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Technical guidance for the container closure system of peritoneal dialysis solution

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Preface .....错误!未定义书签。

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Foreword

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

This standard is under the jurisdiction of China National Pharmaceutical Packaging Association.

Drafting unit: Shandong Quality Inspection Center For Medical Devices.Chinese PLA General Hospital,Baxter (China) investment Co., Ltd. Fresenius Medical Care R&D (Shanghai) Co.,Ltd. Huaren Pharmaceutical Co.,Ltd. China Resources Double-Crane Pharmaceutical Co., Ltd. WEGO Terumo(WEIHAI) Medical Producks Co.,Ltd. RENOLIT Plastic Tech. (BJ） Ltd. Sealed Air (China) Co., Ltd. Austar Lifesicences Limited

Major drafter: Hongyu Luo, Jianhui Zhou, Biao Wang,Vera Liu. Congri Yang, Frank Gong, Xiaojun Chu, Shengmin Shen, Xianzhong Huang, Sheng Huang, Xinhua Lei, Qiang Wu, Wenfang Zhang, Bi Wang, Yi Zheng, Chunming Wu, Mars Ho, Xin Zhang, Yong Shen.

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, frangible) in contact with the solution are classified as pharmaceutical packaging and subject to the management as required by Associated Review & Approval . 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, there is no detailed requirements for the components subject which are managed as medical devices, just indicate that the components subject need to meet the relevant regulatory requirements. But because components subject is an impartible part of the Container Closure System of Peritoneal Dialysis Solution, so the performance requirements of the intended use to be met after product combination is also 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 Guidance is to provide guidance to the enterprises for continuous improvement from design R&D, 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 life quality.

Technical guidance for the container closure system of peritoneal dialysis solution

1 Scope

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 (abbreviation: Container Closure System of PD).

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, rubber and so on.

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.

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

2 Terms and Definitions

Below terms and definitions are applicable to the guidance.

2.1

Peritoneal Dialysis (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 and Automated Peritoneal Dialysis in clinical practice.

2.1.1

Continuous ambulatory peritoneal dialysis, CAPD

The solution is changed manually by the patient or medical staff, after replacement

of solution, the patients can freely do their daily activities.

2.1.2

Automated peritoneal dialysis, APD

Various PD types using peritoneal dialysis machine for the exchange of peritoneal dialysis solution.

2.2

Container closure system of peritoneal dialysis solution

The sum of pharmaceutical packaging of peritoneal dialysis solution and other functional components, generally including but not limited in solution bag, injection port, frangible component or administration port, three-way connection (if applicable), 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 shelf life and the safety and convenience during clinical application.

3 General

The purpose of this Guidance 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 guidance 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 R&D, manufacturing and use to reduce the risk of invasion by foreign microorganisms and delay the deterioration of peritoneal function in patients, ensure the medication safety and improve the patient operation convenience and the quality of life.

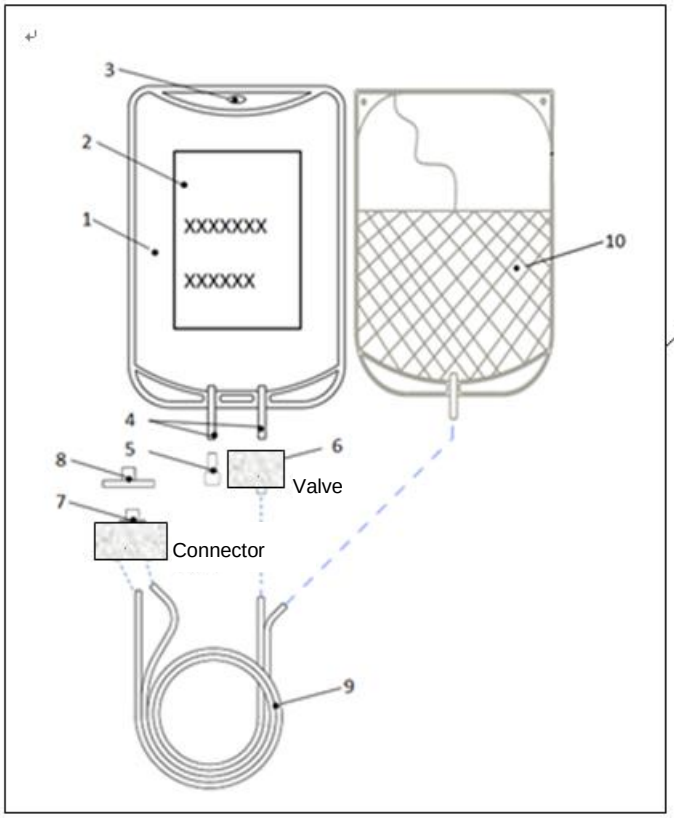
The components in Container Closure System of Peritoneal Dialysis Solution should meet the requirements of national pharmacopoeia or other relevant standards. The design, manufacturing, production quality management, transportation validation and evaluation, functional requirement and safety assessments of Container Closure System of Peritoneal Dialysis Solution shall meet the safety and convenience requirement during manufacturing, storage, transportation and use of Peritoneal Dialysis Solution. Control and manage the change if any change of Container Closure System of Peritoneal Dialysis Solution, to ensure the safety and effectiveness.

