



Technical Report No. 77

第77号技术报告

The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

运用吹-灌-封技术制造无菌药品



PDA The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology Technical Report Team
美国注射剂协会运用吹-灌-封技术制造无菌药品技术报告团队

Authors
作者

Martin Haerer, Holopack Verpackungstechnik, Team Co-leader Tim Kram, Rommelag USA, Inc.
(BFS IOA)

Kenneth Muhvich, Micro-Reliance, LLC, TeamCo-leader Stacey Largent, Merck
(PDA)

Peter Åkerman, AstraZeneca

Jesper Laursen, MELITEK A/S

Jaime Blanco, Genentech

Matt Payne, Ritedose Corporation

Nermin Cehajic, KemPharm, Inc.

Patrick Poisson, United Therapeutics

Kevin Downey, Teva Pharmaceutical

Chuck Reed, Reeds and Rushes, LLC

Ty Duginske, Baxter

Otto Schubert, Maropack AG

Andrew Goll, Weiler Engineering, Inc.

Jerry Webb, Nephron Pharmaceutical Corporation

This technical report was developed and written in cooperation with the Blow-Fill-Seal International Operators Association (BFS IOA). The content and views expressed in this technical report are the result of a consensus achieved by the PDA authoring task force and are not necessarily views of the organizations they represent.

该技术报告是与吹-灌-封国际运营商协会合作制定和编写的。本技术报告中所表达的内容和观点是美国注射剂协会创作工作组达成的共识的结果，并不一定意味着他们所代表的组织。

The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

使用吹-灌-封技术制造无菌药品

Technical Report No. 77

第77号技术报告

ISBN: 978-0-939459-94-0

© 2017 Parenteral Drug Association, Inc.

©2017注射剂药品协会，股份有限公司

All rights reserved.

