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Guidelines for Basic Intravenous Infusion Evaluation in Clinical Use (Trial)

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Introduction

This guideline put forward the items, contents, reference standards, indicators and reference scores for the evaluation of basic intravenous (IV) infusion in clinical use. Establishment of evaluation items of this guideline fully considers the factors affecting the product quality in the production process and those affecting the drug safety and convenience in use of medical institutions. The evaluation items of basic intravenous infusion mainly include four aspects: the quality system of IV production enterprises, the safety of IV products, the compatibility of the drugs and packaging system, the effectiveness and convenience in clinical use.

1. Quality system of IV production enterprises

The establishment and perfection of enterprise quality system is not only the obligation that drug production enterprise should fulfill as the main body of product quality responsibility, but also an important part of the life cycle management of the produced drugs. The establishment of enterprise quality system is conducive to promoting the scientific, standardized and institutionalized supervision work, and it will benefit the implementation of product quality subject responsibility. It is of a great significance to control drug quality, reduce safety risks and ensure the public medication safety from the source. This guideline reflect the improvement of the quality system of enterprise through the report and monitoring of drug adverse events.

2. Safety of IV products

The safety of IV products in this guideline refers to the safety during clinical use, mainly including bacterial endotoxin, insoluble particles, leakage rate and quality of rubber stopper.

3. The compatibility of the drugs and packaging system

The production of IV products is basically subject to high temperature sterilization, and its packaging system is in direct contact with the liquid medicine for a long time, and the risk of interaction between the packaging system and the preparations is high. The chemical substances migrate from packaging system into the preparation, and the adsorption of the preparation by packaging materials may affect the safety, effectiveness and economy of the drug. The compatibility of the packaging system includes: the compatibility of basic intravenous infusion with packaging material before drug admixture, the compatibility of basic intravenous infusion with packaging material after drug admixture.

4. Effectiveness and convenience of clinical use

The effectiveness of clinical use refers to the ability of an IV product to deliver a certain amount of preparation or to deliver the preparation at a certain speed according to the requirements of the treatment. The effectiveness mainly includes infusion mode, pressure infusion (only applicable to plastic containers), drainage residual , and • the protectiveness of overpouch (only applicable to plastic containers). The convenience in clinical use means that the design of the packaging system should match the specific dosage form, route of administration and design performance. It mainly includes clearness, completeness and legibility of labels, transparency of containers, smoothness of

the edges of container and overpouch, weight capacity of hanger ring (hole), convenience of admixture and infusion, scientific design of the package and carton performance.

The evaluation method of this guideline is to score evaluation items respectively according to evaluation indicators, and these evaluation items are divided into subjective and objective ones. Evaluation items with reference standards (according to relevant regulations, standards and literatures) are objective ones; those without reference standards and assessed by assessor based on product samples or data are subjective ones.

This guideline is intended for use by medical institutions in evaluating basic intravenous infusion. Medical institutions may select and adjust evaluation items, contents, indicators and reference scores in this guideline for evaluation.

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This guideline is drafted in accordance with the regulations of GB/T1.1-2009.

Guidelines for Basic Intravenous Infusion Evaluation in Clinical Use

1 Scope of application

This guideline is applicable to the evaluation of basic intravenous infusion and their clinical use by medical institutions. This guideline mainly includes the definition of basic intravenous infusion, evaluation items and their clinical significance, evaluation, etc.

2 Normative references

GB/T6543-2008 *Corrugated Carton*

Good Manufacturing Practice (2010 edition)

Chinese Pharmacopoeia (2015 edition)

YBB00042005-2015 *Halogenated Butyl Rubber for Injection*

YBB00232004-2015 *Pharmaceutical Synthetic Polyisoprene Liners*

YBB00342002-2015 *General Requirement for Multi-layer Co-extrusion Film and Bag for Infusion*

YBB00102005-2015 *3-layer Co-extrusion Film (I) and Bag for Infusion*

YBB00112005-2015 *5-layer Co-extrusion Film (I) and Bag for Infusion*

CFDA *Technical Guidelines for Compatibility Study between Chemical Drug Injection and Plastic Packaging Materials*

3 Definition of basic intravenous infusion

Large volume injection usually refers to liquid sterilization preparation with volume of 50 ml or more and directly injected into the body by intravenous drip. According to the usage, it can be divided into five categories: body fluid balance infusion, therapeutic infusion, nutrient infusion, blood volume expansion infusion, and dialysis and contrast infusion. Among them, the body fluid balance infusion is also called basic intravenous infusion, which is mainly used to regulate the metabolism of the human body, maintain the osmotic pressure of body fluid, correct the acid-base balance of body fluid, and serves as the infusion carrier of therapeutic drugs. Examples are glucose injection, sodium chloride injection, glucose and sodium chloride injection, compound sodium chloride injection, sodium lactate ringer's injection, etc.