Medical device components such as transfer tubing, drainage bag, used in Container Closure System of Peritoneal Dialysis Solution shall meet the relevant regulatory requirement.

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.

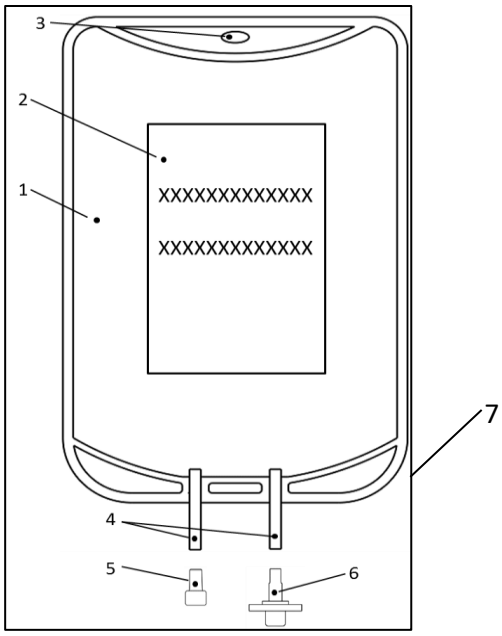


Explanation,

1. Solution bag
2. Label area
3. Hole for hanging
4. Connective tubing
5. Injection port
6. Frangible Component (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



Explanation,

1. Solution bag
2. Label area
3. Hole for hanging
4. Connective tubing
5. Injection port
6. Frangible component 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 treatment.

4.2.2 Connective tubing

Connective tubing is short tube on the solution bag and drainage bag used for connecting the injection port, frangible component, connector and transfer tubing.

4.2.3 Injection port

Port used for injecting the drug.

4.2.4 Frangible Component (if applicable)

A single used-activated valve used for connecting the solution bag and transfer tubing. It remains in off position before use, and can be opened easily by multiple modes once in clinical 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

Keep the sterility of connection port of patient end at patient connection port of three-way connection or other connection.

4.2.7 Transfer tubing

Tubing 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 enterocoelia.

4.2.9 Frangible Component and Administration Port

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

4.2.10 Overwrap bag

External bag used to prevent damage of content in the overwrap bag after sterilization, also has the function of dust prevention and moisture and gas blocking, and is convenient for the patient to open.

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 of foreign microorganism 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 tubing 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 structure to form the maximum sealing with connector.

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 Compositions as below,

(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) Frangible component 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 size 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 stand the sterilization method of peritoneal dialysis solution so as to ensure the functional 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 corresponding 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 design of easy-to-tear film or opening.