保留所有权利

Table of Contents

目录

1.0 Introduction.....7

第 1.0 章-介绍.....7

1.1 Purpose.....7

第 1.1 节-目的.....7

1.2 Scope.....7

第 1.2 节-范围.....7

1.3 BFS Process Outline.....8

第 1.3 节-吹-灌-封工艺概况.....8

2.0 Glossary of Terms.....10

第 2.0 章-术语.....10

2.1 Abbreviations.....11

第 2.1 节-缩写.....11

3.0 BFS Equipment.....12

第 3.0 章-吹-灌-封设备.....12

3.1 Shuttle Type Machines (Open Parison Process).....12

第 3.1 节-往复式机械(开放型胚工艺).....12

3.2 Rotary Filling Machines (Closed Parison Process).....13

第 3.2 节-旋转式灌装机械(密闭型胚工艺).....13

3.3 Additional Applications.....14

第 3.3 节-其它应用.....14

4.0 Benefits & Special Considerations of BFS Technology.....16

第 4.0 章-吹-灌-封技术的优点及特殊考虑.....16

4.1 Benefits.....16

第 4.1 节-优点.....16

4.2 Special Considerations.....16

第 4.2 节-特殊考虑.....16

5.0 Design.....18

第 5.0 章-设计.....18

5.1 Product Design.....18

第 5.1 节-产品设计.....18

5.1.1 Aseptic Processing versus Terminal Sterilization.....18

第 5.1.1 小节-无菌工艺与最终灭菌.....18

5.1.2 Terminal Sterilization.....18

第 5.1.2 小节-最终灭菌.....18

5.1.3 Polymer.....18

第 5.1.3 小节-聚合物.....18

5.1.4 Product Applications.....20

第 5.1.4 小节-产品应用.....20

5.1.5 Container Design.....21

第 5.1.5 小节-包装容器设计.....21

5.1.6 Secondary Packaging.....22

第 5.1.6 小节-第二层包装.....22

5.2 Equipment Design.....22

第 5.2 节-设备设计.....22

5.2.1 General.....22

第 5.2.1 小节-总体要求.....22

5.2.2 Product Pathway.....23

第 5.2.2 小节-产品通道.....23

5.2.3 Mold Design.....24

第 5.2.3 小节-模具设计.....24

5.2.4 Vacuum System.....24

第 5.2.4 小节-真空系统.....24

5.2.5 Deflashing.....24

第 5.2.5 小节-修边.....24

5.2.6 Equipment Monitoring.....25

第 5.2.6 小节-设备监控.....25

5.3 Facility Design.....25

第 5.3 节-设施设计.....25

5.3.1 Aseptic Processing Area.....25

第 5.3.1 小节-无菌工艺区.....25

5.3.2 Polymer Storage and Distribution.....26

第 5.3.2 小节-聚合物储存和分发.....26

5.3.3 Utilities.....26

第 5.3.3 小节-公用设施.....26

6.0 Operational and Qualification Considerations.....28

第 6.0 章-运行与确认注意事项.....28

6.1 BFS Process Validation and Advanced Technology.....28

第 6.1 节-吹-灌-封工艺验证与先进技术.....28

6.2 Evaluating Critical BFS Process Parameters for Quality and Sterility..... 28

第 6.2 节-质量和无菌相关的吹-灌-封关键工艺参数评估 28

6.3 Quality Attribute Critical Process Parameters 30

第 6.3 节-质量属性关键工艺参数..... 30

6.3.1 Air Flow Rate..... 30

第 6.3.1 小节-空气流速..... 30

6.3.2 Main Mold Vacuum Delay Timer..... 30

第 6.3.2 小节-主模具的真空延时器..... 30

6.3.3 Bottle Blowing Timer..... 30

第 6.3.3 小节-吹瓶延时器..... 30

6.3.4 Seal Mold Vacuum Delay Timer..... 31

第 6.3.4 小节-密封模具真空延时器..... 31

6.4 Sterility Assurance-related Critical Process Parameters..... 31

第 6.4 节-无菌保证相关的关键工艺参数..... 31

6.4.1 Fill Nozzle Down Delay Timer..... 31

第 6.4.1 小节-灌装头下降延时器..... 31

6.4.2 Bottle Blowing Timer..... 31

第 6.4.2 小节-吹瓶延时器..... 31

6.4.3 Bottle Vent Timer..... 31

第 6.4.3 小节-瓶排气延时器..... 31

6.4.4 Master Fill Timer..... 31

第 6.4.4 小节-主灌装延时器..... 31

6.4.5 Individual Fill Timers..... 31

第 6.4.5 小节-单个灌装延时器..... 31

6.4.6 Fill Nozzle Up Delay Timer..... 31

第 6.4.6 小节-灌装头上升延时器..... 31

6.5 Implementation..... 32

第 6.5 节-执行..... 32

6.6 Pre-process Preparation of Critical Areas..... 35

第 6.6 节-关键区域生产前准备..... 35

6.6.1 Sanitization of Machine Surfaces..... 35

第 6.6.1 小节-设备表面卫生..... 35

6.6.2 Cleaning of Product Contact Surfaces..... 35

第 6.6.2 小节-产品直接接触表面清洁..... 35

6.6.3 Sterilization of Product Pathway..... 35

第 6.6.3 小节-产品通道灭菌..... 35

6.7 Product Validation..... 36

第 6.7 节-产品验证..... 36

6.7.1 Container Closure Integrity Testing..... 36

第 6.7.1 小节-容器密封完整性试验..... 36

6.7.2 Leak Detection..... 37

第 6.7.2 小节-检漏..... 37

6.7.3 Campaign Fill/Holding Time..... 37

第 6.7.3 小节-集中灌装/工艺持续时间..... 37

6.7.4 In-Process Sampling..... 37

第 6.7.4 小节-中控取样..... 37

6.8 Equipment Validation..... 38

第 6.8 节-设备验证..... 38

6.8.1 Critical Zone Control..... 38

第 6.8.1 小节-关键区域控制..... 38

6.8.2 Air Shower Design (Open Parison Machines)..... 38

第 6.8.2 小节-风淋系统设计(管型胚开放式机型)..... 38

6.8.3 BFS Machine Room Environment..... 38

第 6.8.3 小节-吹-灌-封一体机房间环境..... 38

6.8.4 Filtration Configuration..... 39

第 6.8.4 小节-过滤系统配置..... 39

6.8.5 Filter Integrity..... 39

第 6.8.5 小节-过滤器完整性..... 39

6.8.6 Air/Gas Filtration..... 39

第 6.8.6 小节-空气/气体过滤系统..... 39

6.8.7 Aseptic Compounding and Other Pre-BFS Product Sterilization Approaches..... 39

第 6.8.7 小节-无菌混合和其它吹灌封前产品灭菌方法..... 39

6.8.8 Environmental Monitoring..... 40

第 6.8.8 小节-环境监测..... 40

6.8.8.1 BFS Shuttle Machines..... 40

第 6.8.8.1 小节-往复式吹-灌-封一体机..... 40

6.8.8.2 BFS Rotary Machines..... 41

第 6.8.8.2 小节-旋转型吹-灌-封一体机..... 41

6.8.9 Extrusion Considerations..... 41

第 6.8.9 小节-挤出注意事项..... 41

6.8.10 Controls..... 41

第 6.8.10 小节-控制..... 41

6.8.11 Downstream Process..... 41

第 6.8.11 小节 - 下游工艺 41

6.9 Process Simulation (Media Fill) for Aseptic Filling Lines..... 42

第 6.9 节 - 无菌灌装线的工艺模拟(培养基灌装)..... 42

6.9.1 Design..... 42

第 6.9.1 小节 - 设计 42

6.9.2 Interventions..... 43

第 6.9.2 小节 - 干预 43

6.10 Gowning..... 44

第 6.10 节 - 更衣 44

6.11 Facility Validation 44

第 6.11 节 - 设施验证 44

7.0 Quality Risk Assessment 45

第 7.0 章 - 质量风险评估 45

7.1 Product Contamination 45

第 7.1 节 - 产品污染 45

8.0 References..... 48

第 8.0 章 - 参考文献 48

9.0 Appendix I: Example of a Quality Risk Assessment..... 51

第 9.0 章 - 附件一：质量风险评估示例..... 51

10.0 Appendix II: Environmental Particle Monitoring Levels..... 59

第 10.0 章 - 附件二：环境微粒监控级别 59

1.0 Introduction

第 1.0 章-介绍

Blow-Fill-Seal (BFS) technology is the integration of plastic blow molding and aseptic filling on a single machine. The technology has been used in manufacturing liquid pharmaceutical product since the 1960s. The final container is created within the machine just prior to aseptic filling and hermetically sealed immediately after filling in one continuous, automated operation. It provides a unique combination of flexibility in packaging design and enhanced sterility assurance and has been accepted worldwide for both aseptic and terminally sterilized liquid products. BFS technology is currently used in more than 50 countries (1-4).

吹-灌-封技术是将塑料吹塑与无菌灌装整合在一台机械上。该技术自20世纪60年代以来一直用于液体药物制造。最终的容器在无菌灌装之前在机械内创建，并且在填充一个连续的自动操作之后立即进行密封。它提供了包装设计灵活性和强化无菌保证独特组合，并已被世界各国无菌与最终灭菌的液体产品所接受。吹-灌-封技术目前用于50多个国家(1-4)。

Considered “advanced aseptic processing,” BFS technology provides advantages over conventional filling when designing controls for the processes. The advanced aseptic processing designation is supported by various experiments that challenged BFS systems through contamination loading of both the surrounding environment and plastic components (5).

考虑到“先进无菌工艺”，吹-灌-封技术在设计过程控制时，与传统灌装比提供了优势。先进无菌加工指定得到各种实验的支持，这些实验通过周边环境和塑料部件的污染负荷对吹-灌-封系统产生挑战(5)。

BFS processing offers a number of other advantages as well. It supports a simplified supply chain, which can result in a level of quality and control of primary packaging materials (i.e., resin only) that is not practical in pre-formed (glass, plastic, etc.) vial/stopper filling. And due to the rapid cool-down following container formation, biological and protein-based products can be safely processed in BFS machines. The equipment supports single-dose container packaging with flexibility for frequent changeover if short production runs are desired. BFS processing is also capable of incorporating pre-molded and pre-sterilized components (inserts) in the basic container, such as silicone stoppers for parenteral applications and injection-molded tip/cap inserts for metered drop control in multi-dose eye drop containers.

吹-灌-封工艺还提供了许多其他优点。其支持简化的供应链，由此可致不能实现预成型的西林瓶或胶塞灌装的内包装材料(玻璃、塑料等)一定水平的质量控制。并且由于容器形成后快速冷却，生物和蛋白质的产品可以在吹-灌-封机械中安全地加工。该设备支持单剂量容器包装，如果需要短期生产，可以具有频繁更换灵活性。吹-灌-封工艺还能够将预成型和预先灭菌的组件(插入物)结合在基本容器中，例如，用于注射的硅胶塞子，以及用于多剂量滴眼剂中的计量滴下控制的顶针盖。

1.1 Purpose

第 1.1 节-目的

The objective of this technical report is to provide recommendations specific to the operation of BFS technology for the manufacture of sterile pharmaceuticals (e.g., ophthalmic, parenteral, and inhalation). The intent is to provide supplemental information to assist the user with interpretation of international standards and regulatory guidance from the perspective of BFS operations. Consideration is given to specific aspects of BFS operations not covered in published information.

本技术报告的目的是提供专门用于制造无菌药物(例如，眼科剂型、注射剂型与吸入剂型)的吹-灌-封技术的建议。目的是提供补充信息，以帮助用户从吹-灌-封操作的角度解释国际标准和监管指导。对发布信息中未涵盖的吹-灌-封操作的具体方面进行了考虑。

1.2 Scope

第 1.2 节-范围

This technical report addresses considerations for BFS technology related to the installation and operation of the machinery and evaluation of related materials and final product containers. Support areas, such as laboratory, solution compounding, gowning airlocks, etc., are not considered specific to BFS and are not included within the scope of this document. This technical report is intended as a guide for the pharmaceutical industry and is not meant to supplant or duplicate any existing regulatory guidance. The content and views expressed in this technical report are the result of a consensus achieved by the members of the authorizing Task Force and are not necessarily the views of the organizations they represent.

本技术报告涉及与机械安装和运行相关的吹-灌-封技术的考虑，以及相关材料和最终产品容器的评估。辅助领域，如实验室、溶液配制、更衣气闸等，不被视为吹-灌-封所特有的，也不在本文件的范围之内。本技术报告旨在作为制药行业的指南，并不意味着取代或复制任何现有的监管指南。本技术报告中所表达的内容和意见是授权工作队成员达成的共识，不一定代表组织的意见。

1.3 BFS Process Outline

第 1.3 节-吹-灌-封工艺概况

BFS technology is a pharmaceutical primary packaging-filling process that combines three operations (container formation, filling, and closure) that are typically performed separately in conventional filling operations. BFS containers are formed from an extruded thermoplastic parison, filled with product, and then sealed in a continuous, integrated, highly automated operation. Originally developed for use in other industries, BFS technology has been adapted for use in the manufacture of sterile pharmaceutical, medical device, biological, and veterinary products. The two most common types of BFS machines are the shuttling machine (open or cut parison) and the rotary machine (closed parison), which are both considered in this document. All steps of the BFS process are conducted under highly classified conditions per current regulatory standards (1,2).

