China National Pharmaceutical Packaging Association

T/CNPPA 3001-2017

Technical Guideline of Infusion Production of Blow Fill Seal (BFS)

Contents

Introduction

The Guidelines specify the technical content and requirements for terminally sterilized infusion products manufactured by the infusion manufacturers using **Blow-Fill-Seal** (BFS) technology.

They are proposed by China National Pharmaceutical Packaging Association.

The drafting units of the Guidelines include China Resources Double-Crane Pharmaceutical Co., Ltd., Zhejiang Center for Drug and Cosmetic Evaluation, B. Braun Medical (Suzhou) Co., Ltd., Rommelag Trading (Shanghai) Co., Ltd., Sichuan Kelun Pharmaceutical Co., Ltd. and Shijiazhuang No.4 Pharmaceutical Co., Ltd.

They are mainly drafted by Zhu Limin, Jin Hong, Qi Jing, Yang Shutao, Wang Xin, Wang Yubo, Hou Junjie, Yu Jialing, and Huang Zhihui.

They are developed on the drafting rule of GB/T1.1.

Technical Guideline of Infusion Production of Blow Fill Seal (BFS)

1 Scope

The Guidelines are used for guiding the manufacture of terminally sterilized infusion products using blow fill seal (BFS) technology.

2 Normative References

The following documents are necessary for the application of this document. For dated referenced documents, only dated versions are applicable to this document. For cited documents without date, the latest versions (including all modification lists) are applicable to this document.

YBB00012003-2015 Tests for cytotoxicity - method IV

YBB00052003-2015 Tests for skin sensitization

YBB00062003-2015 Tests for intracutaneous irritation

YBB00042003-2015 Tests for acute systemic toxicity

YBB00032003-2015 Tests for hemolysis

Chinese Pharmacopoeia

3 Terms and Definitions

The following terms are only used in this Guideline.

3.1

Blow fill seal (BFS) infusion technology is a kind of infusion production technology integrating blow molding, liquid filling and sealing of infusion container at the same station of the same equipment, which provides effective contamination prevention through airtight BFS system and airflow control system[1].

3.2

BFS infusion

The infusion production using blow fill seal (BFS) technology.

3.3

Blow- molding

A process of melting appropriate plastic pellets at high temperature into tube blank and squeezing the blank into the container mold.

3.4

Microbial contamination level

A test of microbial population before infusion sterilization under specified production conditions to evaluate the degree of microbial contamination during infusion production.

3.5

Visible foreign matters

Insoluble substances visually observed under specified production conditions, which are generally kinds of harmful particles with particle size greater than 50μm.

3.6

Insoluble particles

Small particle impurities produced during drug production via different ways with particle size of 1μm-50μm, which are a kind of moveable and non-metabolic harmful particles that

cannot be observed by naked eyes.

3.7

Integrated closure

A process of sealing to form an integrated sealing part of the container in the infusion production using BFS technology.

3.8

Cleaning in Place (CIP)

A process of automatically and continuously cleaning all the tubes and filter elements in direct contact with the product under hermetic condition using water for injection as per process conditions.

3.9

Sterilizing in Place (SIP)

A process of automatically and continuously sterilizing all the tubes and filter elements in direct contact with the product under hermetic condition and using saturated pure steam.

3.10

Self-evacuation

A process of automatically discharging of drug through the infusion set without air in the packaging system during infusion.

3.11

Plastic pellets Raw materials used for producing BFS infusion container, including polypropylene **pellets** and polyethylene **pellets**.

3.12

Component

BFS infusion components are defined as all the sealing package system for accommodating and protecting the drugs, including the packaging container and combined closure in direct contact with the drugs.

4 Technical Features of BFS Infusion

This technology combines the blow-molding of container with the filling of product and a sealing operation in one piece of equipment. From a microbiological point of view, the sequence of forming the container, filling with sterile product, and formation and application of the seal are achieved aseptically in an uninterrupted operation with minimal exposure to the environment. Based on the design principle, BFS infusion technology avoids additional substances which may affect the drug quality during production such as microorganisms, visible foreign matters, and insoluble particles.

4.1 Sterile filling system design based on infusion safety

4.1.1 “Blow, fill and seal” sterile production system design

BFS equipment shall be installed in Class C or D clean area as per different processes and the personnel shall wear Class A/B cleanroom garment. Under dynamic states, the environment shall meet the microbial standards; under static states, the environment shall meet the microbial and suspended particle standards. The equipment design using “black and white partition” technology further reduces the area of clean area and human intervention.

4.1.2 Class A air shower system

BFS infusion equipment is equipped with a Class A air shower system for providing Class A clean air protection to blow-molding, filling and sealing area to ensure that infusion production is completed under sterile conditions and eliminate microbial contamination.

4.1.3 Automatic control without human interference

With modular design, BFS technology is computer-controlled to integrate the processes which are most possibly exposed to ambient environment during production like blowing, filling and sealing into the same module without human intervention.

4.2 Cleaning in place and sterilizing in place (CIP/SIP)

BFS technology provides CIP/SIP design for continuous cleaning in place and sterilizing in place of all the tubes and filter elements in direct contact with the product under hermetic condition， provides an overall-process parameter control and ensure the sterile state of the tubes and related facilities and control contamination and cross contamination during production.

