6.3 Manufacturing Process Transfer: QRM Application to Start-Up Evaluation

6.3.1 Use of Quality-by-Design Principles

The example in this section shows how quality-by-design principles can help the technology transfer team plan appropriate activities to mitigate risks along the project path (23).

The objective of this example is the technology transfer of an injectable, small-volume parenteral solution from the manufacturing site of the originator firm (SU) to the manufacturing site of a CMO (RU). Supporting information and concepts can be found in PDA Technical Report No. 44: Quality Risk Management for Aseptic processes and PDA Technical Report 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations (7,21).

As described in Figure 6.3.1-1, by processing the deliverables received by the SU, including information on the process and product to be transferred to the new site, the RU can conduct a risk analysis followed by a mitigation plan using a risk priority numbering approach.

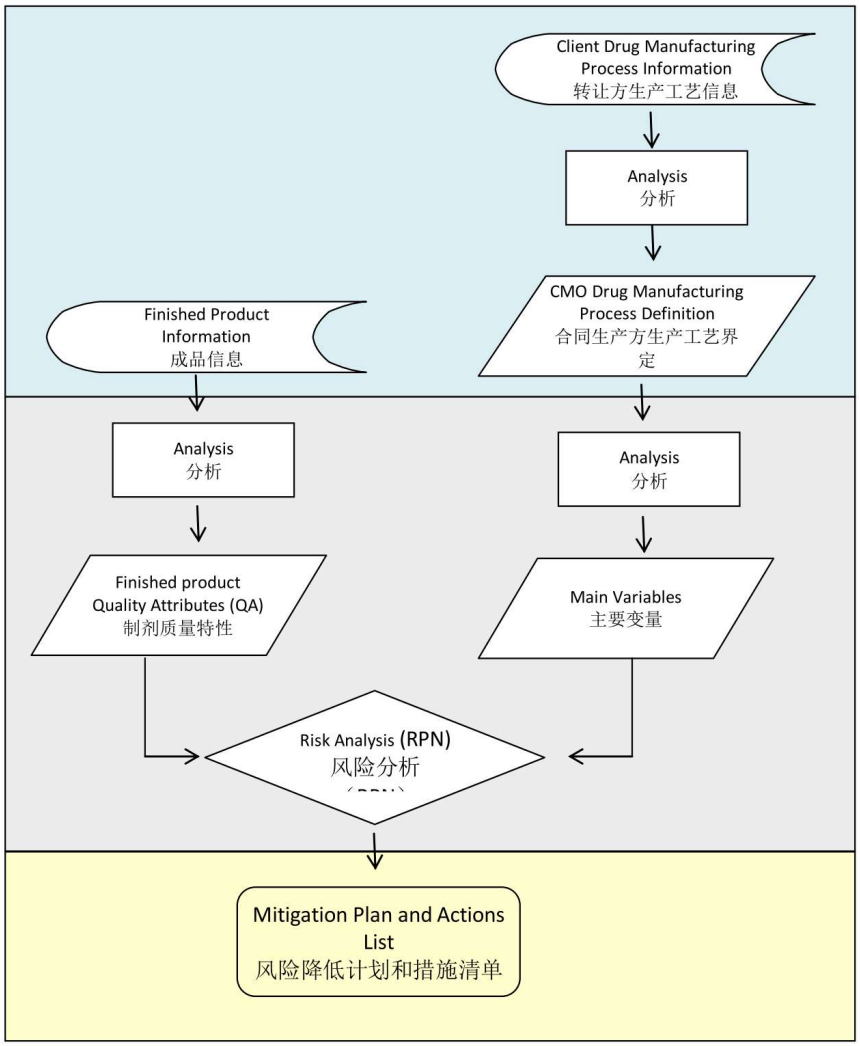

Figure 6.3.1-1 Overall Process Mapping 流程图

As a first activity based on site knowledge, the RU develops a new manufacturing process scheme that accounts for the modifications needed to implement the original manufacturing process at the new site.