4 Evaluation items and their clinical significance

4.1 Establishment of the adverse event reporting and monitoring system in the enterprise (Evaluation item 1)

Clinical significance: It indicates the safety issue of the IV product in clinical use

4.2 Bacterial endotoxin (Evaluation item 2)

Clinical significance: Trace of bacterial endotoxin into the body can cause a series of pathological and physiological responses, such as fever, vasodilation, increased vascular permeability,

neutrophilic granulocytosis, complement activation, decreased blood pressure, even diffuse intravascular coagulation (DIC) and multiple organ failure or even shock, death in severe cases.

4.3 Sub-visible particles (Evaluation item 3)

Clinical significance: The sub-visible particles cannot be metabolized in blood vessels. Once enter into vital organs, sub-visible particles can cause granuloma, pyrogenic reaction and other injuries.

4.4 Leakage rate (Evaluation item 4)

Clinical significance: It indicates the integrity of container and the contamination risk level.

4.5 Quality of rubber stopper (Evaluation item 5)

Clinical significance: The quality of rubber stopper indicates the possibility of puncture scraps , needle sliding and leakage.

4.6 The compatibility of basic intravenous infusion with packaging system before admixture (Evaluation item 6)

Clinical significance: It indicates the IV infusion is safe throughout the shelf life.

4.7 The compatibility of basic intravenous infusion and packaging system after admixture (Evaluation item 7)

Clinical significance: It indicates the IV infusion is safe after drug admixture.

4.8 Infusion method (Evaluation item 8)

Clinical significance: Whether the exhaust pipe/needle needs to be connected during the infusion process. Fully closed infusion system can avoid the contamination to the drugs from external introduced air.

4.9 Pressure infusion (only applies to plastic containers) (Evaluation item 9)

Clinical significance: Pressure infusion is a kind of clinical need. It requires high performance of container integrity.

4.10 Drainage Residual (Evaluation item 10)

Clinical significance: It indicates the usage rate of infusion solution. The less the solution residual is, the more solution is used (Especially in the infusion of expensive drugs)

4.11 The protectiveness of overpouch (only applies to plastic containers) (Evaluation item 11)

Clinical significance: It indicates the protective ability of overpouch to primary container and the feature of ready-to-use.

4.12 The clearness, completeness and legibility of labels (Evaluation item 12)

Clinical significance: It indicates the integrity and accuracy of label contents. The higher the clarity, the more convenient for operators to check the drug information, which will increase the accuracy of drug use.

4.13 Container transparency (Evaluation item 13)

Clinical significance: It indicates the transparency of containers. The higher the transparency, the easier the solution check.

4.14 Smoothness of the edges of container and overpouch (Evaluation item 14)

Clinical significance: Prevention of occupational injury.

4.15 The weight capacity of hanger ring (hole) (Evaluation item 15)

Clinical significance: It indicates the convenience of infusion container and its weight capacity during infusion.

4.16 The convenience of admixture and infusion (Evaluation item 16)

Clinical significance: It indicates the convenience of admixture and infusion and whether the infusion set is easy to fall off.

4.17 Scientific design of the package (Evaluation item 17)

Clinical significance: It indicates the relationship between product design, quality, ease of use and safety of infusion.

4.18 Carton performance (Evaluation item 18)

Clinical significance: It indicates the protection for the product, the convenience and safety during storage and transportation.

5 Evaluation

5.1 The evaluation method for clinical use of basic intravenous infusion is to score the evaluation items respectively according to evaluation indicators. Among evaluation items, 1-8 are objective items, with a reference score of 100 points; 9-18 are subjective items, with a reference score of 100 points.

5.2 The evaluation of basic intravenous infusion in clinical use includes the evaluation content, reference standard, evaluation indicator and reference score. The specific content is shown in the attached table: *Evaluation Form for Basic Intravenous Infusion in Clinical Use*.

5.3 The *Evaluation Form for Basic Intravenous Infusion in Clinical Use* can be used as a reference for medical institutions to evaluate comprehensively the quality of products when choosing basic intravenous infusion.

5.4 Each medical institution may select or add evaluation items according to the actual situation, and adjust the evaluation methods, evaluation indicators and scores.