4.3 Sealing performance of BFS infusion technology

Leak tightness is a basic condition to protect infusion product from external microorganisms and other effects during production and storage and ensure the product stability. BFS infusion technology improves the leak tightness of infusion in plastic package and reduces risks.

When BFS technology is used to produce infusion, the three processes of blowing, filling and sealing are completed at the same time under airtight condition to form an integrated structure of bag body, integrated cap and ring-pull, which is then moved out under sealed condition.

4.4 Self-evacuation performance of the integrated container produced with the BFS technology

When using the infusion container produced with the BFS technology, the container has self-evacuation function during intravenous infusion through parameter control of container appearance and production process so as to avoid contamination during clinical injection.

5 BFS infusion production technology

BFS infusion production technology is a kind of technology used for infusion production. And it is a fully automated process integrating blow- molding, filling and sealing of infusion bag in the same sealed mold[3]. In comparison with traditional infusion technology, this technology is used for infusion production. Attentions shall be paid to the design, verification and validation of equipment and workshop as well as process control and other key control points.

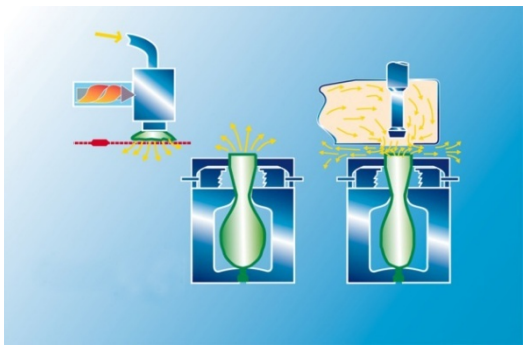
5.1 Working principle

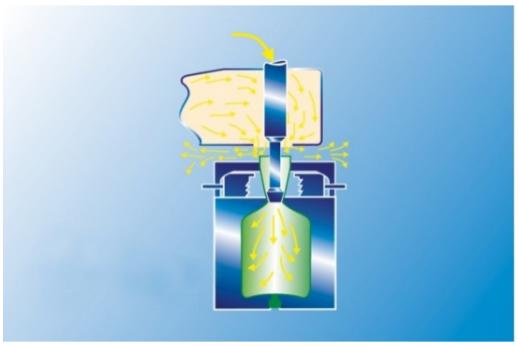
5.1.1 Extrusion

The tube blank produced by plastic pellets enters into the opened blowing mold and the head of the tube blank is cut below the extrusion head.

5.1.2 Molding

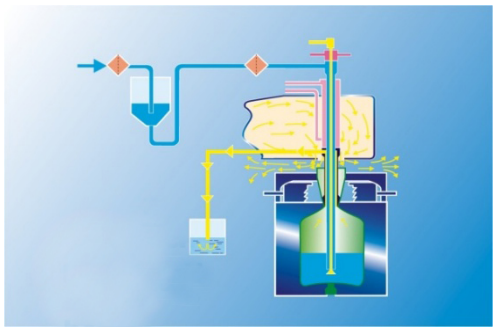
Fold the main mold, and seal the bottom of the container; lower the specially-made mandrel unit to the neck of container and use the compressed air to blow the tube blank into a container.





5.1.3 Filling

Through specially-made mandrel unit, fill the solution accurately measured by the measurement unit into the container.



5.1.4 Sealing

After retrieving the specially-made mandrel unit, fold the head mold and complete the sealing by vacuum.

5.1.5 Opening the mold

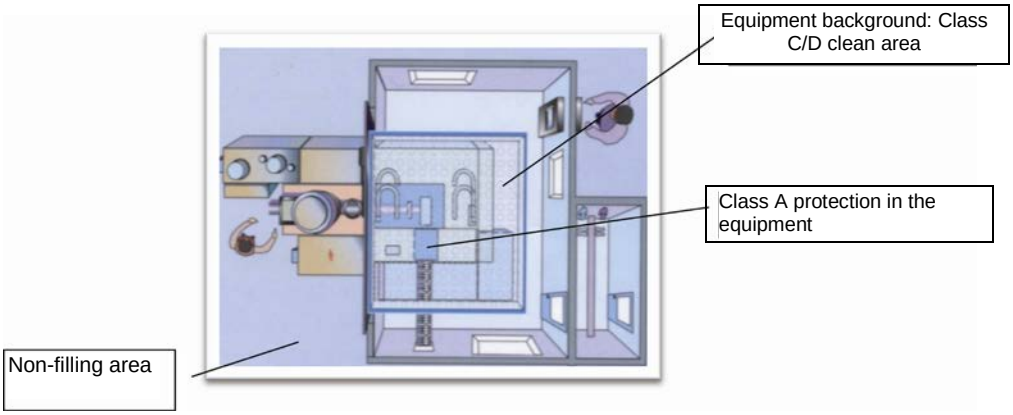
After the mold is opened, the container is delivered out of the equipment, and the equipment steps into the next production cycle. Through a delivery system, the container is delivered to the next process.