The RU defines the main variables that could affect product quality attributes based on the new process scheme (Table 6.3.1-1). The main variable categories include:

- Process/facility
- Primary packaging components
- APIs and excipients

Table 6.3.1-1 Examples of variables definitions

List of Main Items Considered for the Evaluation	Relative Variables		
Process	· Mixing · Holding · Compounding · Grade C filtration · Grade A filtration	· Filling · Stoppering · Crimping · Solution transfer · Steam terminal sterilization	· Identification · Wrapping · Visual Inspection · Secondary packaging · Line cleaning
Primary packaging and GMP materials	· Stoppers · Vials · Seals	· Filters · Disposable tubes · Disposable bag	· Fixed tube · Gasket
API and excipient attributes	· API pH · API appearance	· API density · API osmolality	· Excipients attributes

The SU transfers the quality attributes of the products to the RU (Table 6.3.1-2).

Table 6.3.1-2 Examples of Quality Attributes Definition

QAs		
Appearance	pH	Volume in container
Identity	Density at 20℃	Cosmetic appearance
Assay	Osmolality	Sterility
Impurity	Particle matter	Endotoxins

The two teams merge the newly developed manufacturing process with the quality attributes of the product received to assess which variables could affect the product and how they can be controlled.

To take further advantage of the analysis, a risk number can be assigned to each variable based on its severity, occurrence, and detection.

This activity, done at the beginning of the project, can detect the most likely potential causes of technical failures during the TTP and allow planning for mitigating those risks. Following ICH Q9, the risk can be estimated based a combination of three main factors:

Severity (S)

Occurrence (O)

Detection (D)

Severity considers the potential impact on the quality attributes of the product and, hence, on patient health. It can be rated based on the table below:

Table 6.3.1-3 Severity Definition and Rating

SEVERITY (S)	RISK CLASSIFICATION	VALUE
No impact on product's quality attributes or on patient health	L	1
Moderate impact on product's quality attributes and on patient health	M	2
Severe impact on product's quality attributes and on patient health	H	3

The occurrence factor is defined as the frequency of occurrence of the event. It can be rated as shown in Table 6.3.1-4.

Table 6.3.1-4 Occurrence Definition and Rating

OCCURRENCE (O)	RISK CLASSIFICATION	VALUE
Highly improbable or impossible that the negative event will occur	L	1
Some possibility that the negative event will occur	M	2
Highly probable or certain that the negative event will occur	H	3

The detection factor is defined as the probability of detecting the events if they occur, based on the control system in place. It can be rated as shown in Table 6.3.1-5.

Table 6.3.1-5 Detection Definition and Rating

DETECTION (D)	RISK CLASSIFICATION	VALUE
Highly probable or certain that the negative event will be detected by the control system in place	L	1
Some possibility that the negative event will be not detected by the control system in place	M	2
Highly improbable or impossible that the negative event will be detected by the control system in place	H	3

Based on the definitions and ratings of severity, occurrence, and detection, risk rank can be calculated using the formula R= S x O x D.

A team evaluation is needed to identify acceptance criteria. For example, in Table 6.3.1-6 a risk (R) < 9 is deemed acceptable and no actions are needed to mitigate this risk.

Based on the risk criteria and ranking, a mitigation plan is established by the team. After the plan is implemented, the risks are evaluated again to confirm that they have been mitigated.