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 refer to the relevant requirement of national regulation on drug instruction and label. It 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, frangible Component 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 validation and demonstrated with stability, to ensure 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:

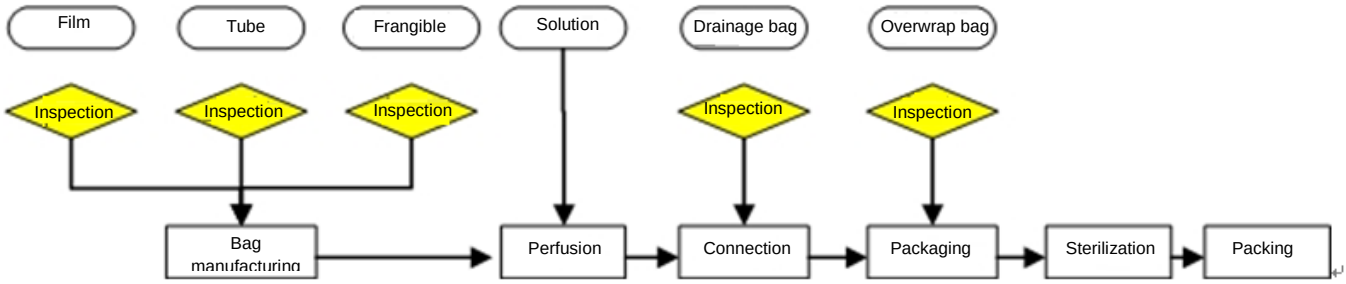


Figure 3 Example of Technological Process

Note: Example of Technological Process is only for reference, enterprise can adjust it according to own process.

6.4 Sterilization of peritoneal dialysis solution product

The Container Closure System of Peritoneal Dialysis Solution shall be sterilized by the same method of peritoneal dialysis solution product. The packaging materials shall bear the sterilization conditions of the product.

The sterilized products shall be sealed tightly with intact outer packaging, without breakage.

6.5 Change control

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.

7 Storage Conditions and Life Time of Packaging Materials and Components

The packaging materials and components used for the peritoneal dialysis solution

shall have sufficient stability under specified storage conditions. The life time of pharmaceutical packaging with stable quality is defined as the stable period of the pharmaceutical packaging within the whole shelf life from the manufacturing date of pharmaceutical packaging to the expiration date of drug. This period is the time when the pharmaceutical packaging is expected to guarantee the quality characteristics under the specified environmental conditions or the specified storage conditions. .

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 materials and components which consist of CCS.

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 pharmaceutical packaging.

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 assay 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 strength of frangible component (if applicable)

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

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 shall be sealed 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 methods shall be justified and set out by reference to the relevant product standards of YBB(pharmaceutical packaging material)/ISO and in combination with features of Container Closure System of Peritoneal Dialysis Solution.

9.3 Bioburden or Sterility

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

9.4 Biocompatibility

The appropriate biological evaluation shall be performed by reference to the relevant standards domestically and internationally. including USP 〈87〉, 〈88〉, ISO 10993 series and so on.

10 Compatibility of the Container Closure System

The Container Closure System of Peritoneal Dialysis Solution and the solution filled shall perform appropriate compatibility study. The compatibility study shall be performed by reference to the relevant guidelines issued by China Food and Drug Administration, including Technical Guideline for Chemical Pharmaceuticals and Elastomeric Closure Compatibility Study (Pilot) and Technical Guideline for Chemical Pharmaceuticals and Plastic pharmaceutical packaging Compatibility Study (Pilot). For the compatibility study of Container Closure System, the intended applicability-safety is met as long as the following conditions are met:

(a) The Container Closure System selects the fully understood materials.

(b) The biocompatibility of Container Closure System has been established (see 9.4)

(c) 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 extractable and leachable study and the toxicological assessment for the data of these chemical

tests.

11 Label, Identification and Instructions for Use of Packaging Materials and Components (if applicable)

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 shall meet the GMP or relevant regulatory requirement.

References

[1] GB/T 4857 (all parts) packages transport packages.

[2] ISO 4180 Packaging – Complete, filled transport packages – General rules for the compilation of performance test schedules.

[3] ISO 10993 Biological evaluation of medical devices.

[4] ASTM D-4169 Standard practice for performance testing of shipping containers and systems.

[5] ISTA International safe transit association.

[6] USP <87> Biological Reactivity Tests, In Vitro.

[7] USP <88> Biological Reactivity Tests, In Vivo.