5.2 Clean workshop and air purification system

5.2.1 Design of clean workshop

The design of clean workshop is divided into two major categories based on the requirements of production process of infusion products, i.e. finally sterilized product and non-finally sterilized product. This Guideline is applicable to finally sterilized BFS infusion. As a result, BFS production process under Class C and Class D settings is used as per the environmental requirements. BFS equipment is equipped with a separate Class A air shower system to provide clean air to the core control area of the equipment. It is necessary for the enterprises to verify the air purification system in the workshop. Meanwhile, during the equipment verification, product process verification and quality control, the Class A air shower system provided by the equipment supplier shall be verified and re-verified.

Schematic diagram for clean workshop of BFS equipment:



5.2.2 Clean compressed air

The clean compressed air system is an auxiliary system which provides the primary equipment with Class A clean compressed air for tube blank supporting, container blowing, air conservation, etc.

The clean compressed air is prepared through drying and sterile filtration. The clean class of air through the end filter of the primary equipment shall comply with the requirements for Class A clean air.

5.2.3 Environmental monitoring plan for clean workshop

Position	Method	Requirement
Class A area in the equipment	Wind speed	Refer to Class A requirements in Article IX of Chapter III in Appendix 1 of Good Manufacturing Practice for Drugs (2010).
	Airborne microorganisms	
	Airborne particles	
	Contact/wiping plate	<1cfu/Φ55mm

Position	Method	Requirement
Equipment background: Class C/D clean area	Wind speed	Refer to Class C and D requirements in Article IX of Chapter III in Appendix 1 of Good Manufacturing Practice for Drugs (2010).
	Airborne microorganisms	
	Airborne particles	
	Contact/wiping plate	25CFU/Φ55mm

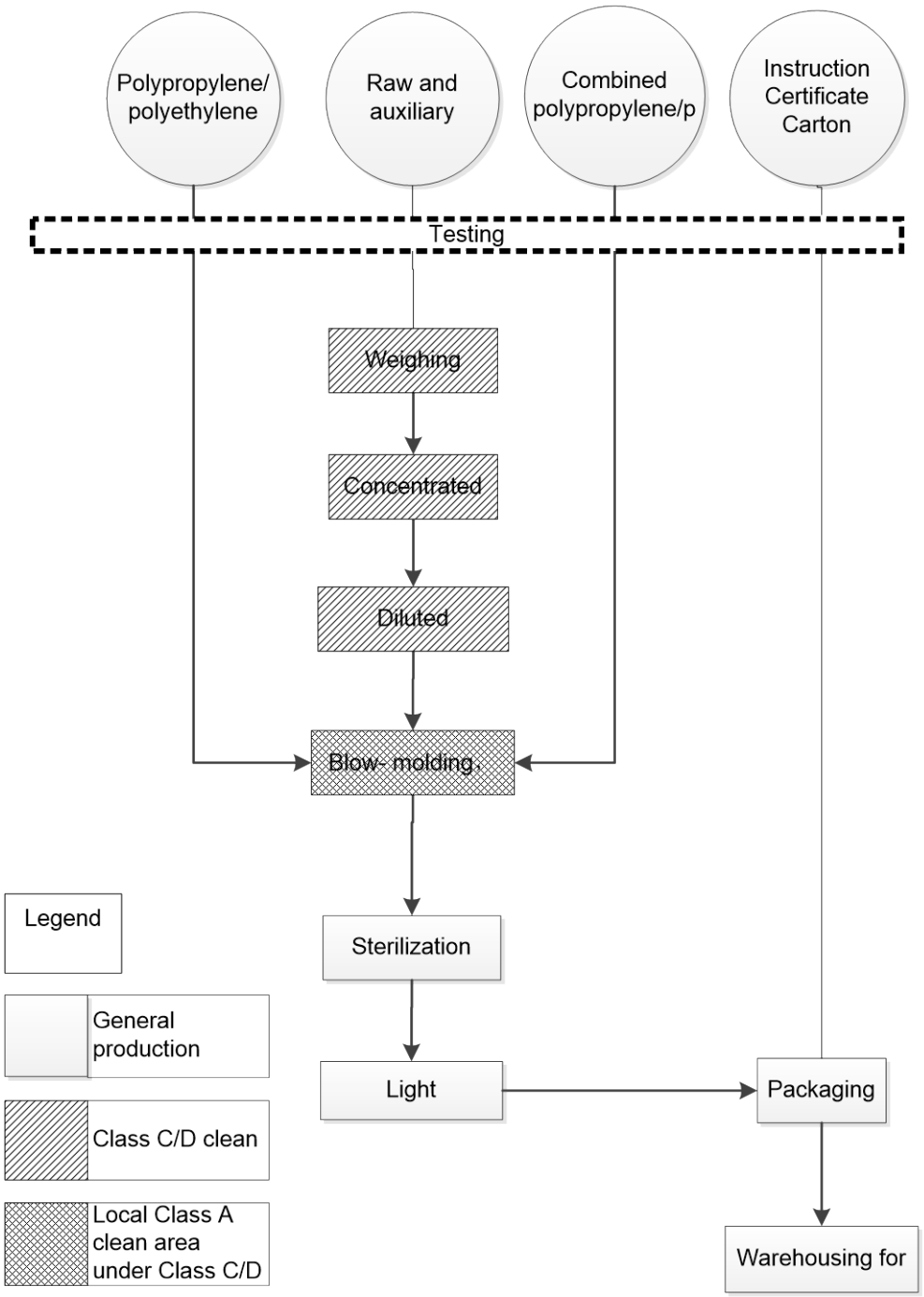
Position	Method	Requirement
Personnel	Contract plate/gloves	Max: 10cfu/25cm^2
	Full contact plate	Max: 40cfu/25cm^2

