Introduction

Peritoneal dialysis (PD) is an effective blood purification procedure features in simple operation, low medical costs and convenience for popularization and application and plays an irreplaceable role in improving the remedy rate of uremia patients in China. Due to the features of the PD treatment, it has a relative high degree of dependence on the container closure system. Therefore, the Container Closure System has a great effect on the drug quality of peritoneal dialysis solution and therapeutic effect on the patients.

According to the China's regulations, some components of the Container Closure System of Peritoneal Dialysis Solution, transfer tubing, drainage bag, connector and protective cap, are classified as managed as Class II medical devices; the soft bag (solution bag) and components (connective tubing, injection port, valve) in contact with the solution are classified as pharmaceutical packaging and subject to the management as required by Associated Review & Approval of Pharmaceutical Pharmaceutical packaging and Pharmaceutical Excipients with Drugs (CFDA Announcement [2016] No.134). The guidelines are the technical guide for drug packaging product. In the preparation of the guidelines, the current supervision situation has been taken into account, for example, in the technical requirements, the components subject to the management of medical device as an impartible part of the Container Closure System of Peritoneal Dialysis Solution, for which, if only the relevant regulatory requirements other than the specific requirements to be met are specified, the performance requirements of the intended use to be met after product combination should also be taken into account in the preparation of the technical requirements of the overall Container Closure System, such as that relevant requirements regarding the fitting performance of connectors, infusion time/drainage time shall also be met.

The purpose of this Guideline is to, through above series guidance technical requirements, provide guidance to the enterprises for continuous improvement from design, research and development, manufacturing, quality control, technical requirements, compatibility study to storage and transportation. The manufacturing units and user units shall provide sufficient guidance for product use so as to ensure the medication safety and improve the patient operation convenience and the quality of life.

Introduction

This standard is indented for guiding the technical research and development, inspection, manufacturing, storage and transportation of the Container Closure System of Peritoneal Dialysis Solution in the industry.

This standard is drafted in accordance with the rules given in GB/T1.1-2009.

This standard is proposed by xxxxx.

Drafting unit: xxxxx

Major drafter: xxxxx

Guidelines for the Container Closure System of Peritoneal Dialysis Solution

1 Scope

1.1 The guidelines specify the term and definition, structure example and functional description of each component, design requirements, manufacturing quality management, packaging material and component storage and effective date of packaging, transportation requirement, function and safety requirement, label identification and IFU requirements for the Container Closure System of Peritoneal Dialysis Solution.

1.2 The guidelines are applicable to the Container Closure Systems of Peritoneal Dialysis Solutions manufactured with various materials.

Currently, the materials which have been used for the Container Closure System of Peritoneal Dialysis Solution include polyvinyl chloride, polyolefins, polycarbonates and rubber, etc.

1.3 The guidelines are applicable to multiple types of peritoneal dialysis solution bags. The Container Closure System is divided into single bag and dual bag by usage mode; the solution bag is divided into single-chamber bag and multi-chamber bag by the structure.

1.4 The guidelines are applicable to multiple kinds of specifications of Container Closure Systems of Peritoneal Dialysis Solutions.

2 Terms and Definitions

2.1

Peritoneal Dialysis (PD)

PD, a treatment technique using human peritoneum as semipermeable membrane, abdominal cavity as exchange space, through diffusion and dialysis, to remove excessive water, metabolite and toxin in the body to achieve the function of blood purification, replacement of renal excretion. PD is divided into Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD) in clinical practice.

2.1.1

Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD refers to the PD where the solution is changed manually by the patient or medical staff and the patients, after replacement of solution, can freely do their daily activities.

2.1.2

Automated Peritoneal Dialysis (APD)

APD refers to various PD types using peritoneal dialysis machine for the exchange of peritoneal dialysis solution.

2.2

Container Closure System of Peritoneal Dialysis Solution

The Container Closure System of Peritoneal Dialysis Solution refers to the sum of pharmaceutical packaging of peritoneal dialysis solution and other functional components, generally including solution bag, injection port, frangible valve or administration port, three-way connection, transfer tubing, drainage bag, overwrap bag and other components. The Container Closure System of Peritoneal Dialysis Solution is intended to package, protect and infuse the peritoneal dialysis solution and can ensure the safety and effectiveness of peritoneal dialysis solution within the life time and the safety and convenience during clinical application.