Attached form: Evaluation Form for Basic Intravenous Infusion in Clinical Use

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
1. Establishment of the adverse event monitoring and reporting system in the enterprise	1. Whether the enterprise has established a drug safety committee involving multiple functions, and BUs with clear processing mechanism for the safety issue; 2. Whether the enterprise submits the Periodic Safety Update Report (PSUR) in time according to the regulations and has the feedback record from the Provincial Center for Adverse Drug Reaction (ADR) Monitoring (Compliance with the Guidance for Periodic Safety Update Report (PSUR)); 3. Establishment of improved safety data processing procedure and computerized data processing system (Excel, Argus, ARISg, etc.) to process adverse event data (including adverse events collected daily, and adverse reactions reported by the National or Provincial Center for ADR Monitoring), as to support safety information updating and related adverse reaction reporting (such as an annual report of adverse reactions or a report of five-year adverse reactions for millions of people); 4. Whether the enterprise has approved by the US Food and Drug Administration (FDA) or EU or Pharmaceutical Inspection Co-operation Scheme (PIC/S) or Japan Pharmaceuticals and Medical Devices Agency (PMDA).	Any notification, warnings and other relevant information in the *Adverse Drug Reaction Reporting* on the website of Provincial or National Center for ADR Monitoring, China and *Pharmacovigilance News*; Good manufacturing practice (GMP) and related international certifications.	Establishment of the drug safety committee involving multiple functions and BUs with clear processing mechanism for the safety issue (SOP)	None	0	(The full score is 10) Actual score:
				Yes	2.5	
			Timely submission of Periodic Safety Update Report (PSUR) and feedback records from the Provincial Center For ADR Monitoring	None	0	
				Yes	2.5	
			Establishment of improved safety data processing procedure and computerized data processing system for adverse drug reaction monitoring	None	0	
				Yes	2.5	
			Approved by the US Food and Drug Administration (FDA) or EU or Pharmaceutical Inspection Co-operation Scheme (PIC/S) or Japan Pharmaceuticals and Medical Devices Agency (PMDA)	None	0	
				Yes	2.5	
2. Bacterial	1. The enterprise provides product bacterial	Chinese pharmacopoeia (2015	Comply with pharmacopoeia standard:		0	(The full score

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
endotoxin	endotoxin assay (EU/mL) data and test method Limit of Determination (LOD); 2. The enterprise provides the bacterial endotoxin internal control limit and release test data of APIs and excipients (including Water for Injection); 3. To provide test report by third party, if necessary.	edition) Product bacterial endotoxin, less than 0.50EU/ml	less than 0.5 EU/ml			is 10) Actual score:
			Superior to pharmacopoeia standard: less than 0.25 EU/ml		5	
			Bacterial endotoxin internal control limit and test data of APIs and excipients	None	0	
				Yes	5	
3. Sub-visible particles	1. The enterprise provides commitment on sub-visible particles; 2. To provide test report by third party, if necessary.	Chinese pharmacopoeia (2015 edition) Light obscuration method: ≥25um, no more than 3 counts/ml; ≥10um, no more than 25 counts/ml; Microscopic method: ≥25μm, no more than 2 counts/ml; ≥10μm, no more than 12 counts/ml. Enterprise standard: Light obscuration method: ≥5um, no more than 50 counts/ml (The specific score can be determined between 11 and 20 according to the commitment of the enterprise).	The enterprise commits to comply with pharmacopoeia standards Light obscuration method: ≥25um, no more than 3 counts/ml; ≥10um, no more than 25 counts/ml; Or microscopic method: ≥25um, no more than 2 counts/ml; ≥10um, no more than 12 counts/ml		0	(The full score is 20) Actual score:
			The enterprise commits superior to pharmacopoeia standards Light obscuration method: ≥25um, no more than 2 counts/ml; ≥10um, no more than 15 counts/ml		10	
			The enterprise commits significantly superior to pharmacopoeia standards Light obscuration method: ≥25um, no more than 1 counts/ml; ≥10um, no more than 5 counts/ml; ≥5um, enterprise to commit		20	
4. Leakage rate	1. The quality problem of the IV product after the opening of the box and before the	Enterprise standard	The enterprise commits leakage rate >0.05%		0	(The full score is 20) Actual

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
	admixture and other operations at clinical institutions. 2. The enterprise provides commitment on leakage rate (different ranges can be chosen, <0.01%, 0.01%-0.05%, >0.05%).		The enterprise commits leakage rate of 0.01%-0.05%		10	score:
			The enterprise commits leakage rate <0.01%		20	
5. The protectiveness of overpouch (only applies to plastic containers)	1. No overpouch; 2. Overpouch that can withstand sterilization; 3. Overpouch that can't withstand sterilization.		No overpouch		0	(The full score is 10) Actual score:
			Overpouch that cannot withstand sterilization		5	
			Overpouch that can withstand sterilization		10	
6. The compatibility of basic intravenous infusion with packaging system before admixture	The enterprise provides the research report of the compatibility between basic intravenous infusion and packaging system, including the data of extractable and leachable of packaging materials, the data of migration and adsorption of packaging system and preparations as well as data of safety evaluation.	CFDA *Technical Guidelines for Compatibility Study between Chemical Drug Injection and Plastic Packaging Materials* and other relevant technical documents	Study reports or results on the compatibility of basic intravenous infusion and package provided by the enterprise	None	0	(The full score is 10) Actual score:
				Yes	10	
7. The compatibility of basic intravenous infusion and packaging system after admixture	1. The enterprise provides data or reference literatures: 2. The compatibility and stability study results of drug solution and packaging system after admixture; 3. The quantity and variety of drugs studied.	CFDA *Technical Guidelines for Compatibility Study between Chemical Drug Injection and Plastic Packaging Materials* and other relevant technical documents	The enterprise provides the compatibility study reports or results of the drug and packaging system after admixture, as well as the quantity and variety of drugs studied	None	0	(The full score is 10) Actual score:
				Yes and ≦10	5	
				Yes and >10	10	