Table 6.3.1-6 Risk Analysis 风险分析

Analysis 分析				Risk Priority Number Evaluation 风险优先级评价				Mitigation Plan 风险降低措施
Item 项目	Variable 变量	QA Impacted 受影响的质量特性	Potential criticality/cause of lack of quality attribute description 质量特性关键程度/造成质量特性缺失的原因	Severity 严重性	Occurrence 可能性	Detection 可检测性	RPN 风险优先级	Consideration / Action 解决思路/措施
Process 工艺	Mixing and compounding 混合和配料	pH	Dissolution speed is insufficient for complete dissolution and a homogenous system. 溶解速度不足以完全溶解，并获得均匀体系	3	3	1	9	During the performance qualification, the mixing device of the tank used in the RU will be challenged. 在性能确认中，对受让方使用的罐混合装置进行挑战
		Osmolality 渗透压	Dissolution speed is insufficient for complete dissolution and a homogenous system. 溶解速度不足以完全溶解，并获得均匀体系	3	3	1	9	Mixing studies will be agreed on by the SU and performed during the engineering batch. 混合研究应获得转让方同意，并在工程测试批进行。
		Appearance 外观	Mixing system is not appropriate to guarantee uniform batch mixing 混合系统无法确保混合均匀	3	3	3	27	The user requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system. 基于胶体体系的特性，受让方配料罐的用户需求已明确混合要求 The initial evaluation and information sharing between SU, RU, and the disposable technology Supplier have identified the appropriate mixing device. 通过转让方、受让方和技术服务商的初步评价和信息分享，已确定适当的混合装置。 The PQ challenge of the mixing system will include appropriate tests suggested by the supplier/owner of the technology 混合系统的PQ挑战试验应包括相关供方/技术所有人建议的测试。
		Density 密度	Temperature of the system is outside the range specified by the SU 系统的温度超出转让方指定的范围	2	1	1	2	No further action needed. The colloidal system is not sensitive to temperature. The RU WFI loop cooling and temperature control system will guarantee a 15-25℃ range. 无需采取进一步措施。胶体体系对温度不敏感。受让方注射用水的回路冷却和温度控制系统将保证温度处于15-25℃的范围
			Sampling mode device can affect the analysis 取样装置可能影响分析结果	3	2	2	12	The sampling system will be made of pharmaceutical-grade glass. The SU has collected data on compatibility, and the solution is declared compatible with glass devices. 取样系统由医药级玻璃制成。转让方已收集相容性资料，证明溶液与玻璃取样装置是相容的。
		Sterility	Preparation time can affect the	3	2	2	12	Validation activities will include hold time challenges according to a

		无菌	bioburden level of the final compounded solution 制备时间可影响配置溶液的生物负载水平				dedicated protocol. 验证活动包括按照制订的方案进行暂存时间的挑战试验 Chemical characteristics and microbiological attributes of the solution will be analyzed. 对溶液的化学和微生物特性进行分析
	Grade C and grade A filtration C级区和A级区过滤	Particulate matter 颗粒性物质	Particles release from disposable hoses may impact the particulate matter profile 一次性管路释放的颗粒可能影响溶液中可见异物组成	3	2	3	18	Use Silicon, platinum-cured, disposable hose certified for pharmaceutical use for solution transfer. 采用铂金固化的一次性硅胶软管进行溶液转移，应有适用制药使用的证明。 To address particle release from the hoses used in grade C, filter the solution three times before filling (0.45µm +0.22/0.2µm in grade C area and 0.22/0.2µm in grade A area). 针对C级区使用软管的颗粒物质脱落，在灌装前将溶液过滤三次（C级区：0.45µm +0.22/0.2µm；A级区：0.22/0.2µm） Regarding the particle release from the hoses used on the filling machine, a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对于灌装机上软管脱落的颗粒，可对产品进行100%的目检。有可见异物缺陷的瓶子将被剔除。
			Mixing system shedding may impact the particulate matter profile 混合系统剥落物可能影响溶液中可见异物组成	3	3	3	18	Supplier has provided leachable/extractable documentation and certifications. 供应商提供溶出试验文件和证明 Compatibility studies to be conducted with specified analytical methods with the supplier. 应和供应商一起按照规定的分析方法进行相容性研究
		Particle matter 可见异物	Release from the filter membrane may impact the particle matter profile of the solution. 过滤膜脱落的颗粒可能影响溶液中可见异物的组成	3	2	3	18	Regarding the release from the filters used in grade C, the solution is sterile filtered before filling. A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对于C级区过滤器的颗粒脱落问题，可在灌装前进行无菌过滤。进行100%的目检。剔除有可见异物缺陷的瓶子。
		Sterility 无菌	A filter with an integrity issue can compromise the sterility of the solution 完整性有问题的过滤器将影响溶液的无菌性	3	1	1	3	The filter arrives in the RU with the integrity certification of the supplier. 受让方购买过滤器时应要求供应商提供完整性证明。 According to the RU's procedure, each 0.22/0.2µm filter is tested after and before use. 按照受让方的程序，每一0.22/0.2µm过滤器在使用前后进行完整性测试。 Leachable/extractable documentation and certifications will be provided by the supplier. 供应商提供溶出试验文件和证明 If needed, specific analysis can be done by the supplier to identify possible leachables and extractables. 需要时，供应商可进行特殊的分析，以找出可能的溶出物 Adsorption and compatibility studies will be performed as a part of the filter validation. 吸附和相容性验证应作为过滤器验证的一部分