3 General

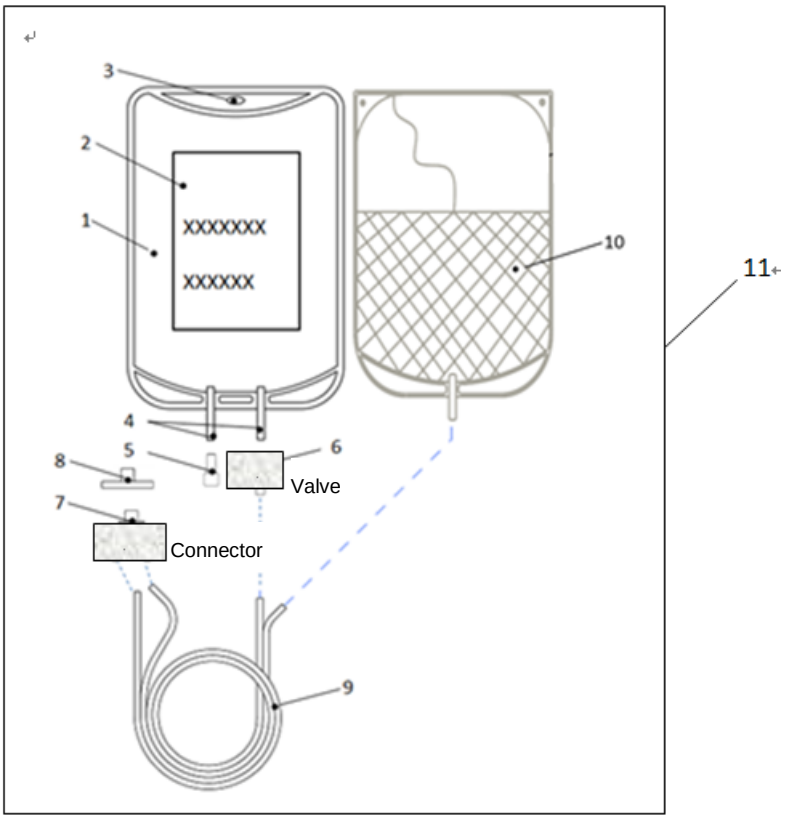
The purpose of this Guidelines is to provide the scientific, objective, feasible decision-making basis for future relevant policies and regulations based on the considerations of clinical application safety through drafting and developing the technical guidelines for the Container Closure System of Peritoneal Dialysis Solution and to provide the guidance of quality control basis to the manufacturing enterprise for this type of product in the industry.

In addition, the guidelines provide guidance for the continuous improvement of design, research and development, manufacturing and use to minimize the peritoneal dysfunction, ensure the medication safety and improve the patient operation convenience and the quality of life.

4 Structure example and functional description of each component

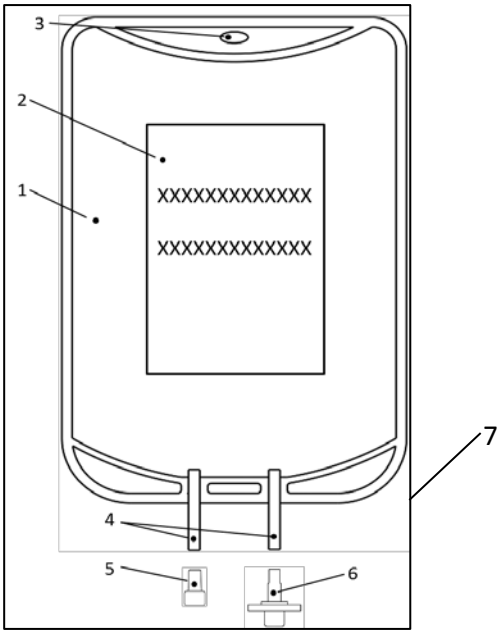
4.1 Structure example, unification of structure naming and definition

Figure 1 and Figure 2 provide the description method of basic structure example of the Container Closure System of Peritoneal Dialysis Solution which is used for the reference of structural description of actual product.