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
8. Infusion method	1. Half-opened infusion system; 2. Fully-closed infusion system.	1. Half-opened infusion system needs to connect exhaust pipe/needle during the infusion process; 2. In the fully-closed infusion system, the exhaust pipe/needle does not need to be connected during the infusion process, and the continuous and uniform infusion speed can be maintained, and the residual liquid in the container after administration does not exceed 5% of the standard capacity.	Half-opened infusion system		0	(The full score is 10) Actual score:
			Fully-closed infusion system		10	
9. Pressure Infusion (only applies to plastic containers)	1. Test method: Take 30 samples of 250 ml plastic container and insert single-use infusion set into medication port of each sample (close the clamps before use). Set pressure cuff at 300 mmHg and observe for 12 hours. No leakage or dislodgement shall be observed at the sealing area, membrane tube (if applicable) and medication port interface. 2. The enterprise provides samples and data	Subjective evaluation	Evaluation based on samples and data provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
10. Drainage Residual	1. Test method: Take 50 samples of plastic container and insert single-use infusion set into medication port of each sample (make sure the vent cap of the infusion set is closed). Flick the infusion port before draining, and make sure the infusion tube is	Subjective evaluation	Evaluation based on samples and data provided by the enterprise	Not bad	0	(The full score is 10) Actual score:

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
	filled with liquid without any bubble. Set the head height at 0.7 m and the flow rate at 210 ml/hour (70±5 drops/minutes). During gravity drainage, observe and record whether containers permit uninterrupted drainage. Pull out the infusion set after drainage (keep the container flat) and record the weights of wet and dry containers (dried for at least 24hours). 2. The enterprise provides samples and solution residual data of different product codes (volumes).			Better	5	
				Good	10	
11. The quality of rubber stopper	The enterprise provides the material description, puncture scraps , puncture force, tightness and retentivity of puncturing point, residue on ignition, and readily oxidizable substance, etc.	Subjective evaluation	Evaluation based on samples and data provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
12. The clearness, completeness and legibility of labels.	1. The enterprise provides samples; 2. The characters are easy to be recognized. The print of labels is clear. The adherence of labels is good.	Subjective evaluation	Evaluation based on samples provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
13. Container Transparency	1. The enterprise provides samples; 2. Easy to check the status of matter contained and its abnormal; 3. The enterprise provides the date of container transparency data.	Subjective evaluation	Evaluation based on samples and data provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
14. Smoothness of the edges of container and overpouch	1. The enterprise provides samples; 2. If the edges and corners of bag are soft, smooth and flat.	Subjective evaluation	Evaluation based on samples provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	

Evaluation items	Evaluation contents	Reference standard	Evaluation indicator		Reference score	
15. The weight capacity of hanger ring (hole)	1. The enterprise provide samples; 2. The hanger ring (hole) is easy to open, it doesn't affect the placement; 3. The enterprise provides weight capacity data of hanger rings of different product codes (volumes). Not break for 60 min: ≤ 250 ml, 7 N >250 ml, 15N	Subjective evaluation	Evaluation based on samples and data provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
16. The convenience of admixture and infusion	Provide samples	Subjective evaluation	Evaluation based on samples provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
17. Scientific design of the package	1. The enterprise provides samples and the design philosophy of products; 2. There are separate medication and infusion ports to facilitate clinical operation and avoid contamination; 3. There are single-use port protectors to ensure the sterility before use.	Subjective evaluation	Evaluation based on samples provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	
18. Carton performance	The material of carton, the properties of crush-resistance, water absorbing and design description.	Subjective evaluation	Evaluation based on the material of carton, the properties of crush-resistance, water absorbing and design description provided by the enterprise	Not bad	0	(The full score is 10) Actual score:
				Better	5	
				Good	10	

Note 1: The *Evaluation Form for Basic Intravenous Infusion in Clinical Use* can be used as a reference for medical institutions to evaluate comprehensively the quality of products when choosing basic intravenous infusion;

Note 2: Each medical institution may select or increase the evaluation items according to the actual situation of this enterprise, and adjust the evaluation methods, evaluation indicators and scores.

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