5.3 Production process

BFS technology has been widely used in the production of eye drops, small solution injection, inhalant, cleaning agent, infusion and other preparations. In comparison with traditional infusion production process, BFS equipment completes the blow molding of container, drug filling and container sealing continuously in the same mold. Meanwhile, a separate air purification system is used to ensure that the product exposure area is sterile so as to realize effective control of contamination and human interference and improve the safety of infusion production. This section introduces the BFS processes for infusion production. For other production process of injections， please refer to Good Manufacturing Practice for Drugs. These processes comply with the technical requirements of sterile drugs-finally sterilized

drugs.

Schematic diagram for production process of BFS infusion



5.3.1 Preparation before production

The mold is an important part for the equipment to complete blowing and molding of plastic bag, drug filling and sealing. It is necessary to detect the running condition of mold closing unit and confirm whether the mold closing unit accurately and steadily operates on

stable linear track. Make sure that the plastic bag is blown, filled and sealed in the mold unit in one time and demoulding is completed successfully.

The vacuum system is an important public system of BFS equipment. The smooth and steady operation of vacuum pump and stable vacuum degree can ensure good blowing and molding of plastic bag and the leak tightness of the plastic bag. Before and during production, the head, neck, body, bottom and ring-pull of the plastic bag shall be considered as the important parameters for intermediate control to validate the operation status of the vacuum system.

The end filter of BFS equipment includes: Class A sterile air supply system, end filter of compressed air and end filter of solution tube. The equipment has Class A air supply system for environmental protection during BFS process. During the process of equipment verification and validation, the separate air supply system shall be verified and the filter shall be monitored regularly to ensure that the filling area environment complies with the process requirements; the end filter of compressed air and end filter of solution tube shall be detected for integrity.

BFS equipment has CIP/SIP system which provides CIP/SIP for all product tubes and discharge tubes. During SIP process, it is required to start sterilization timing when all the temperature probes reach the sterilizing temperature and automatically dry the filter for further use until set time.

In addition to the above requirements, it is necessary to validate the hydraulic system, pneumatic system, cooling water system and lubricating system regularly as per the equipment requirements during the Machine qualification.

5.3.2 Blowing, filling and sealing operation

The plastic pellets are sucked into the automatic feeder by vacuum system. The temperature of the screw of vacuum suction extruder shall be adjusted to comply with the set value with the accuracy of within 2°C to ensure that the extruded tube blanks are continuous and uniform with identical length and that the waste can be removed automatically. The equipment has a warning device for shortage of filling materials to ensure continuous operation of the equipment.

The mold is under airtight condition after cutting off the bag blank. The BFS mandrel system is used for blowing, filling and sealing; the head mold is closed for sealing. During the production, it is necessary to detect the product appearance to ensure the product is smooth, burr-free, extrusion-free, damage-free and bubble-free with clear writing and tick marks.

According to the design requirements, the BFS system may have additional outer cover welding process to meet the users' demand for clinical dosing and needle holding. An oscillator is additionally installed in the outer cover for timely and correctly delivering the cover to the guide bar of the welding machine to ensure no blocking of cover.

5.3.3 Leak detection

Leak detection refers to the seal integrity test for the container. The seal integrity damages of BFS infusion usually occur in the working process of container. The cover design of BFS infusion is associated with the risk of liquid leakage during use in the process of outer cover welding. Therefore, the research on the seal integrity of the container shall be emphasized in the life cycle of drugs, and the seal integrity verification as well as verifications for the most rigorous sterilization condition, microorganism invasion and vacuum state challenge shall be performed as required; the seal integrity test shall be performed for the production process after completing BFS processes.

The seal integrity test for BFS infusion is often performed in BFS processes using online and non-online tests. The online test is the most ideal and direct test method, of which the commonly used method is to test whether the container has defects using the principle of high voltage or pressure test. While the non-online test can adopt weighing method and vacuum test method.

5.3.4 Production process control

The production process control for BFS infusion shall be performed for all processes as per the GMP. Moreover, different intermediate control parameters shall be monitored, e.g. defect in container molding or connector, sealing, weight difference, material loading, liquid leakage (pressure-tolerance), etc.

5.4 Verification and validation

BFS technology is used in infusion production, whose advantage is to guarantee the safety of infusion production process by controlling the contamination and personnel interference in the production process. In various links such as product overall planning, product research, process design, equipment selection and engineering control, only verification, validation and requalification for operation process may realize the advantage above.

The verification and validation shall be performed for utilities including the air purification system, process water, clean compressed air, sterilization, product process and cleaning system in the workshop as per relevant regulations/guidance of direct-contact drug packaging materials and drugs.

The verification for BFS equipment shall include: design qualification (DQ), installation qualification (IQ), operation qualification (OQ) and performance qualification (PQ).

5.4.1 Design qualification

Design qualification refers to validating whether the reasonability of enterprise review design, technical parameters set in the equipment, the selected raw materials, materials used for BFS equipment, control system and the connection logicality of process system comply with the requirements of GMP.