吹-灌-封技术是一种药品内包装灌装工艺，其结合了常规灌装操作中通常实施的三个操作(容器形成、灌装与密封)。吹-灌-封容器由挤出的热塑性型坯形成、灌装产品，然后以连续、整合的高度自动化操作密封。吹-灌-封技术最初用于其他行业，已经适用于无菌制药、医疗器械、生物制品与兽药产品的制造。吹-灌-封机械的两种最常见的类型是往复式(开放或切割型坯)以及旋转式机械(密闭型坯)，这两种机械都在本文中予以考虑。吹-灌-封工艺的所有步骤均按照目前的监管标准进行严格分类条件进行(1,2)。

In BFS processes, a thermoplastic polymer is used to form the primary container. Granulated polymer (plastic pellets) is supplied by a closed pathway via vacuum transfer. The system feeds polymer pellets into a standard plastic hot melt extrusion process. In the extrusion process, the polymer is heated to temperatures in excess of 170°C and subjected to pressures over 20,000 kPa (200 bar).

在吹-灌-封工艺中，采用热塑性聚合物形成内包装主容器。颗粒状聚合物(粒状颗粒)在封闭通道通过真空转移。该系统将聚合物颗粒送入标准塑料热熔体挤出工艺。在挤出过程中，将聚合物加热超过170°C的温度，并承受20,000kPa(200bar)以上的压力。

The temperature, pressure, and encapsulation within the plastic in the extruder reduce the probability that any contaminants (such as particulates, fungal and bacterial endospores, and endotoxins) may come in contact with the final filled product (6).

挤出机中的塑料的温度、压力与密闭减少了任何污染物(诸如，微粒、真菌、细菌芽胞、内毒素)可能与最终灌装产品接触的可能性(6)。

The plastic polymer is extruded into one or more continuous plastic tubes called parisons. Sterile filtered air or other gases are supplied through the extruder head at sufficient pressure to prevent the parisons from collapsing. The BFS process uses one of two mechanical methods to form the container(s): 1) vacuum on the mold only; or 2) a blowing process in combination with vacuum on the mold. Vacuum is employed with both methods to remove air around the container to aid in container formation. Containers larger than 30 mL typically require the addition of blowing with sterile air to complete the container formation.

将塑料聚合物挤出成一个或多个称为型坯的连续塑料管。除菌过滤的空气或其它气体以足够的压力通过挤压机头供应，以防止型坯坍塌。吹-灌-封工艺使用两种机械方法之一形成容器：1)仅在模具上真空;或2)与模具上的真空组合的吹塑工艺。两种方法都采用真空除去容器周围的空气以帮助容器形成。大于30mL的容器通常需要用无菌空气吹入来完成容器的形成。

During operations, the liquid formulation is supplied to the BFS system through a closed, sterile product pathway. The product pathway in BFS is an inherently safe design. It is completely closed and all product-contact surfaces, including the tank, hoses, filter housings, fill system, and filters (if provided, based on product specifications) are typically cleaned and sterilized in place before production begins.

在操作过程中，液体制剂通过封闭的无菌产品通道供应给吹-灌-封系统。吹-灌-封的产品通道是一种固有的安全设计。其完全密闭，所有产品接触表面，包括罐、软管、过滤器壳体、灌装系统与过滤器(如果根据产品规格提供)通常在生产开始之前进行清洁与灭菌。

The most common dosing mechanism is time pressure dosing (TPD). Other acceptable dosing systems include pumps and positive displacement systems. Upon completion of the dosing step, the top portion of the mold either closes (shuttle style) or rotates into compression (rotary style) to seal the container(s) and complete the BFS process.

最常见的定量机制是时间定量。其它可接受的定量系统包括泵与主动替代系统。在定量步骤完成后，模具的顶部部分闭合(往复式)或旋转挤压(旋转型)，以密封容器并完成吹-灌-封工艺。

The range of products that can be filled using BFS technology includes solutions, emulsions, suspensions, and low and high viscosity products, such as gels, creams, and ointments.

可以使用吹-灌-封技术灌装的产品范围包括溶液、乳液、悬浮液以及低粘度和高粘度产品，诸如凝胶、霜剂与软膏。

Typical solutions can be processed with integrated sterile filtration. Suspensions, emulsions, and highly viscous products can be processed with recirculation and without terminal filtration where a bulk sterilization process is implemented. In addition, BFS

containers can be terminally sterilized by steam and other methods when required. Certain large molecule products cannot be sterile filtered or terminally sterilized, however, thus aseptic transfer of the product to the BFS machine is required.

典型的溶液可以通过集成除菌过滤进行处理。当原料药进行了灭菌处理时，悬浮液、乳液和高粘度产品可以通过再循环和无最终过滤进行处理。此外，吹-灌-封容器可以在需要时通过蒸汽和其它方法进行最终灭菌。某些大分子产物不能进行除菌过滤或最终灭菌，因此需要将产品无菌转移至吹-灌-封机械。

BFS machine output (containers per hour) is dependent upon product and polymer physical characteristics, and container design. The number of containers produced per cycle is only limited by the number of containers that can be formed by the mold. The cycle time is dependent upon the product filling characteristics (e.g., viscosity, foaming) and the resin-dependent formation time required in mold.

吹-灌-封机械输出(每小时产出容器)取决于产品和聚合物的物理特性以及容器设计。每个循环产生的容器数量仅受到可以由模具形成的容器数量的限制。循环时间取决于所需的产品灌装特性(例如，粘度、发泡)及模具中树脂的形成时间。

2.0 Glossary of Terms

第 2.0 章-术语

Advanced Aseptic Process

先进无菌工艺

A process in which direct intervention with open product containers or exposed product contact surfaces by operators wearing conventional cleanroom garments is not required and never permitted (3).

不需要并且不允许使用穿着常规洁净室服装对开放产品容器或暴露产品接触面进行直接干预的工艺(3)。

Air Shower

风淋

A device fitted to a BFS machine which provides, at a minimum, a continuous flow of Grade A quality air supply over the filling needles and the point-of-fill. The air shower is also known as a nozzle shroud in shuttle type machines.

安装在吹-灌-封机械上的装置，至少在灌装针头与灌装点上至少提供A级优质空气供应的连续气流。风淋在往复式机械中也被称为喷口整流罩。

Critical Processing Zone

关键工艺区域

The location within the aseptic processing area in which product and product contact surfaces are exposed to the environment. The Critical Processing Zone is dependent upon machine design and includes, but is not necessarily limited to, the parison extrusion and cutting area, mold transfer area, air shower, and point-of-fill.

位于无菌工艺区域内的产品以及产品接触表面暴露到环境的位置。关键工艺区域取决于机械设计，包括但不限于型坯挤出与切割区域、模具转移区域、风淋以及灌装点。

Dynamic (in operation)

动态(操作中)

BFS machine line fully operational and filling, with the number of allowed operating personnel present as during normal running conditions.

吹-灌-封机械生产线全面运行与灌装，在正常运行条件下，允许存在一定数量的操作人员。

Mandrel

心轴

Specialized filling needles on certain BFS machines which also act to form the container.

一些吹-灌-封设备中用于容器成型的特殊灌装针头。

Parison

型胚

The “tube” of polymer extruded by the BFS machine from which the containers are formed.