			A filter can become clogged 滤器可能被堵塞	3	1	1	3	Clogging of the filter with potential impact on the sterility of the overall process is evaluated in a preliminary phase of the transfer, including supplier trial scale up of their size. Analysis of the exact filtration system and critical process parameters that will be used during drug manufacturing are necessary. Both velocity max or pressure max trials are reliable and can anticipate potential failures. Media fill challenge of the filter change procedure is a valid practice to downgrade the associated risk and estimate the impact on sterility as a result of the filter change. 在转移的前期应对过滤器的堵塞以及其对整个工艺无菌性的潜在影响进行评价，这包括供应商的批量放大试验。需要对药品生产中使用的具体过滤系统和关键工艺参数进行分析。最大流速或最大压力试验都是可靠的，并能预估可能的故障。过滤器更换程序的培养基灌装挑战试验是降低相关风险，以及估计过滤器更换对无菌影响的一种好方法。
		pH	Adsorption on the membrane filter can impact density, osmolality, and pH of the solution 过滤膜的吸附可能影响溶液的密度、渗透压、pH	3	3	3	27	Adsorption studies will be done as a part of the filter validation. 吸附研究应作为过滤器验证的一部分进行 High impact has to be considered in the case of biological compounds due to the potential impact of changes in preservative concentrations. 因为防腐剂浓度变化的潜在影响，对于生物制品尤其应考虑吸附的重大影响
		Density 密度	Incompatibility between filter and solution can modify the system's chemical profile. 过滤器和溶液不相容，可能改变系统的化学成分	3	3	3	27	Compatibility studies will be done as a part of the filter validation. 相容性试验应作为过滤器验证的一部分进行
		Sterility 无菌	Clogging issue can have an impact on the microbiological growth attributes and chemical characteristics of the solution. 堵塞可能对微生物生长、溶液的化学特性有影响	3	3	2	18	The appropriate size of the filter will be defined in the RU with a specific laboratory trial with the filter supplier. The solution will be filtered through the filter until clogging occurs. Volume filtered, time of filtration, surface area, and flow rate will be analyzed and correlated. 过滤器尺寸应由受让方和过滤器供应商一起通过试验确定。将溶液通过过滤器直到发生堵塞。对过滤的溶液体积、过滤时间、表面积和流速进行分析和关联。 The RU's minimum filter size will be defined. A dedicated protocol and report will be issued with the results of the trial. 确定受让方的最小过滤器尺寸。应建立单独的方案、报告，并应包括试验结果。
			Holding time before filtration can increase the bioburden of the compounded solution. 过滤前暂存时间可能会增加配制溶液的生物负载	3	2	2	12	During the validation activities, the holding times will be challenged according to a dedicated protocol. 在验证时，应根据单独的方案进行暂存时间的挑战试验 The chemical characteristics and microbiological growth attributes of the solution will be analyzed. 对溶液的化学特性和微生物生长特性进行分析
	Filling 过滤	Volume in container	Incorrect filling weight can result in out-of-range container volume. 灌装重量不正确会导致装量超标	3	1	1	3	No further actions are needed because the RU's procedures are already in place to periodically check the weight of the solution dosed into the vials during filling activities. 无需采取进一步措施，因为受让方有程序要求在灌装过程中定期检查瓶中溶液

