opinions, the guiding principles were revised and improved, and in accordance with the

The relevant provisions of the Vaccine Administration Law of the People's Republic of China have updated relevant technical requirements.

2. Main framework and content

This guideline provides grading indicators for adverse events in vaccine clinical trials.

It consists of two parts. The first part is clinical observation indicators, including adverse events at the vaccination site (local), vital signs, and adverse events at non-vaccination sites (systemic); the second part is laboratory test indicators (including blood biochemistry, blood routine, urine routine, etc.). In addition, this guideline also explains and stipulates the general principles for grading other adverse events, correlation evaluation and safety reporting.

3. Revision instructions

The main revisions include:

(1) General principles for grading adverse events: For clinical abnormalities not covered in the grading table, clarify the general principles for grading assessment.

(2) Regarding clinical observation indicators

1. Update the induration, swelling, flushing,

Grading criteria for rash and itching; added grading criteria for cellulitis.

2. Update the grading standards for fever and hypertension in the vital signs grading table; add

Hypotension grading criteria.

3. Analyze non-vaccination site adverse events according to MedDRA SOC terminology.

Collectively classified.

4. Update the non-vaccination site adverse event grading table for headache, dyspnea,

Grading standards for new-onset convulsions, anorexia, etc.; increased insomnia, mental disorder, non-vaccination

Grading standards include itching at the site and pain at non-inoculated sites.

(3) About laboratory testing indicators

1. Update the blood biochemical index grading table for elevated creatinine, elevated bilirubin, Hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypercalcemia, hypocalcemia, pancreatic enzymes, Creatine phosphokinase and other grading standards; increase hyperglycemia (fasting) and hypoglycemia scores level standards.

2. Update the routine blood examination grading table for low hemoglobin, low white blood cells, Grading standards for neutropenia and thrombocytopenia;

3. Update urine protein, urine sugar, and urine red blood cells in the routine urine examination grading table Grading standards.

(4) Add relevance evaluation and safety report

To emphasize the judgment of the correlation between adverse events and experimental vaccines, as well as the safety Reporting requirements, adding post-vaccination causal link in the preamble and at the end evaluation, special attention should be paid to adverse reactions related to vaccination, and according to ICH Relevant requirements for timely reporting of Unexpected Serious Adverse Reaction Reports (SUSAR) and R&D In-Process Periodic Security Report (DSUR).

(5) Other revisions

1. Change the original title "Guidelines for Grading Adverse Reactions in Clinical Trials of Prophylactic Vaccines" "Guidelines" were changed to "Guidelines for Grading Adverse Events in Clinical Trials of Prophylactic Vaccines" Guidelines" to reduce ambiguity and align with similar foreign guidelines.

2. Revise “local/systemic adverse events” to “vaccination site/non-vaccination site” "adverse events" to facilitate a more accurate description; at the same time, the original expression method is consistent with both habits toward clinical research.

3. The overall sentence expression, wording and word order issues have been modified. For details, see

Text content of this guideline.