由形成容器的吹-灌-封机挤出的聚合物的“管”。

Static (at rest)

静态(静止)

BFS machine line with conveyor belts at rest but with air shower and room ventilation in operation, extruder (heated, not running) and mold carriage in standby. No operating personnel present (1,2).

吹-灌-封机械生产与输送带静止，但风淋与房间通风在运行中，挤出机(加热，但不运行)并且模具托架待机状态。无操作人员(1,2)。

Zone of Protection/Machine Shroud

产品保护区/设备保护罩

A system fitted to a BFS machine to direct a flow of HEPA-filtered air over the Critical Processing Zone of the machine.

安装在吹-灌-封机械上的一个系统，用于将高效过滤器过滤的空气引入到机械的关键工艺区域。

2.1 Abbreviations

第 2.1 节-缩写

BFS	Blow-Fill-Seal 吹-灌-封
CIP	Clean-in-place 在线清洗
CCI	Container closure integrity 容器密封完整性
EtOH	Ethyl Alcohol 乙醇
HDPE	High density polyethylene 高密度聚乙烯
LDPE	Low density polyethylene 低密度聚乙烯
LVP	Large volume parenteral 大容量注射剂
PP	Polypropylene 聚丙烯
QbD	Quality by Design 质量源于设计
SIP	Sterilization-in-place 在线灭菌
SVP	Small volume parenteral 小容量注射剂
WFI	Water-for-Injection 注射用水

3.0 BFS Equipment

第 3.0 章-吹-灌-封设备

For both shuttle and rotary type BFS machines, the filling mandrels are typically cleaned prior to use with a clean-in-place (CIP) process followed by sterilization-in-place (SIP). The filling environment is maintained under Grade A conditions with HEPA- or sterile-filtered overpressure air (2).

对于往复式与旋转式两种吹-灌-封机械，灌装心轴通常在使用前用在线清洁工艺进行清洁，随后进行在线灭菌。通过高效过滤器，或者除菌过滤后的压缩空气来维持灌装环境达到A级(2)。

3.1 Shuttle Type Machines (Open Parison Process)

第 3.1 节-往复式机械(开放型胚工艺)

In an open parison process, a parison is continuously formed through the plastic extrusion process. A downward flow of sterile filtered air (parison support air) is passed through the parison to prevent the molten plastic tube from collapsing. Other gases (e.g., inert gases) can be substituted for the process air during the BFS process. The two halves of a mold close around the parison to form the body of the container. Simultaneously, the newly formed container in the mold is cut free from the parison by a “knife.” Vacuum is then applied to the mold to begin container formation and continues until formation is completed. Figure 3.1-1 illustrates an open parison BFS process.

在开放式型坯工艺中，通过塑性挤出工艺连续形成型坯。除菌过滤空气(型坯支撑空气)的向下流过型坯，以防止熔融塑料管塌陷。其它气体(例如，惰性气体)可以在吹-灌-封工艺中代替工艺空气。模具的两半靠近型坯，以形成容器的主体。同样地，模具中新形成的容器通过“刀”从型坯中切割出来。然后将真空物施加到模具上以开始容器形成并继续直至形成完成。图3.1-1说明了一个开放的型坯吹-灌-封工艺。



Step 1 Parison positioning

第一步：型坯定位

Step 2 Filling mandrel/nozzle insertion and container formation

第二步：填充轴心/喷嘴插入，容器成型

Step 3 Container filling with product

第三步：容器灌装产品

Step 4 Sealing

第四步：密封

Step 5 Container release

第五步：释放容器

Figure3.1-1Diagrammatic Representation of the Open Parison BFS Process

图3.1-1：开放式型坯的吹-灌-封工艺动态示意图

Once formed, the mold is rapidly transferred (shuttled) a short distance from beneath the parison head into the filling position (Figure 3.1-1, Step 1). This transfer typically takes less than one second. The filling mandrel (filling nozzle) is lowered into the plastic tube. At this point, sterile filtered air is supplied to complete container formation, if necessary (blowing step; Figure 3.1-1, Step 2). Subsequently, the container is filled with a metered volume of the product (Figure 3.1-1, Step 3). During the liquid fill, headspace gas is displaced from within the container, either through the mandrel or directly to the ambient atmosphere, depending on container configuration. The filling mandrel is then raised and the upper section of the mold (head/seal mold) is closed, hermetically sealing and automatically forming the still-hot plastic above the main mold (Figure 3.1-1, Step 4). The entire mold assembly then opens, releasing the formed, filled, and sealed container (Figure 3.1-1, Step 5).

一旦形成，模具将从型坯头下方快速转移(往复)到灌装位置(图3.1-1，第一步)。此转移通常需要不到一秒钟。灌装心轴(灌装喷嘴)下降到塑料管中。此时，如有必要，提供除菌过滤的空气以完成容器的形成(吹塑步骤；图3.1-1，第二步)。随后，容器中灌装了计量过体积的产品(图3.1-1，第三步)。在液体灌装期间，顶空气体在容器内转移，或者通过心轴或直接到环境大气，这决定于容器的配置。然后将填充心轴抬起，模具的上部(头部/密封模具)关闭，密封并自动地在主模具上形成仍然热塑料(图3.1-1，第四步)。然后，整个模具组件打开，释放形成的、灌装的并已经密封的容器(图3.1-1，第五步)。

Containers can be discharged from the machine as single containers, “packs” of several containers, or strips of multiple containers, depending on product requirements. After discharge, containers are mechanically deflashed (i.e., plastic waste removed) and separated. Deflashing typically occurs directly after discharge of the container. The deflashing unit can be placed in the clean room,

directly connected to the mold, or placed outside the clean room in the packaging area, just downstream of the BFS filling process, to minimize the potential for particulate generation in the cleanroom. This may depend on the resin type used and container design. Deflashing can be done in the cleanroom, if desired, because the container is already closed. BFS is a continuous process with one complete cycle typically completed within 10-20 seconds, depending on container design and fill-volume.

根据产品要求，容器可以作为单个容器、几个容器的“一组”，或多个容器条从机器排出。排放后，容器进行机械修边(即，去除塑料废物)并分离。通常在容器排出后直接进行修边。修边单元可以放置在洁净室中，直接连接到模具，或者放置在洁净室外面的包装区域，就在吹-灌-封灌装工艺的下游，以尽量减少洁净室中产生颗粒物的可能性。这可能取决于使用的树脂类型与容器设计。因为容器已经密闭，如果需要，可以在洁净室中进行修边。吹-灌-封是一个连续工艺，一个完整的循环通常在10-20秒内完成，具体取决于容器设计以及灌装量。