		装量						重量。
		Particle matter 颗粒性物质可见异物	Particle released from the tube can impact the particle matter profile of the solution. 管路释放的颗粒会影响溶液中可见异物的组成	3	2	3	18	Certified silicon, platinum cured, disposable hose for pharmaceutical uses will be chosen for the solution transfer. 采用医药级的一次性铂金固化硅胶管进行溶液转移 A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对产品进行100%的目检。剔除有可见异物缺陷的瓶子
	Stoppering 压塞	Sterility 无菌	Incorrect positioning of the stopper on the vials can result in incorrectly closed containers. 加塞位置不正确导致容器密封不正确	3	1	1	3	An appropriate sensor device is in place in the RU to check the correctness of the position of the stopper on the vials before the crimping step. 受让方有适当感应装置在轧盖前检查胶塞位置是否正确
	Crimping 轧盖	Cosmetic appearance 微小外观缺陷	Incorrect sealing of the vials can result in cosmetic defects 轧盖不当导致的微小缺陷	2	1	1	2	No further actions are needed because according to the Receiving Unit standard approach, a validation of crimping will be done. 无需采取进一步措施，接收方有相应标准程序，并进行轧盖的验证 The validation will take into consideration the cosmetic appearance of the vials. 验证中需考虑瓶子的微小外观缺陷 Moreover, according to the RU's standard approach, the cosmetic appearance of the crimped vials is periodically checked during the batch. 而且，根据受让方标准程序，该批生产过程中将定期对轧盖后瓶子的外观进行检查。
		Sterility 无菌	Incorrect sealing of the vials can result in non-closure of the vials 轧盖不当导致瓶子密封不严	3	3	3	27	Validation of the crimping step will be done. During validation, the correctness of the crimping will be challenged from a cosmetic point of view and from a container closure point of view by a dye intrusion test. Vials will be analyzed by ultraviolet-visible light spectroscopy after immersion in a solution of methylene blue. 对轧盖进行验证。验证中通过染料浸入试验对轧盖中微小外观缺陷和容器密封性进行挑战。将瓶子浸入亚甲蓝溶液中，然后采用紫外-可见分光光度法进行分析
	Steam terminal sterilization 终端蒸汽灭菌	Sterility 无菌	Assurance of an appropriate sterility cycle has to be guaranteed to provide the required lethality. 应有适当的灭菌行程，提供所需的致死率。	3	3	2	18	The terminal steam sterilization cycle will be validated to guarantee sterility assurance. 对终端的蒸汽灭菌行程进行验证，确保无菌
		pH	pH shift due to thermal stress can modify the chemical characteristics and, consequently, the stability of the solution after the terminal sterilization. 因热应力导致的pH漂移，可能改变灭菌后溶液化学特性、稳定性。	3	3	1	9	A technical report on the previous lots manufactured will be shared between RU and SU. The pH shift will be calculated. 受让方和转让方应共享以前生产批次的技术报告。计算pH的漂移大小。 Based on the report, an appropriate pH range prior to terminal sterilization will be set. 根据该报告，确定终端灭菌前适当的pH范围 An in-process control and an appropriate pH adjustment step prior to terminal sterilization will be introduced in the batch record to guarantee the correct pH of the final sterilization solution.