5.4.1.1 Infusion bag

In addition to the appearance and overall dimensions meeting the design requirements, the design of infusion bag mainly focuses on the thickness of bag wall and thickness-thinness ratio of the same bag wall, smooth external surface of the bag, as well as accurate volume scale mark. Moreover, the change of sterilized bag type shall meet the design requirements under the given sterilization condition for labeling.

5.4.1.2 Material requirements

The materials used for BFS equipment need to focus on mold materials selection and selection of materials for solution-contact tubes. The material of the mold shall be the one made of high thermal conductivity copper and alloy steel with stable physicochemical property, which does not fall off or contaminate the heat seal surface. It can guarantee good molding of infusion bag with smooth and burr-free surface and high accuracy; The material of sterile solution-contact tube shall be 316L stainless steel, whose inner surface is electro-polished, of which fineness shall be <0.7μmRa. Other materials such as hose and sealing gasket shall be non-toxic, with stable physicochemical property, not producing chemical reaction with solution or releasing particles, and can tolerate the temperature of CIP/SIP pure steam sterilization. They are durable, anti-aging and not easy to deform. Ducts, valves and pipes can resist sterilization process without any dead space or blind tube. The pipes and valves are equipped with quick clamp for removing and cleaning, so as to guarantee no residue after the content is discharged

5.4.1.3 Control requirements

The equipment control system is a key part to implement the control of process and parameter of BFS equipment. It is generally controlled by the whole-course PLC. For design qualification for the control system, one is to confirm the design has met the requirements as per the requirements of URS. And on the other hand, confirm the implementation of the control system is safe and reliable, which may protect all electrical and mechanical components. The electrical and mechanical self-locking and interlock systems shall control all the operations of the equipment, where no omits are allowed.

5.4.1.4 Extruder system

The extruder system includes: automatic feeding device, extruder and the control system for tube blank wall thickness. The automatic feeding device can automatically add plastic particles into the extruder. In case of lack of particles, it may alarm so as to guarantee continuous, safe and steady feeding. The extruder sets up the melting temperature according to different plastic particles and the equipment requires the cooling water system with accurate temperature control to guarantee stable temperature with small fluctuations in the heating zone; The even wall thickness of the infusion bag is guaranteed by controlling the extrusion head clearance to make the extruded tube blank with different thickness at different parts.

5.4.1.5 Bag molding, filling and sealing

The equipment completes blow- molding, filling and sealing in one time, which is the core to achieve three-in-one bag manufacturing, filling and sealing. The BSF system generally includes mandrel unit and time-pressure metering control. The mandrel unit is designed to be in the mandrel tube, which may inlet compressed air to blow, while the vacuum start to help mold the infusion bag and fill the solution through the mandrel accurately. Due to exact filling based on constant filling time and pressure, the time-pressure meter can set up the filling time of each mandrel and the filling pressure of the buffer tank, so as to adjust the loading at any time.

5.4.1.6 CIP/SIP

It may automatically clean and sterilize all pipelines and discharge pipelines and its online sterilization process is controlled by temperature and time. During online sterilization, only when the temperatures of the 24 temperature testing points reach the sterilization temperature at the same time, will the sterilization start. If the temperature of any testing point does not reach the required one, the sterilization fails and this process shall be repeated as required.

5.4.1.7 Terminal filter unit

Supply sterile air of class A locally: collect the ambient air in the area where the equipment is, deliver it to the mandrel filling zone after precise filtration, and guarantee the cleanness level required in the filling.

5.4.1.8 Welding cap unit

It is divided into welding cap infusion bag and non-welding cap infusion bag according to the appearance design of the infusion bag. The welding cap infusion bag equipment provides cover conveyor and hopper oscillator; the welding machine can meet the welding requirements of the maximum production speed, accuracy and tightness without leakage.

5.4.2 Installation qualification

Confirm that the host installation, connection part, electric circuit and instruments of the supplier meet the design requirements, complying with the requirements of enterprise products, production process, equipment maintenance, cleaning and disinfection. Moreover, the IQ also provides some available information and necessary suggestions, so as to confirm the operation of equipment or system.

IQ shall focus on the following items:

5.4.2.1 Host installation

Perform acceptance test on the equipment for the key design performance indicators. At the same time, validate the design requirements on the equipment by commissioning. Generally, enterprises will perform the qualification during the acceptance test. Therefore, the IQ organized by enterprises is mainly intended to validate that the installed complete machine has been adjusted horizontally and the track center line of the whole production line has been aligned in a straight line to reach stable operation state.

5.4.2.2 Complete machine connection and utility system installation

Confirm that all the parts are connected tightly and reliably without looseness. all the pipelines are connected tightly without looseness or leakage, the protective cover of main

moving parts is well installed, the safety gate of the equipment peripheral is installed correctly and securely, and anchors are free from looseness. The track of complete machine is connected smoothly, and no dead space is in the installation connection, which is helpful for cleaning and disinfection.