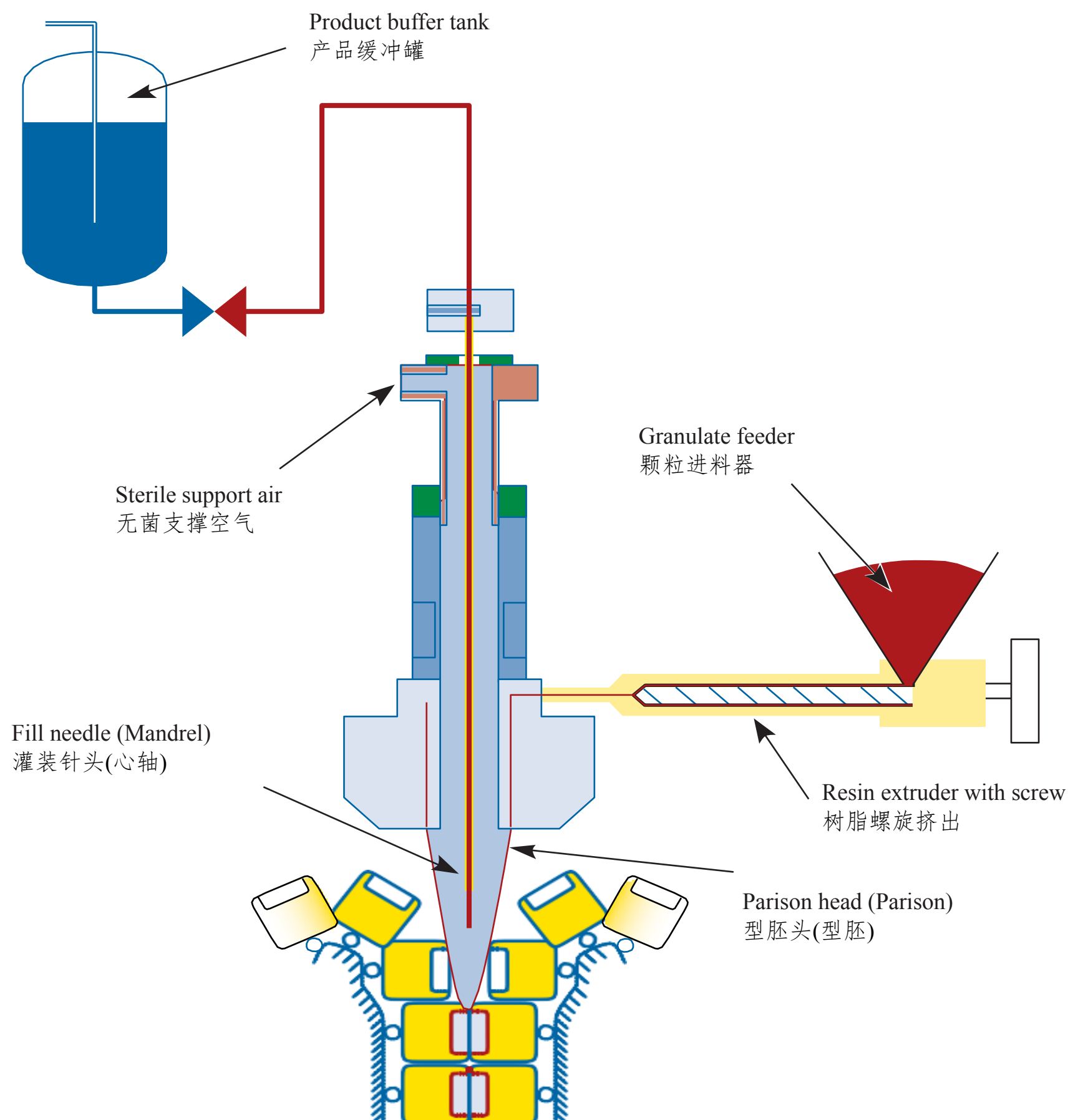


Figure 3.2-1 Rotary BFS Machine Schematic

图片3.2-1：旋转型吹-灌-封设备原理图

3.2 Rotary Filling Machines (Closed Parison Process)

第 3.2 节-旋转式灌装机械(密闭型胚工艺)

BFS technology can also be applied to an operation using a rotary system in which the containers are formed using a closed parison process. The forming, filling, and sealing of the containers in the closed parison process is identical to the open parison process, except that there is no parison cutting between each BFS cycle. Rather, the containers emerge in a continuous ribbon and are separated after being discharged from the machine. In the closed parison process, the possibility of environmental contamination

is markedly reduced. Each mold set on the chain closes on the parison, sealing the previous container and forming a new container.

吹-灌-封技术可应用到旋转系统的操作中，该系统中的容器采用密闭的型坯工艺。在密闭型坯工艺中，容器的成形、灌装、密封与开放式型坯工艺相同，只是在每个吹-灌-封循环之间不存在型坯切割。而是，容器出现在连续的单板带中，并且从机器排出后分离。在封闭的型坯工艺中，环境污染的可能性明显降低。链条上的每个模具都在型坯上闭合，密封前一个容器并形成一个新的容器。

Rotary BFS machines use multiple matched mold sets affixed to two chains that move in continuous mirrored, counter-rotating loops. With rotary technology, the filling mandrels pass directly through the extruder head, as illustrated in Figure 3.2.1. During cleaning and sterilization, the filling mandrels are retracted back into the extruder head.

旋转式吹-灌-封机器使用多个匹配的模具固定在两个链条上，这两个链条在连续的镜面反向旋转回路中移动。通过旋转技术，灌装心轴直接通过挤出机头，如图3.2.1所示。在清洁和灭菌期间，将填充心轴缩回到挤出机头部。

For both shuttle and rotary type BFS machines, the filling mandrels are typically cleaned prior to use with a clean-in-place (CIP) process followed by sterilization-in-place (SIP). The filling environment is maintained under Grade A conditions with HEPA- or sterile-filtered overpressure air (2).

对于往复与旋转式吹-灌-封机器，灌装心轴通常在使用前用在线清洁工艺进行清洁，随后进行在线灭菌。使用高效过滤器或除菌过滤的超压空气维持灌装环境(2)。

The extruder forms a continuous single oval parison which is fed into the rotating mold mechanism. The molds and chain move at the same speed as the extruded plastic parison. Sterile filtered air or other gas under positive pressure is passed into the parison to prevent it from collapsing. As the mold sets rotate, they close around the parison tube to form new container bodies and seal off the preceding set of molded containers. The containers are formed within the mold through vacuum only. This process is illustrated in Figure 3.2-2.

挤出机形成连续的单个椭圆形型坯，其被馈送到旋转模具机构中。模具与链条以与挤出的塑料型坯相同的速度移动。正压得除菌过滤空气或其它气体进入型坯，以防止其塌陷。当模具组旋转时，其围绕型坯管闭合以形成新的容器体并密封前一组模制容器。容器通过真空只在模具内形成。该过程如图3.2-2所示。

To protect the product from the heat present in the extruder head, each filling mandrel is enclosed within a double-walled cooling jacket. In production, the filling is performed immediately after the container is formed. During liquid filling, the headspace gas within the container is displaced back into the enclosed parison area. The containers are then discharged from the machine in a continuous strip or ribbon. Typically, the ribbon of containers is then mechanically deflashed and separated outside the filling room, according to sterile processing guidance (2). A single molding and filling cycle (step) takes approximately three to four seconds to complete.

为了保护产品免受挤出机头部存在的热量的影响，每个灌装心轴封闭在双层冷却套中。在生产中，在容器形成后立即进行灌装。在液体灌装期间，容器内的顶部空间气体被移回到封闭的型坯区域中。然后将容器从机器中以连续的带或条排出。根据无菌工艺指南，通常容器带随后进行机械修边并在灌装室的外部分离(2)。单个成型与灌装循环(步骤)需要大约三到四秒钟才能完成。

3.3 Additional Applications

第 3.3 节-其它应用

Open parison BFS machine designs can accommodate insertion of secondary components, such as needles, rubber stoppers, and controlled-drop inserts, before the container is sealed. Any such components should be sterilized using a validated process prior to aseptic transfer into the BFS machine through a decontaminated isolator. Bags containing the sterile secondary components need to be decontaminated using a qualified process as they are transferred into the isolator.