1. Solution bag
2. Label area
3. Hole for hanging
4. Connective tubing
5. Injection port
6. Valve (if applicable, various models are available)
7. Connector (various models are available)
8. Protective cap
9. Transfer tubing
10. Drainage bag
11. Overwrap bag

Figure 1 Dual Bag



1. Solution bag
2. Label area
3. Hole for hanging
4. Connective tubing
5. Injection port
6. Valve and administration port
7. Overwrap bag

Figure 2 Single Bag

4.2 Functional description of each component

4.2.1 Solution bag

Used for the identification of the volume and the storage, identification and use of peritoneal dialysis solution. The bag has a hole for hanging the solution bag during dialysis. Label area on the surface is used for printing product label.

4.2.2 Connective tubing

Connective tubing is short tube on the solution bag and drainage bag used for connecting the injection port, \frangible valves and connectors.

4.2.3 Injection port

Port used for injecting the drug.

4.2.4 Valve (if applicable)

A single-activated valve used for connecting the solution bag and transfer tubing. It remains in off position, and can be opened easily by multiple means such as frangible part, before use.

4.2.5 Connector

Connector used for connecting the transfer tubing and external short tube, provided in multiple modes.

4.2.6 Protective cap

Protect the sterility of connection port of patient end at patient connection port of three-way connection.

4.2.7 Transfer tubing

Tube used for infusing the peritoneal dialysis solution and discharging the drainage fluid.

4.2.8 Drainage bag

Container used for collecting the drainage fluid in human body.

4.2.9 Valve and administration port

Port used for peritoneal dialysis solution infusion on the solution bag.

4.2.10 Overwrap bag

External bag used to safeguard the sterile sate of peritoneal dialysis solution in the shelf life of the drug with the function of dust prevention and water, gas and light blocking. Additional, it is convenience in use for the patients.

5 Design requirements

The Container Closure System of Peritoneal Dialysis Solution shall use the materials which comply with the suitability and safety need. The peritoneal dialysis is generally performed at home and the replacement of PD solution is done by the patient (or the family member) who has been trained. Therefore, the Container Closure System of Peritoneal Dialysis Solution has special requirements different from the general drug packaging. The Container Closure System shall be designed in such a way that the manufacturing, storage, transportation and use of peritoneal dialysis solution are safe and convenient. The design shall prevent contamination of peritoneal dialysis solution during manufacturing, storage and transportation and minimize the contamination and achieve the intended function during clinical application.

5.1 The peritoneal dialysis system shall be designed to reduce the risk of peritonitis in the patients. The entire Container Closure System of Peritoneal

Dialysis Solution shall be a fully sealing system.

5.2 The solution bag shall be transparent and designed to be convenient for observing the liquid before use;

5.3 The length of solution tube shall be easy for the patient to use and meet the requirements that the whole process of dialysis can be completed through the action of gravity when the solution bag is hung at a certain height.

5.4 The opening of protective cap shall be designed to be easy for single use. The protective cap shall be designed into female luer or other suitable connector to form the maximum sealing.

5.5 The volume of drainage bag shall be larger than the labelled volume and easy for the user to weigh the solution after dialysis.

5.6 The drainage bag shall be transparent and designed to be convenient for the user to observe the solution after dialysis such as turbidity, floccule and color. The drainage bag shall not be adhesive after sterilization.

5.7 The information in the label area shall be legible with the generic name of drug, lot number specification, date of manufacture and shelf life clearly marked.

5.8

(a) Connective tubing: The connective tubing shall be transparent and designed to be convenient for solution infusion and insertion of injection port and administration port and to be completely sealed after the insertion of injection port and administration port.

(b) Injection port: No severe sink mark defect. The components shall be tightly engaged free of loosening or poor engagement.

(c) Valve and administration port: No severe sink mark defect. The components shall be tightly engaged free of loosening or poor engagement.

(d) Connector: The connector shall ensure the seal and tight engagement of connecting pieces and avoid contamination.

Other components shall meet the design requirements.

5.9 The peritoneal dialysis solution has different kinds of specifications (such as glucose concentration, calcium ion concentration). The Container Closure System of Peritoneal Dialysis Solution should be designed rationally to help the patients to distinguish.