5.4.2.3 Water, Power and Air

Check that the connection of the electric circuit is consistent with the circuit diagram of the equipment and meets the requirements. The connection of the electric circuit is secure, the instruments are installed, and insulation protection, emergency stop button and alarm system are all in good condition. The cooling water and compressed air required for the operation have been prepared, the compressed air for tube blank support, blowing and filling are filtrated through a 0.2um filter, and various indexes meet the design requirements.

5.4.3 Operation qualification

On the basis of IQ meeting the requirements, OQ for the equipment shall be performed. The equipment and system are commissioned to proper working state so as to check the stability of various parameters, the production of accepted products and safety guarantee in the equipment operation, to ensure each system of the equipment operates steadily and operation parameters meet the design requirements.

BFS equipment operation qualification items:

5.4.3.1 Mold closing unit

Firstly, confirm that the mold closing unit operates accurately and steadily on the stable linear track, the closing and opening actions of the mold achieve the ideal state, the plastic bag can be blown, filled and sealed on the mold unit in one time, and the demolding process successfully completes after opening the mold.

5.4.3.2 Hydraulic system

The hydraulic pump operates steadily, its temperature is consistent with the set value and the relevance between the hydraulic system and the safety gate is valid; the driving parts of the equipment moves accurately and steadily (e.g. mold closing unit).

5.4.3.3 Vacuum system

For the vacuum system of BFS equipment, in addition to completing the equipment operation, it also conducts a comprehensive evaluation on the design parameters, actual operation as well as plastic granule performance and other associated factors through operation qualification due to its close relevancy with the head, neck, body, bottom and ring-pull of the infusion bag during the molding process of the container.

5.4.3.4 Water cooling system

The water cooling system of BFS equipment distributes the cooling water to various pipe systems via the flow distribution system. During the equipment operation, check whether the temperature of cool water at water use site is within the setting range and whether there is any alarm for temperature and flow.

The water cooling system used for mold cooling is a key factor to affect the container molding in the BFS operation, such as: cooling molding of the head, neck, body, bottom and ring-pull of the infusion bag. It shall be dynamically verified during the equipment operation to ensure the parameter design is reasonable and the operation is steady.

5.4.3.5 Extruder system

The extruder system shall control the hot melting of plastic pellets , continuous extruding of the tube blanks, wall evenness and length consistence. The parameters above are closely associated with the temperature set value and stability of the extruder screw. The index deviations shall be repeatedly confirmed in the operation process, while it is required to confirm that the automatic suction device can timely supplement polypropylene plastic particles to the extruder hopper and there a warning for lack of feedings.

5.4.3.6 Bag manufacturing, filling and sealing

The key for the application of BFS technology in the infusion production is that the BFS equipment can complete blowing, filling and sealing in one time in the operation process. During OQ, check the adjustment of filling load, loading and leakage when the equipment is in continuous operation; the appearance of the filled product is smooth without bur, extrusion, bubble or damage, and check whether scale mark is legible.

5.4.3.7 CIP/SIP

The online cleaning and sterilization (CIP/SIP) of BFS equipment is an automatic control unit, which is linked with the main equipment control system. OQ dynamic check equipment performs CIP/SIP for all pipelines and discharge pipelines. The time of CIP/SIP achieves the set value, which enables next SIP automatically. Start timing when all temperature probes achieve the sterilization temperature, and achieve the setting time; the drying will be performed for the filter after checking the sterilization.

In the process of OQ, operation qualification shall also be performed for cutting unit, bag transfer, terminal filter, exhaust discharge, welding cap unit and output station.

The OQ for BFS equipment will be performed for 4 hours continuously. Observe whether the operation at each station during operation meet the requirements above.

5.4.4 Performance qualification

By continuous trial production, filling with water for injection and operating for 4h continuously, dynamic monitoring shall be performed for suspended particles in Grade A area and check the appearance and dimension, bag weight, welding cap effect, drop test and visible foreign matters for the bag quality at 5min after start-up, 2h after operation and 5m before completion, respectively. After completing continuous operation, conduct CIP and SIP, fill with water for injection, take samples of the filled liquid and detect the microbial limit.

6 Raw Material pellets and Sealing System Component of BFS Infusion Package

6.1 Plastic pellets

The plastic pellets used in BFS infusion packages include polypropylene and polyethylene. For application, applicable plastic pellets shall be chosen according to the nature of the drug and based on the scientific research evaluation and verification & validation.

Besides the current relevant guidance, the plastic pellets shall meet the requirements for the following indicators.

6.1.1 Density

The density of the plastic pellets will affect the barrier property of the infusion container directly and the corporations shall select the plastic pellets conforming to the process conditions of the infusion products based on the technical requirement.

The density of polypropylene (PP) **pellets** used for BFS infusion package is 0.86-0.91g/cm^3 and 0.91-0.937g/cm^3 for low-density polyethylene (LDPE) granule.

6.1.2 Antioxidant

Antioxidant is a kind of chemical substance. A small amount of antioxidant in polymer system will delay or inhibit the polymer oxidation so as to prevent the aging of the polymer and extend its service life; therefore, antioxidant is a common additive for plastic package processing.

The antioxidants added to the polypropylene plastic **pellets** of BFS infusion package should meet the requirement of the type of antioxidant in the European Pharmacopoeia. They may contain at most 3 antioxidants with total content no more than 0.3%. And the polyethylene particles shall contain no additive [4].