开放型坯吹-灌-封机器设计可以在容器密封之前适应插入第二部件，例如，针、橡胶塞、液滴控制插件。在通过净化隔离器无菌转移到吹-灌-封机器之前，应使用经过验证的方法对任何此类组分进行灭菌。因为转移到隔离器中，含有无菌第二部件袋子需要使用经过确认工艺进行净化。

A variation of the shuttle type machine partitions the filling step from the surrounding environment; blowing and filling activities take place at two separate stations. This machine variation has multiple molds rotating on a horizontal plane.

往复型设备的另一种变体，将灌装步骤与周围的环境分开。吹制和灌装在两个独立的工作站运行。这种设备的变体有多种在同一水平面旋转的模具。

Some BFS machines also have co-extrusion capability, which enables production of a multi-layer container to provide particular barrier properties according to the application (e.g., to minimize vapor loss or prevent gas ingress).

一些吹-灌-封机器还具有共挤能力，其可以生产多层容器以根据应用提供特殊的阻隔性能(例如，减少蒸汽损失或防止气体进入)。

A reciprocating single-mold variation, based on the closed parison rotary technology, also exists. Reciprocating BFS machines use

a single, vertically reciprocating, matched mold set to produce a continuous ribbon of finished product.

也有基于密闭旋转技术的往复式单模变型。往复式吹-灌-封机器使用一个垂直往复运动的匹配模具，来生产连续的成品带。

Additionally, BFS machines can be adapted to accommodate heat-sensitive products (e.g., proteins, vaccines, biologics, and other large molecules). Process variables can be modified to ensure that there is no degradation of the product, such as modifying the chilled water loop and controlling the product temperature (chilling) prior to and after filling. Machine parameters can also be adjusted, including modification of fill systems, to provide additional cooling.

此外，吹-灌-封机器可以应用于热敏产品(例如，蛋白质、疫苗、生物制品与其它大分子)。可以修改工艺变量，以确保这些产品不会降解，诸如，在灌装之前与之后修改冷冻水循环并控制产品温度(冷却)。机器参数也可以调整，包括灌装系统修改，以提供额外的冷却。

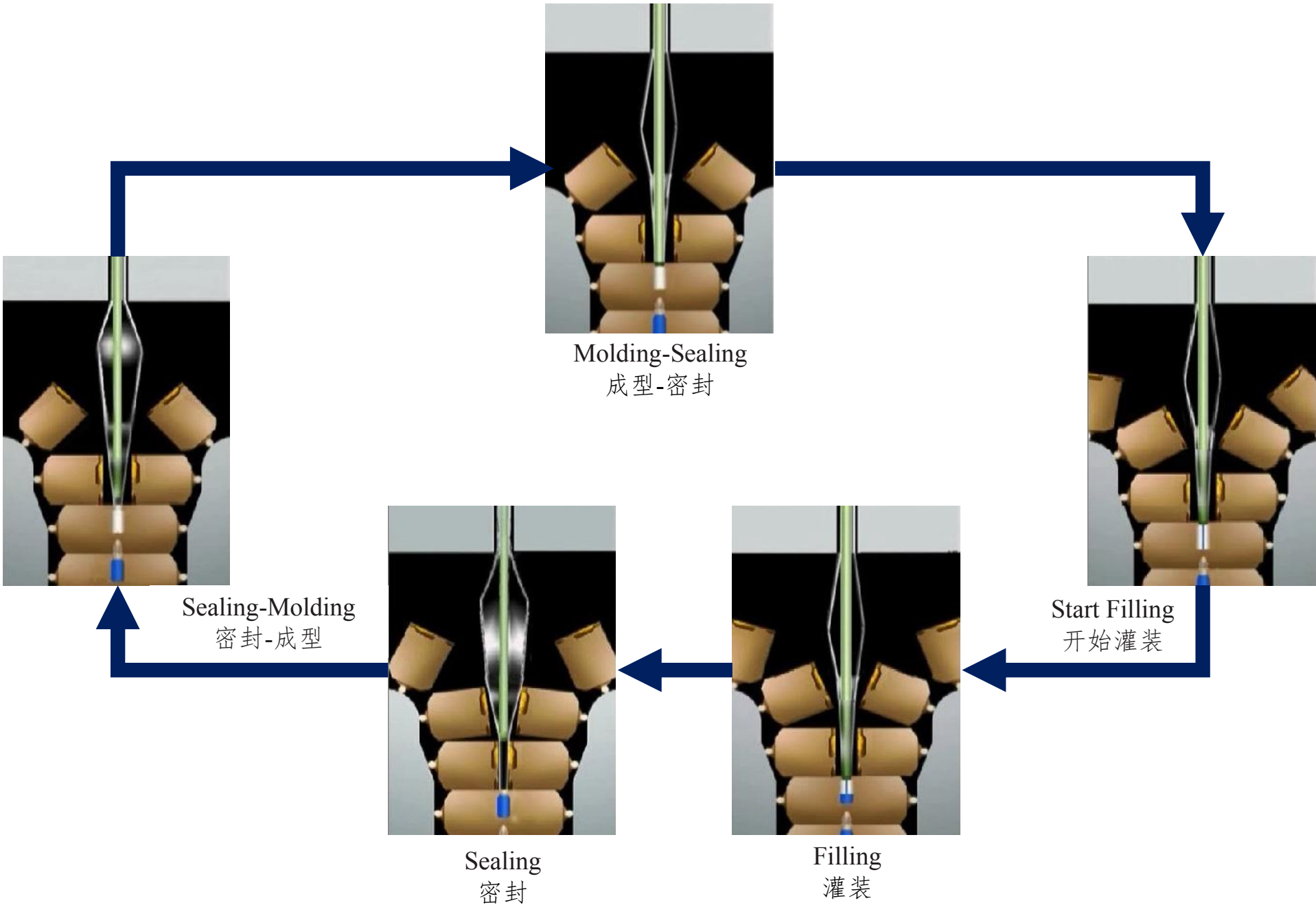


Figure 3.2-2 BFS Process Detail for Rotary Machines

图片3.2-2：旋转式吹-灌-封机械工艺细节

4.0 Benefits & Special Considerations of BFS Technology

第 4.0 章-吹-灌-封技术的优点及特殊考虑

Properly designed and controlled BFS technology operations can offer advantages over conventional aseptic processing and filling operations, as outlined in Section 4.1. However, implementation of BFS operations requires a comprehensive assessment and understanding of the process to ensure manufacturing compatibility with BFS technology. These considerations are presented in Section 4.2.