5.10 The overwrap bag shall be so designed that its materials can withstand the

sterilization method of peritoneal dialysis solution so as to ensure the integrity of overwrap bag during sterilization, storage and transportation, to enable easy observation on the state of peritoneal dialysis solution product after sterilization, to provide barrier performance according to the characteristics of different PD solution, and to provide convenience in use for the patients according to the material or the structure, such as the use of easy-to-tear film or notch

5.11 The dimension of carton box shall ensure the space to place the drug horizontally in order. The information on the carton box shall be legible with the generic name of drug, lot number specification, date of manufacture and shelf life clearly marked. The packaging of carton box shall be able to bear a certain pressure to ensure that the box is tight without omission and damage during the handing and shipping of the drug and ensure that the box will not be extruded or damaged while stacking the drug.

5.12 The stacking method of peritoneal dialysis product shall be validated.

6 Manufacturing Quality Management

6.1 Manufacturing conditions

The manufacturing of Container Closure System of Peritoneal Dialysis Solution shall comply with the relevant national regulations.

The manufacturing conditions of Container Closure System of Peritoneal Dialysis Solution shall be suitable to the manufacturing conditions and quality requirements of peritoneal dialysis solution with corresponding risk prevention measures.

6.2 Raw material control

The Container Closure System of Peritoneal Dialysis Solution involves many types of components, mainly including pharmaceutical packaging and medical device. The components classified as pharmaceutical packaging such as solution bag, connective tubing, injection port, valve and overwrap bag shall comply with the requirements of relevant regulations and enterprise controlling standards for pharmaceutical packaging; the components classified as medical device such as transfer tubing and drainage bag shall comply with the requirements of relevant regulations and enterprise controlling standards for medical device.

6.3 Manufacturing process control

The manufacturing process of Container Closure System of Peritoneal Dialysis Solution shall be subject to reliable verification and demonstrated with stability. The key processing points shall be confirmed and a description shall be provided that they have no unacceptable effect on the physical, chemical and biological properties

of the product.

According to the manufacturing processing, there shall be verified key manufacturing steps, key process parameters and quality control index of intermediate for controlling the manufacturing process. Example of general technological process:

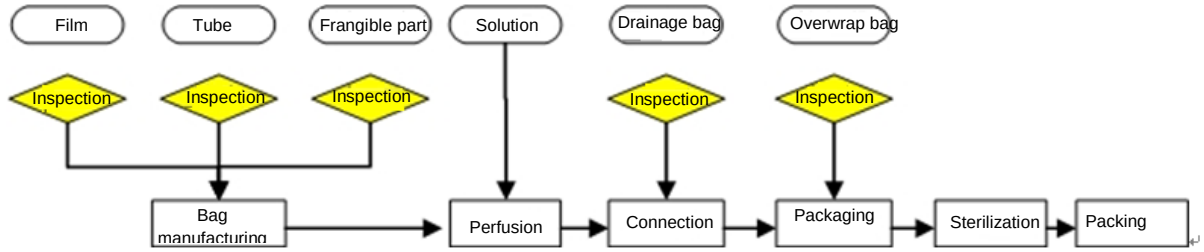


Figure 3 Example of Technological Process

6.4 Sterilization of peritoneal dialysis solution product

The peritoneal dialysis solution product shall be sterilized by moist heat sterilization or other validated methods, comply with the national sterilization requirements and ensure the required sterile level and be verified and implemented. The Container Closure System shall be suitable to the sterilization method. The pharmaceutical packaging shall bear the sterilization conditions of the product.

The sterilized products shall be sealed tightly with intact outer packaging; the component content of peritoneal dialysis solution and 5-hydroxymethyl furfural and other impurities shall comply with the standard requirements.

6.5 Change control

6.5.1 The enterprise shall establish the change control process to assess and manage the change so as to confirm that the change complies with the requirements of mandatory standards and the intended use and has no effect on the product safety and effectiveness.