								在批记录中增加终端灭菌前的中控和pH调整步骤，保证灭菌后溶液pH的正确 The validation batches manufactured in the RU will undergo a stability study to confirm that no changes of the system profile have occurred. 受让方生产的验证批应进行稳定性研究，确保效期内产品质量稳定
		Appearance 外观	Flocculation and coagulation events due to thermal exposure may impact the use and stability of the solution. 曝热导致的絮凝和凝固事件可能影响溶液的使用和稳定性	3	3	1	9	Appearance is one of the tests performed on the solution at the end of the process after the terminal sterilization. 外观是终端灭菌后溶液测试项目之一
	Identification 标识	Cosmetic appearance 微小外观缺陷	An incorrect setting of the laser printer used for the identification of the vials could impact vial identification. 标识物的激光打印机设置错误，影响产品的正确标识	3	1	1	3	No further actions are needed. The RU's procedure that is already in place guarantees the correctness of the setting of the laser printer. Moreover, during the production activities, the accuracy of the vial identification label is checked periodically. 无需采取进一步措施。受让方有程序保证激光打印机设置正确。而且，生产中还定期检查标识物的准确性
	Wrapping (bulk package) 包裹（散装）							
	Visual inspection 目检	Cosmetic appearance 微小外观缺陷	A defects checklist that has not been properly reviewed can lead to vials sent to the SU not matching the SU's expectation. 缺陷清单未被适当审核，导致发给转让方的瓶子不符合转让方的要求。	3	1	1	3	A checklist dedicated to the products will be generated based on the RU's experience and the SU's requirements. The checklist will be reviewed and approved by the SU as well. Appropriate training will be conducted for the visual inspection department operators. 根据受让方的经验和转让方要求建立产品专用清单。该清单也应得到转让方审核和批准。对目检人员应进行适当培训。
	Secondary packaging 外包装							
	Line cleaning 清场	Density, osmolality, and impurity 密度、渗透压和杂质	Possible residual material from the previous batch may be transferred to the next batch and could modify the chemical profile of the solution. 上一批次可能的残留物转移至下一批次，并改变溶液的化学特性	2	3	2	12	Specific cleaning validation activities will be done to validate the cleaning procedure to be applied after each batch is manufactured. 进行特定的清洁验证，对每批生产后采用的清洁程序进行验证
			An incorrect average run length (ARL) can lead to a false evaluation of the cleanliness status of the line. 错误的平均运行长度（ARL）会导致对生产线清洁状态的错误评价	3	1	2	6	As a part of the cleaning validation, appropriate calculation will be done to define the ARL based on current guidelines. 作为清洁验证的一部分，按照现有指南通过适当计算确定ARL All cleaning validation activities will be detailed in dedicated protocols and reports reviewed and approved by the SU. 所有清洁验证活动应在验证方案、报告中详细描述，并由转让方审核和批准
			Use of an inappropriate analytical method can lead to false results.	3	1	2	6	A specific method to analyze the WFI at the end of the cleaning procedure will be developed and validated to guarantee the accuracy and