The manufacturers can develop their own standard by referring to the Standard for Pharmaceutical Packaging Materials YBB and the European Pharmacopoeia concerning the

testing methods and limit specifications of the antioxidant of polyolefin **pellets** used for infusion products, combining with the selected plastic pellets and research data on the product compatibility.

6.1.3 Melt index

The melt index reflects the melting property of the plastic pellets. In order to ensure the repeatability of the bag making process, the melt index of the particle should be controlled.

6.1.4 Biological indicator of plastic pellets

The BFS infusion container is an aseptic container, and the biological indicators, such as cytotoxicity, skin sensitization, intracutaneous irritation, acute systemic toxicity and hemolysisof the plastic pellets used for production should meet the specification.

6.1.4.1 Cytotoxicity

Test as per the test for cytotoxicity (YBB00012003-2015), with method IV, The result shall meet the specification.

6.1.4.2 Skin sensitization

Test as per the test for skin sensitization (YBB00052003-2015); the sensitization response shall be no greater than Grade I.

6.1.4.3 Intracutaneous irritation

Test as per the test for intracutaneous irritation (YBB00062003-2015), and there should be no stimulation reaction.

6.1.4.4 Acute systemic toxicity

Test as per the test for acute systemic toxicity (YBB00042003-2015), and it shall be free of acute systemic toxicity.

6.1.4.5 Hemolysis

Test as per the test for hemolysis (YBB00032003-2015), and the hemolysis ratio should meet the specification.

6.2 BFS infusion container

The BFS infusion container shall be applicable to the intended clinical use of the packaged drugs. During the product development, the container shall be subject to evaluation and research concerning the protective effect, compatibility, safety and functionality as per relevant technical requirements.

Integrated polypropylene (polyethylene) infusion bag is an important packaging component of the BFS infusion package system. The infusion bag adopts BFS technology with blowing, filling and sealing processes completed all at once in the closed mold under the protection of Class A air shower to form a sealed container, which is different from the other plastic packages manufactured with the two-step method. As a result, such bag is named as integrated polypropylene (polyethylene) infusion bag.

6.2.1 Protective effect of integrated polypropylene (polyethylene) infusion bag

Generally, the protective effect of the packaging container will be confirmed by research of its sealing integrity and temperature adaptability, which is the basic content in drug stability research throughout the life cycle of drug process design, commercialized production process research, drug shelf life stability research, etc. As for the large volume injection, apart from the packaging materials meeting the product process requirement, the biggest challenge for the container is that at the infusion production and product storage stage, the packaging materials shall meet the requirements of barrier property and sterile protective barrier so as to meet the intended safety requirement.

6.2.1.1 Sealing integrity of integrated polypropylene (polyethylene) infusion bag

Generally the methylene blue solution permeability, microbial invasion and other tests are used to confirm the integrity of the sealing of integrated polypropylene (polyethylene) infusion bag during production so as to determine the compliance of the packaging container with the production process.

6.2.1.2 Temperature adaptability of integrated polypropylene (polyethylene) infusion bag

The temperature adaptability of integrated polypropylene (polyethylene) infusion bag focuses on the investigation of the sealing integrity of the packaging container under different storage conditions and the measurement of the pressure resistance, dropping resistance and transparency of the product under different temperatures.

6.2.2 Compatibility of Integrated polypropylene (polyethylene) infusion bag

The compatibility of integrated polypropylene (polyethylene) infusion bag focuses on the investigation of the impact of packaging materials on the drug, the degree of the migration of the materials and additives used by the packaging container into the drug, and the adsorption degree of the packaging material of the active ingredients and functional excipients, certifying that there is no serious interaction between the packaging materials and the drug, which may result in the change of drug effectiveness and stability or safety risk by preliminary stability test, acceleration test and long-term stability test, so as to confirm that the packaging materials can ensure the stability of the drug quality and own good compatibility with the drug.

The main research on the compatibility between drug and packaging material include: extraction test, interaction research (including migration test and absorption test) and safety research. Refer to Technical Guidance for Study of Compatibility between Chemical Injections and Plastic Packaging Materials for the technical requirement.

For integrated polypropylene (polyethylene) infusion bag migration test, according to clause 3.1.6 of the 8th ed. European Pharmacopeia (Polypropylene for Containers for Parenteral and Ophthalmic Preparations), the content of individual antioxidant shall not exceed 0.3%, and the total content shall be no more than 0.3%.

Absorption test is the research for investigating whether the active ingredients or excipients will be adsorbed or immersed into the packaging materials to cause quality change of the preparations during usage of the integrated polypropylene (polyethylene) infusion bag.

6.2.3 Safety of integrated polypropylene (polyethylene) infusion bag

The investigation of the safety of integrated polypropylene (polyethylene) infusion bag refers to the analysis and summarization of the type and content of the extractables and leachables based on the information of the extractables obtained by extraction test and leachables information obtained by migration test to conduct necessary compound attribution or structure identification and attribute its safety risk level based on the structure type and to conduct safety evaluation through bacterial endotoxin, cytotoxicity, intracutaneous stimulation, acute systemic toxicity and hemolysis tests.