如第4.1节所述，正确设计和控制的吹-灌-封技术操作可以提供优于常规无菌工艺与灌装操作的优点。然而，实施吹-灌-封操作需要对工艺进行全面评估与理解，以确保制造与吹-灌-封技术的兼容性。这些考虑见第4.2节。

4.1 Benefits

第 4.1 节-优点

- Duration of exposed product and container:** In the BFS process, the final container is formed immediately prior to filling, filled, and sealed in a continuous operation, typically exposing the open container for a relatively short duration of less than 10 seconds. The resulting benefit may be a risk reduction for viable microbial and foreign particle contamination of product.
产品与容器暴露时间：在吹-灌-封的工艺中，最终容器形成后紧接着灌装、密封，形成连续的操作，通常开放容器的暴露时间相对较短，少于10秒。得益于降低了微生物与见异物对产品污染的风险。
- Container processing:** The risk of foreign particle generation during production, processing, packaging, and storage/transport of glass vials and rubber stoppers are reduced due to the direct nature of BFS technology container formation and sealing process. In addition, since the final container is formed just prior to filling, procedures for line clearance are simplified.
容器处理：由于吹-灌-封技术容器形成与密封工艺的特性，降低了玻璃瓶与橡胶塞生产、加工、包装，及储存与转移中可见异物产生的风险。另外，由于容器形成后紧接着灌装，简化了清场程序。
- Level of automation:** BFS machines are highly automated, reducing the number of operations and personnel required. The reduction of personnel and interventions reduces the potential for human error and contamination risks resulting from human intervention.
自动化水平：吹-灌-封机械是高度自动化的，降低了操作与所需求的人员数量。减少人员与干预就降低了人员错误与人员干预导致的污染风险。
- Machinery design:** BFS machines can be designed with air management configurations (e.g., critical fill-zone area shrouded under a continuous flow of positive-pressure, sterile filtered air), thus minimizing the impact and risks posed by human intervention. After any critical intervention, the product pathway is steam sterilized-in-place before aseptic filling is resumed.
设备设计：吹-灌-封机械可以配备空气管理(例如，采用持续的正压除菌过滤空气覆盖关键灌装区域)，这样减少了由于人员干预带来的影响与风险。在关键干预之后，无菌灌装之前，对产品通道重新用蒸汽在线灭菌。
- Manufacturing space:** BFS process design allows for reduced space requirements since the critical fill zone resides within the BFS machine. The BFS process does not require washing, depyrogenation, cooling, accumulation, filling, stoppering, or capping stations.
生产空间：由于关键灌装区域设置在吹-灌-封设备内部，吹-灌-封工艺设计降低了对空间要求。吹-灌-封工艺不要求清洗、除热源、冷却、组装、灌装、加塞或轧盖位置。
- Material supply chain:** BFS reduces the number of suppliers and logistics of material supply, for primary packaging raw materials, and it provides added controls. For BFS, the resin supplier is the only primary packaging raw material vendor in the supply chain for the container formed in the BFS process.
物料供应链：对于内包装原料，吹-灌-封降低了供应商数量与物料供应的物流，并且提供了额外的控制。对于吹-灌-封，树脂供应商是吹-灌-封工艺中形成容器时使用的唯一内包装原料供应链的供应商。

4.2 Special Considerations

第 4.2 节-特殊考虑

- Processing temperature:** Containers are formed at elevated temperatures. Product temperature sensitivity should be considered when designing the process. Process parameters and equipment may be required to minimize high temperature impact to the product.
工艺温度：容器在高温下形成。在设计工艺的时候需要考虑产品的温度敏感性。工艺参数与设备应该降低高温对产品影响。

2. **Container material permeability:** Plastics used to form BFS containers may be permeable to gas or moisture. Product stability should be considered when selecting and designing the packaging. Package design, including the use of secondary pouching (i.e., foil pouches) may be considered to reduce the potential for moisture loss or oxygen ingress to the product. Selection of secondary packaging materials (e.g., labels, overwrap) and the potential volatile compounds from packaging/shipping materials must also be considered due to the semi-permeability of some BFS containers.

包装材料渗透性：用于形成吹-灌-封容器的塑料可能渗透气体或水分。在设计中选择包装时需要考虑产品稳定性。包装设计，包括使用第二层包装小袋(铝箔袋)可能需要考虑降低潜在水分损失或氧气进入产品。由于一些吹-灌-封容器的半渗透性，需考虑第二层包装材料(例如，标签、外包装)的选择，以及来自包装或者运输材料的潜在可挥发成分。

3. **Particulate generation:** Historical batch data has shown there is less impact on the final BFS processed product from nonviable particulates as compared to products filled in glass containers (e.g., glass fragments from chipping, vials open prior to the filling point, etc.) (7). However, management of nonviable particulate generation in BFS processes (Section 6.8.8) should still be considered.

粒子产生：历史批数据表明，与在玻璃容器灌装的产品相比较(例如，剥落玻璃碎片、灌装点之前开放小瓶等)，不可见粒子对最终吹-灌-封产品产生的影响要小(7)。但是，仍然要考虑吹-灌-封工艺中不可见粒子产生管理。

4. **Non-unidirectional air flow:** Airflow within the BFS machine environment may be not be unidirectional in some areas due to the nature of the process. Airflow patterns are affected by thermal currents and equipment operation, and should be considered during cleanroom design and installation. Performance of smoke studies can be useful in evaluation of the design.

非单向流：在一些区域，由于工艺的本质，吹-灌-封机械环境内的层流可能不是单向流。受热气流与设备操作的影响，在洁净房间设计与安装时需考虑气流流型。烟雾试验结果对于设计的评价很有帮助。

5. **Hydraulic and cooling systems:** Systems designed to operate equipment and control container formation (i.e., mold) temperature may be in relatively close proximity to the filling operation. Procedural and equipment design controls for hydraulic and cooling systems within the BFS machine (proper preventative maintenance and functional verification) should be considered to prevent potential particulate or water droplet contamination.

液压与冷却系统：设计用于操作设备与控制容器成型(例如，吹制)温度的系统与灌装操作相对贴近。应考虑吹-灌-封设备内部的用于液压和冷却的程序与设备设计控制(恰当地预防性维护与功能确证)，来预防潜在的粒子或水滴污染。

6. **Visual inspection:** Formed plastic containers may be partially translucent and therefore difficult to inspect for particles in product. Material selection and product characteristics may present challenges for visual inspection of production and media filled samples, particularly for parenteral products (e.g., resin clarity/color, suspension products).

目检：成型的塑料容器可能部分半透明，因此不容易检查产品内的粒子。物料的选择和产品特性对于产品和培养基灌装样品，尤其是注射剂产品的目检提出了挑战(例如，树脂呈明度/颜色、混悬液产品)。

7. **Process line condensate:** High cleanroom humidity in combination with low temperature cooling water may have the potential to cause condensation in areas close to the filling zone. Process design and facility environment control, as well as use of insulation and process line covering, should be part of the design qualification for a BFS process.

生产线冷凝物：洁净区高湿度连同冷却水低温，有可能导致灌装附近区域冷凝现象。吹-灌-封工艺设计确认需考虑工艺设计与设施设备控制，并使用保温以及生产线覆盖。

8. **Resin bioburden:** Potential of polymer contamination due to inappropriate handling and/or storage should be considered. Resin should be stored in a controlled (temperature, humidity, and security) area.

树脂生物负荷：需要考虑因不恰当的处理，和/或，存储导致的聚合物潜在污染。应将树脂存储在控制区域(温度、湿度、安全性)。

5.0 Design

第 5.0 章-设计

5.1 Product Design

第 5.1 节-产品设计

5.1.1 Aseptic Processing versus Terminal Sterilization

第 5.1.1 小节-无菌工艺与最终灭菌

Sterile drug products are routinely manufactured by aseptic processing with BFS technology. While it is generally recognized that the preferred method for the preparation of sterile products is terminal sterilization in the final container, the ability to terminally sterilize a product depends upon the stability of the product formulation. When the product cannot be subjected to terminal sterilization, as proven by product development studies, acceptable sterile manufacturing alternatives such as bulk sterilization or advanced aseptic processing (with or without filtration, depending on the material) should be considered. Advanced aseptic processing using current BFS technology can be considered if:

吹-灌-封技术通常用无菌工艺制造无菌药品。虽然普遍认识到，用于制备无菌产品的优选方法是在最终容器中的最终灭菌，但是产品进行最终灭菌的能力取决于产品配方的稳定性。当产品不能进行最终灭菌时，如通过产品开发研究证明的，应考虑可接受无菌制造替代，如原料药灭菌或先进无菌工艺(用或不用过滤，取决于物料)。如果满足以下条件可考虑采用现行吹-灌-封技术先进的无菌工艺：

- The product formulation itself is not compatible with terminal sterilization methods.
制剂本身无法与最终灭菌方法兼容
- The manufacturer can demonstrate that ease of patient use or utility is gained from the use of a heat labile container even if the formulation itself is heat stable (e.g., ease of drug delivery, process considerations). A guidance document produced by the EU Committee for Proprietary Medicinal Products (CPMP) describes the decision trees for the selection of sterilization methods (8).