6.5.2 When the name of enterprise, manufacturing address, formulation and process, quality standards and the factors which may affect the product quality are changed, the enterprise shall conduct corresponding assessment actively to verify and validate the change, inform the drug manufacturing enterprise in time and report relevant documents to China Food and Drug Administration as required.

6.5.3 The validation methods and activities of the change shall be suitable to the risk level. The change evaluation and validation shall comply with the requirements of relevant national regulations or technical documents. The drug manufacturing enterprise shall master the change of pharmaceutical packaging in time, make study and assessment according to relevant

technical guidelines, file a supplementary application for the drug for the change of pharmaceutical packaging which affects the drug quality in accordance with the relevant regulations in the Measures for the Administration of Drug Registration, and file to the provincial food and drug administration for the change of pharmaceutical packaging which has no effect on the drug quality according to Item 36 in Annex 4 Supplementary Application of the Measures for the Administration of Drug Registration.

6.5.4 The implementation of the change shall have complete records. The quality management departments shall keep all the change documents and records.

7 Storage Conditions and Life Time of Pharmaceutical Packaging and Components

The pharmaceutical packaging and components used for the peritoneal dialysis solution shall have sufficient stability under specified storage conditions. The life time of pharmaceutical packaging refers to the period in which the stability of the pharmaceutical packaging is maintained throughout the whole shelf life from the manufacturing date of pharmaceutical packaging to the expiration date of drug product. The storage conditions and life time of pharmaceutical packaging and components are generally verified and validated by the manufacturer of pharmaceutical packaging. The study conclusion is provided to the manufacturing enterprise of peritoneal dialysis drug as information for use to guide the drug manufacturing enterprise to store the pharmaceutical packaging and components under specified conditions; meanwhile, the drug manufacturing enterprise shall, according to the shelf life of the drug packaged in the pharmaceutical packaging and in combination with the life time of the provided pharmaceutical packaging and components, determine the deadline used for appropriate drug production link.

The life time of materials and components of the Container Closure System of Peritoneal Dialysis Solution is generally determined through accelerated test and long-term test. These two tests may be made by reference to the regulations of relevant guidance documents domestically and internationally so as to determine the life time of pharmaceutical packaging and components.

The data and report of accelerated test and long-term test shall be completed and filed for supporting subsequent regulations and document requirements for the quality relevant to the life time of packaging material.

It should be noted that the life time of pharmaceutical packaging and components provided by the packaging manufacturer shall be determined through accelerated test (generally called accelerated aging test for polymer) and long-term test (generally called real-time aging test as well) based on the consideration of storage environment factors such as temperature, humidity, illumination, oxidation and other

environment effect factors. Since the manufacturer of peritoneal dialysis drug product has the processing technologies of pharmaceutical packaging and components in subsequent drug production process such as the soldering of connective tubing, sterilization of final product and other process engineering, these processing technologies generally become the factors which may affect the pharmaceutical packaging and components. Therefore, the manufacturer of peritoneal dialysis drug product is responsible for the verification and validation during the use of pharmaceutical packaging and components, drug filling until the final product is formed and subsequent drug storage that the Container Closure System of Peritoneal Dialysis Solution can meet the relevant functional and protective requirements after above processes.

8 Transportation Requirements

The peritoneal dialysis solution product is a large volume injection with large dependence on the packaging during transportation. The manufacturing enterprise of peritoneal dialysis solution shall take full consideration of the climatic characteristics of geographic area for potential customers after product marketing and the transportation, storage and distribution used during the development of Container Closure System of Peritoneal Dialysis Solution and design rational shape of Container Closure System, packing method and stacking method of outer box.

The manufacturing enterprise of peritoneal dialysis solution should evaluate and confirm the ability of Container Closure System of Peritoneal Dialysis Solution to protect the peritoneal dialysis solution product and shall meet the technical requirements. The laboratory simulated transportation may be used to assess the ability of Container Closure System to protect the product or the actual transportation mode of the product may also be used for evaluation. The test sample shall be the finally formed peritoneal dialysis solution products.

The laboratory simulated transportation test may be made by reference to the recommendations of the guideline or standard of ASTM D-4169, ISTA series, ISO 4180 and GB/T 4857 series domestically and internationally and in combination with transportation mode, packaging mode and transportation environment to select appropriate test conditions for the simulated transportation test. The conditions which may occur during the actual transportation shall be taken into full consideration such as the temperature and humidity conditions, atmospheric pressure, vibration, impact, drop during transportation. Appropriate items shall be selected for comprehensive assessment of transportation.