6.2.4 Functionality of integrated polypropylene (polyethylene) infusion bag

The functionality of integrated polypropylene (polyethylene) infusion bag refers to the ability of the infusion product to realize export and infusion of preparations via the function of the container during clinical application to ensure the safety and effectiveness of the drug.

Generally, the functionality of integrated polypropylene (polyethylene) infusion bag investigates the puncture force of the product, impermeability of the puncture site, evacuation test, blood return test, suspension force, etc.

6.3 Outer cover

The infusion packages can be subject to the product design of multiple types as per the

various enterprise demands. As the clinical application scope is increasingly expanding, the requirement for the design and function of the outer cover of the infusion bag is increasing. Elastomer polypropylene/polyethylene combined cover (easy to tear) is the most widely used and safe BFS infusion outer cover. It will be fused with the bag body during production through hot melting to form a sealing system to ensure the leak tightness while exporting the liquid.

7 Quality Features of BFS Infusion

7.1 Insoluble particles

The insoluble particles of BFS infusion shall meet the requirements of Chinese Pharmacopoeia at least, where the insoluble particle of basic infusion shall meet the following index:

Item	BFS basic infusion	Chinese Pharmacopoeia
≥5μm/ml	≤10 particles/ml	—
≥10μm/ml	≤5 particles/ml	≤25 particles/ml
≥25μm/ml	≤1 particles/ml	≤3 particles/ml

7.2 Bacterial endotoxin

It shall be tested as per the method in the Chinese Pharmacopoeia and meet relevant requirement. For the basic infusion produced with BFS technology, the content of bacterial endotoxin shall be limited to 0.25EU/ml.

Instructions for Compilation of Technical Guideline of Infusion Production of Blow Fill Seal (BFS)

I. Overview

With the advance of the pharmaceutical equipment and intellectualization level, the drug safety and product quality are guaranteed effectively. Ministry of Industry and Information Technology (MIIT) specified explicitly in the 12th Five-Year Plan for Medical & Pharmaceutical Industry in 2012, “to encourage the application of advanced equipment contributing to the improvement of the production quality, and encourage the introduction, application, digestion and absorption of the ‘blow-fill-seal’ technology”. The newly issued GMP (2010 version) lists the BFS technology in Chapter V, “Sterile Drug” Annex and specifies the management of the technology and its production process.

Some manufacturers have applied the BFS technology to infusion production in China, and the BFS technology has been verified helpful for improving the safety of the infusion products.To boost and regulate the application of the BFS technology in the infusion manufacturing in China, to address the hidden safety troubles of the infusion products during production and improve the infusion product quality effectively, in June 2015, China National Pharmaceutical Packaging Association (CNPPA) and China Pharmaceutical Association of Plant Engineering (CPAPE) organized and established a project team for drafting the Technical Guideline of Infusion Production of Blow Fill Seal (BFS) (hereinafter referred to as the Guideline) and held the kick-off meeting. In the meeting, a decision was made to establish technical guidance for the BFS technical features, working principle, requirement for production and BFS basic infusion product standard based on the previous studies and the experience in the application of the BFS technology in China.

II. Instructions for Establishment and Requirements of the Technical Guidance Project

1. Name

Based on the purpose of formulating the “Technical Guidance”, combining with the issued descriptions on the blow-fill-seal (BFS) technology at home and abroad, the name is defined as Technical Guideline of Infusion Production of Blow Fill Seal (BFS).

2. Scope of application

As a supplement to the GMP and other industrial technical standard, the “Technical Guidance” serves as guidance for infusion products produced with BFS technology and requiring terminal sterilization.

3. Terms and definitions

The guideline is prepared as per the description of the blow, fill and seal (BFS) technology in 2010 version GMP, USP and EU GMP.

The names to be defined and the technical terms to be distinguished from others are defined or explained in the “Technical Guidance”.

4. Technical features of infusion production of blow fill seal (BFS)

The quality superiorities of the BFS infusion production will be realized through the BFS equipment。 Therefore, the “Technical Guidance” highlights the core technology of the equipment and the plant design and other hardware systems for ensuring the equipment operation based on the product specification supplied by the supplier and the EU standard, including sterile filling system designed based on the safety of the large volume injection，cleaning in place and sterilization in place (CIP/SIP);， sealability of BFS infusion technology; self-evacuation performance of the integrated container produced with the BFS technology.

5. Technology of infusion production of blow fill seal (BFS)

According to the requirement for the design of the BFS equipment, this section focuses on the working principle, clean workshop and air purification system, process and main operations with special emphasis on the control and validation of the production process.

6. Raw material particles and sealing system of BFS infusion package

In accordance with the Technical Guideline for Study of Compatibility between Chemical Injections and Plastic Packaging Materials, this Guideline regulates the packaging system, and commonly used polyethylene and polypropylene plastic particles that may affect the quality of BFS infusion products. Its main content includes plastic particles, BFS infusion container, and outer cover.

7. Quality features of BFS infusion

Through the research on the system quality of the BFS technology infusion products, the items with safety superiorities confirmed by the test are listed in the Guideline, including insoluble particle, and bacterial endotoxin.

Based on the demands of the use safety of the infusion and the testing data of multiple batches of basic infusion, the limits of insoluble particles and bacterial endotoxin are confirmed ,which are stricter than those in the current Chinese Pharmacopoeia.

8. References

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