			不正确的分析方法将导致错误的结果					reproducibility of the results obtained. 应建立对清洁结束时WFI进行分析的方法，并进行验证。保证获得结果的准确性和重现性。
Primary Packaging & GMP materials 内包材和GMP物料	Stoppers 胶塞	Impurity 杂质	Cross-contamination with other products can compromise the quality of the solution. 与其他产品的交叉污染将降低溶液质量	3	2	3	18	All lines and machine parts in contact with the product will be dedicated to avoid cross contamination. 与产品接触的所有生产线和机器部件应专用，以避免交叉污染。
			An impurity from the stopper can modify the solution's chemical profile. 胶塞引入的杂质会改变溶液的化学组成	3	2	3	18	
			The coating material can modify the solution's chemical profile. 涂布物质可能改变溶液的化学组成	3	2	3	18	The stopper components have been chosen by the SU during the development studies. 在开发研究时转让方已对胶塞组分进行研究
		Appearance 外观	Substances released from the stopper or from the coating can include flocculation or coagulation events in the solution. 胶塞或涂布物质释放物质可导致溶液絮凝或凝结。	3	2	1	6	The same stoppers will be used to guarantee the lack of anomalous interactions with the stopper coating and rubber. 采用相同的胶塞，确保不会与胶塞涂布物和橡胶发生异常作用。 Stability data were collected by the SU, no interaction issues were reported to RU. 转让方已收集稳定性数据，没有向受让方报告相互作用问题。
			Substances released from the stopper or from the coating can modify the appearance of the solution. 胶塞或涂布物质释放物质可改变溶液外观	3	2	1	6	
		Sterility 无菌	The bioburden of the stopper can impact the effectiveness of currently used and validated sterility cycles. 胶塞的生物负载可影响所采用的经验证灭菌方法的有效性	3	1	3	9	A risk assessment will be done to compare the stoppers currently used in RU with the SU stoppers to evaluate the possibility for using a sterilization cycle already validated by the SU. In cases which no comparable stoppers are found, a new stopper sterilization cycle will be validated. 进行风险评估，对受让方和转让方使用的胶塞进行比较，以评价采用转让方已验证的灭菌方法的可行性。
		Particle matter 可见异物	Release from the stopper may impact the particle matter profile of the solution 胶塞释放的颗粒性物质可影响溶液的可见异物组成	3	2	3	18	A final 100% visual inspection will be done, vials with a particle matter defect will be rejected. 进行100%目检。剔除有可见异物缺陷的瓶子
	Vials 瓶	Impurity 杂质	Impurities released from the glass can impact the solution profile. 玻璃释放的杂质可影响溶液化学组成	3	2	3	18	
			Leachables and extractables from the glass can modify the chemical profile of the solution. 玻璃溶出物可改变溶液的化学组成	3	2	3	18	Type I glass of USP / EP grade will be used. The validation batches produced will be analyzed via a stability study. All release tests will be repeated regularly during the stability program to confirm that no anomalous changes to the system profile have occurred. 采用USP/EP级Ⅰ类玻璃。验证批应进行稳定性考察。在考察期间定期重复所有放行测试项目，以确认产品质量的稳定性。
		Appearance 外观	Leachables, extractables, and ions can induce flocculation or coagulation of the system. 溶出物和离子可导致溶液系统的絮凝或凝	3	2	1	6	

			结					
		Cosmetic appearance 微小外观缺陷	Vials of finished product can be rejected for cosmetic defects. 成品可能因为微小缺陷而剔除	2	2	1	4	No further actions are needed. Incoming statistical checks will be done on each lot of vials prior to use. An agreement with the supplier is in place that defines appropriate AQLs for each defect. These AQLs are in line with the cosmetic requirements received by the SU. 无需采取进一步措施。在进厂使用前对每批瓶子进行取样检查。同供应商一起建立各缺陷项适当的可接受质量水平。这些可接收质量水平应与转让方收到的对微小缺陷要求相一致
		Endotoxins 内毒素	An incorrect depyrogenation cycle can impact the endotoxin level of the final product. 不当的除热原工艺可影响成品的内毒素水平	3	1	3	9	Validation activities will be done on the funnel to determine an appropriate depyrogenation cycle. 进行隧道烘箱验证，确定合适除热原方法 A maintenance program is in place for all of the equipment used in production. 生产中所有设备均应建立维护计划 The raw data of each vial depyrogenation cycle must be attached to the executed BR. 每一除热原行程的原始数据必须附在已执行批记录后
		Particle matter 可见异物	Material released from the glass can modify the particle matter profile of the final product. 玻璃释放的物质可改变制剂中可见异物的组成	3	1	1	3	Type I glass of USP/EP grade will be used. A validated cycle will be applied to wash the vials before the depyrogenation step. 采用USP/EP级Ⅰ类玻璃。应对除热原前洗瓶步骤进行验证 A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 进行100%目检。剔除有可见异物缺陷的瓶子
	Seals 密封件	Cosmetic appearance 微小外观缺陷	Damaged seals can impact the crimping step and / or lead to rejected vials. 密封件损坏可影响轧盖和/或导致产品报废	2	2	1	4	No further actions are needed. Incoming statistical checks will be done on each lot of seals prior to use. 无需采取进一步措施。在进厂使用前对每批密封件进行取样检查
	Filters 过滤器	See filtration step of the process section. 见工艺部分过滤步骤						
	Plastic Disposable Bag for solution preparation 配液用一次性塑料袋	Density, osmolality, and pH 密度、渗透压和pH	Impurities from the product contact layer can modify solution chemical characteristics. 与产品接触表面的杂质可改变溶液化学特性	3	3	3	27	Leachables / extractables documentation and certifications will be provided by the supplier. 供应商应提供溶出试验文件和证明 In case of further necessity, specific analyses can be done by the supplier to identify possible leachables and extractables. 必要时，供应商应特定分析，以识别可能的溶出物
		Appearance 外观	Release from the product contact layer of the bag can generate flocculation or coagulation events. 产品接触面释放物可导致絮凝或凝结问题	3	3	1	9	Compatibility studies will be done together with the supplier using specific analytical methods. 和供应商仪器采用特定分析方法进行相容性研究
		Impurity	Leachables and extractables from the	3	3	3	27	Appropriate in-process controls of pH, density, osmolality, and appearance, are established to check the correctness of the prepared solution's attributes.