The actual transportation evaluation should, in accordance with the actual transportation and storage requirements of the product, evaluate the effect of season, routine, road condition and vehicle on the product, and through improving the

packaging system, packaging mode, loading capacity and loading mode, ensure that the Container Closure System provides effective protective ability of the product under possible environment conditions during circulation of the product and avoid the occurrence of compressional deformation or damage and leakage at the client for easy use.

9 Technical Requirements

The Container Closure System of Peritoneal Dialysis Solution shall meet the designed intended use according to the product (such as thickness and dimension of solution bag). The relevant technical requirements which should be considered include but not limited to the contents specified in this Guidelines.

9.1 Physical requirements

9.1.1 Thickness and dimension of peritoneal dialysis pouch body:

Different specifications of peritoneal dialysis pouches shall have the thickness and dimension which comply with the intended design and have appropriate tolerance range.

9.1.2 Leakproofness of packaging system (integrity of packaging system)

The Container Closure System of Peritoneal Dialysis Solution shall remain sealed when exposed to external environment and pressure to reduce the contamination risk of microorganism or foreign substances and therefor minimize the occurrence of peritonitis.

9.1.3 Drop resistance

The anti-dropping requirement is used for characterizing the possible drop from a certain height during simulated handling and use. After the simulated drop test, the Container Closure System of Peritoneal Dialysis Solution shall still meet the leakproofness requirements. The anti-dropping requirement belongs to a physical index relevant to the safety. The Container Closure System of Peritoneal Dialysis Solution shall be able to protect the product and have no damage or leakage after appropriate drop test.

9.1.4 Transparency and transmittance

The solution bag shall be transparent enough after sterilization for the user to observe the possible particle and abnormal color in the solution bag. The overwrap bag should be convenient for the manufacturer and user to observe the possible leakage and other adverse conditions through the overwrap bag.

9.1.5 Water vapor permeability

For the Container Closure System of Peritoneal Dialysis Solution, the moisture loss shall be taken into consideration and the component content of peritoneal dialysis solution shall meet the requirements within certain shelf life.

9.1.6 Insoluble particle

The insoluble particles in the solution contacting parts and flowing parts of Container Closure System of Peritoneal Dialysis Solution shall comply with the requirements of current Chinese Pharmacopoeia.

9.1.7 Leakproofness at injection site

The injection port shall be convenient for the user to inject and there shall not be any leakage during and after injection.

9.1.8 Breaking force of frangible part (if applicable)

The frangible part shall be able to bear the stress during the manufacturing, storage and transportation of peritoneal dialysis solution product. Before use, the frangible part shall remain sealed and shall be easy to open for the user before PD.

9.1.9 Fitting performance of connector

After removing the protective cap, it shall be convenient for connecting to the catheter or other components at the patient end and the leakproofness shall be maintained after connection. The connection between the connector and the connected catheter or between the components shall be free of any leakage under certain pressure and any loosening at certain tensile force after connection.

9.1.10 Hanging force

During use, the solution bag shall be easy to hang up for the patient and the hole for hanging shall be able to bear corresponding tensile load within certain time.

9.1.11 Infusion time/drainage time

The time to infuse the peritoneal dialysis solution into the patient and drain the solution from the abdominal cavity to the waste bag should be assessed with appropriate method.

9.1.12 Protective cap

The protective cap should be steady but easy to dismantle.

9.1.13 Multi-chamber open control

For multi-chamber bag product, the multi-chamber pressure shall meet the clinical demand and product design requirements. The pseudo soldering site at multi-chamber shall achieve rigorous isolation from different chambers during

manufacturing, storage and transportation and can be opened under certain external force during clinical application. The particle count shall comply with the regulations of Chinese Pharmacopoeia after opening.

9.2 Chemical requirements

The appropriate chemical requirements and test method shall be justified and developed by reference to the relevant product standards of YBB/ISO and in combination with features of Container Closure System of Peritoneal Dialysis Solution.