制造商可以证明，即使制剂本身是热稳定的(例如，易于药物给药、工艺考虑)，使用热稳定性容器也可以使患者易于使用或实用。欧盟专利药品委员会制定的指南文件描述了选择灭菌方法的决策树(8)。

5.1.2 Terminal Sterilization

第 5.1.2 小节-最终灭菌

To meet regulatory requirements, terminal sterilization of BFS containers can be considered under certain conditions. If a BFS product is to be terminally sterilized, then consideration must be given to the product type, resin grade, and container design when selecting time and temperature combinations or other exposure parameters for cycle development and subsequent validation. Polypropylene (PP) or High Density Polyethylene (HDPE) resin grades are typically used for moist heat terminal sterilization. Containers formed from these resins are able to withstand thermal input at the standard sterilization temperature of 121 °C. Containers formed from Low Density Polyethylene (LDPE) resin grades, which have deformation temperatures typically < 115 °C, may be terminally sterilized at lower temperatures using a bioburden-based-approach to achieve the required sterility assurance level (SAL) (9). Container deformation from sustained exposure to heat and pressure is a potential risk with any resin, especially LDPE. It is critical that load patterns, container orientation, and counter pressure be established to mitigate that risk, be explicitly defined in an SOP, and be adhered to during terminal sterilization activities. An inspection for defects post-terminal sterilization should be performed.

为满足法规要求，可以在一定条件下考虑吹-灌-封容器最终灭菌。如果要对吹-灌-封产品进行最终灭菌，则在选择时间与温度组合，或其他暴露参数进行循环开发和后续验证时，必须考虑产品类型、树脂等级与容器设计。由于形成的容器能够在121℃的标准灭菌温度下耐热，聚丙烯或高密度聚乙烯树脂级别容器通常用于湿热最终灭菌。由低密度聚乙烯树脂级别形成容器，其变形温度通常<115℃，可以使用基于生物负载的方法在较低温度下最终灭菌，以达到所需的无菌保证水平(9)。容器从持续暴露于热与压力变形是任何树脂，特别是低密度聚乙烯的潜在风险。建立负荷模式，容器方向与反压力以减轻风险至关重要，在标准操作规程中应明确定义，并在最终灭菌活动中遵守。应进行最终后灭菌后的缺陷检查。

5.1.3 Polymer

第 5.1.3 小节-聚合物

The primary resins used for BFS technology are LDPE, HDPE, or PP. A specific resin is typically selected based upon container characteristics (e.g., geometry, functionality), product stability, and end-user requirements.

吹-灌-封技术的首选树脂是低密度聚乙烯、高密度聚乙烯，或者是聚丙烯。通常基于包装容器的特性(例如，几何学、功能性)、产品稳定性和最终用户的要求选择特定的树脂。

Characterization of the polymer is described in the vendor’s Drug Master File and can be used as part of the evaluation process. Compliance with regulatory requirements, such as those for extractables and leachables, should be considered (see EMA and USP guidances) (10,11,12).

在供应商的药品主文件中描述了树脂的特性，并且可用于评估过程的一部分。需考虑符合法规的要求，诸如，可萃取物与溶出物方面(见欧洲药品管理局以及美国药典指南)(10,11,12)。

The parameters in Table 5.1.3-1 should be evaluated when selecting a polymer for use with a particular product:

在选择一个特定产品使用的聚合物时需要考虑表5.1.3-1中参数。

Table 5.1.3-1 Parameters for Assessing Polymer Selection

表5.1.3-1 选择评估聚合物的参数

Parameter 参数	Characteristics 特性
Chemical/physical properties (compatibility of resin and product) 化学/物理性质(树脂与产品兼容性)	Density 密度
	Melt index 熔融指数
	Clarity (container opacity) 透明度(容器不透明度)
	Melting point 熔点
	Shrinkage 收缩性
	Catalysts/Additives 催化剂/添加剂
Mechanical container characteristics 容器机械特性	Product dispensing characteristics (hydrophobicity, adherence to container wall), 产品配制特性(疏水性、包装容器壁的粘附性)
	Softness, malleability, collapsibility 柔软度、延展性、易坍塌性
	Rigidity 硬度
	Opening 开启
	Coloration 着色
	Vial separation (multiple container blocks) 小瓶分离(整板小容器)
Processing characteristics 工艺特性	Parison swell (extrusion, ballooning) 型胚膨胀(挤压、充气)
	Extrusion temperature 挤出温度
	Processability (resin and tooling compatibility)

	加工性能(树脂与工具相容性)
	Performance of extruder and knife (cleaning and maintenance) 挤出机与刀具性能(清洁与维护)
Barrier properties 阻隔性能	Moisture vapor transmission rate 水气渗透率
	Oxygen transmission rate 氧气渗透率
	Environmental stress crack rate (freeze/thaw cycle evaluation) 环境应力开裂率(冷冻/解冻循环评价)
	Light transmission 透光率
	Protection from volatiles (labels, inks, secondary packaging) 对挥发物防护(标签、油墨、第二层包装)
Sterilization compatibility 灭菌耐受性	Moist heat 湿热
	Irradiation (e-beam, gamma, pulsed UV) 辐射(电子束、伽马射线、紫外脉冲)
	Other (ozone, ethylene oxide) 其它(臭氧、环氧乙烷)

5.1.4 Product Applications

第 5.1.4 小节-产品应用

BFS technology can be an attractive option for filling injectable solutions, such as small volume parenteral (SVP) and large volume parenteral (LVP) solutions, because BFS offers the ability to eliminate many potential viable microbial contamination steps and the related costs common to conventional aseptic liquid filling operations that use glass vials with rubber stoppers.

由于吹-灌-封提供了一个消除很多潜在微生物污染步骤的能力，并且相对于使用玻璃瓶和橡胶塞进行传统无菌操作降低了成本，对于灌装注射液，例如，小容量注射剂和大容量注射剂，吹-灌-封技术是一个有吸引力的选择。

Methodologies for advanced aseptic filling of preservative-free and heat-sensitive products have been developed using BFS processes. Both large and small molecule formulations are routinely processed with BFS technology.

对于灌装没有防腐剂和热敏感产品的先进非最终灌装方法，该方法在使用吹-灌-封工艺的情况下取得了发展。大分子和小分子两个剂型通常都采用吹-灌-封技术。

Typical product applications in both unit dose and multidose formats include the following:

对于单元剂量与多剂量形式，通常产品应用包括：

- Injectable/parenteral solutions
 注射剂溶液
 - Biotherapeutics/biopharmaceuticals
 生物治疗药物/生物技术药品
 - Vaccines
 疫苗
 - Sterile inhalation solutions/suspensions for nebulization
 无菌吸入溶液/雾化混悬剂
 - Ophthalmic preparations
- Wound care
 伤口护理
 - Herbal/oral nutraceuticals
 植物/口服保健营养品
 - Oral solutions
 口服液
 - Diagnostics
 诊断剂
 - Medical devices