9.3 Bioburden

The sterility assurance level of the final product shall be able to be ensured.

9.4 **Biocompatibility** made by reference to the relevant guidelines issued by China Food and Drug

The appropriate biological evaluation shall be made by reference to the relevant standards domestically and internationally

Note: the solution tube and drainage bag used for the Container Closure System of Peritoneal Dialysis Solution shall comply with the requirements of the relevant regulations.

10 Compatibility of the Container Closure System (Safety)

The Container Closure System of Peritoneal Dialysis Solution and the solution filled shall be subject to appropriate compatibility study. The compatibility study shall be Administration. For the compatibility study of Container Closure System, the intended applicability-safety is met as long as the following conditions are met:

(1) The fully understood materials shall be selected for the Container Closure System. .

(2) The biocompatibility of Container Closure System has been established (see 8.3)

(3) The safety and compatibility study is to establish the safety of Container Closure System in combination with the chemical test and toxicological assessment. The safety of Container Closure System is determined through appropriate chemical test such as extractables and leachables study and the toxicological assessment of the data of these chemical tests.

11 Label, Identification and Instructions for Use of Pharmaceutical packaging and Components

11.1 The supplier of materials and components shall provide appropriate information

11.2 Label, identification and instructions for use of Container Closure System of Peritoneal Dialysis Solution

11.2.1 The label of Container Closure System of Peritoneal Dialysis Solution shall include

(a) Product name

(b) Specification and model

(c) Lot No.

(d) Date of manufacture and shelf life

(e) Approval No. (pharmaceutical packaging, medical device registration certificate number or filing certificate number)

(f) Information of manufacturing enterprise (name, registration address, manufacturing address and contact information)

(g) Storage method (describe the special storage and operation conditions)

(h) Necessary cautions and considerations

11.2.2 The instructions for use of Container Closure System of Peritoneal Dialysis Solution shall include

(a) Product name

(b) Specification and model

(c) Information of manufacturing enterprise (name, registration address, manufacturing address and contact information)

(d) Approval No. (pharmaceutical packaging, medical device registration certificate number or file certificate number)

(e) No. of product technical requirements

(f) Product composition and structure

(g) Instructions or diagram for installation and use as well as special instructions for safe use of medical device which is used by the customs (single bag);

(h) Product maintenance method, special storage, transportation conditions and methods;

(i) shelf life of the product

(j) Explanation of figure, symbol and abbreviation on the label

(k) Development or revision date of instructions;

(l) If the product should be installed or used with other medical devices, the requirements, instructions for use and considerations for combined use shall be indicated

(m) For the single use product, the word or symbol of “single use” shall be indicated. For the sterilized product, the sterilization method and processing method after the sterile packaging is damaged shall be indicated. For the product which shall be disinfected or sterilized before use, the disinfection or sterilization method shall be described

(n) According to the product characteristics, other considerations to which attentions shall be paid shall be proposed

11.3.1 The label of each component of Container Closure System of Peritoneal Dialysis Solution shall include

(a) Product name

(b) Specification and model

(c) Lot No.

(d) Date of manufacture and shelf life

(e) Information of manufacturing enterprise (name, manufacturing address and contact information)

(f) Storage method (describe the special storage and operation conditions)

(g) Necessary caution and considerations

11.3.2 The instructions for use of each component of Container Closure System of Peritoneal Dialysis Solution shall include

(a) Product name

(b) Specification and model

(c) Information of manufacturing enterprise (name, manufacturing address and contact information)

(d) Component material description and function description

(e) Product maintenance method, special storage, transportation conditions and methods

(f) Shelf life

(g) Explanation of figure, symbol and abbreviation on the label

(h) Development or revision date of instructions

(i) If the product should be installed or used with other medical devices, the requirements, instructions for use and considerations for combined use shall be indicated

(j) For the single use product, the word or symbol of “single use” shall be indicated. For the sterilized product, the sterilization method and processing method after the sterile packaging is damaged shall be indicated. For the product which shall be disinfected or sterilized before use, the disinfection or sterilization method shall be described;

(k) According to the product characteristics, other cautions to which attention shall be paid by the operators and users.