		杂质	product contact layer can modify the chemical profile of the solution. 产品接触面溶出物可改变溶液化学组成				进行适当的中间控制，包括pH、密度、渗透压和外观，检查配制的溶液特性是否正确 A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 进行最终的100%目检，剔除有可见异物缺陷的瓶子
		Particle matter 可见异物	Release from the product contact layer of the bag can modify the particulate matter profile of the final product. 产品接触面释放物可改变产品的可见异物组成	3	1	1	3
	Filters 过滤器	See filtration step of the process section. 见工艺部分过滤步骤					
	Fixed transfer line and contact parts of the filling machine 灌装机上固定转移管路和接触部件	Density, osmolality, and pH 密度、渗透压和pH	Adsorption to the lines or product contact parts can impact the chemical profile of the solution. 管路或产品接触面的吸附可影响溶液的化学组成	3	2	2	12	The chemical and microbiological characteristics of the solution prepared will be analyzed prior to filling, and a complete set of analyses will be done at the end of the manufacturing for release of the lots. 在灌装前进行配制溶液的化学和微生物特性检查，在产品放行时进行全面检验
			Incompatibility issues can modify the chemical profile of the solution. 不相容问题可改变溶液的化学组成	3	2	2	12	The compatibility of the system with all the materials used throughout the process will be confirmed with the SU. If there are no data available or in case of doubt, appropriate compatibility studies can be agreed with the SU and performed in RU. 系统与工艺中使用所有物质的相容性应由转让方确认。如果没有相关数据或存在疑问，应同转让方协商适当的相容性试验，并在受让方进行
		Sterility 无菌	Inappropriate sterilization procedures can negatively impact the sterility assurance of the process. 不当的灭菌程序会降低工艺的无菌保证水平	3	1	3	9	A validation of the SIP cycle will be done. Dedicated procedures will be issued to manage the sterilization of the line. 进行在线灭菌行程的验证。采用特定的程序进行管理的灭菌 All the raw data of the temperature profile during sterilization will be attached to the executed BR for each batch. 灭菌过程所有温度原始数据应附在每批已执行批记录后 A bioburden analysis of the solution at the end of the preparation and prior to terminal sterilization will be established as in-process controls. 作为中控步骤，在配制后和最终灭菌前进行溶液的生物负载检查
	Gasket (PTFE and silicon) 垫圈（PTFE和硅胶）	Density, osmolality and impurity 密度、渗透压和杂质	Adsorption to the lines can impact the chemical profile of the solution. 管路的吸附可影响溶液的化学组成	3	2	2	12	The chemical and microbiological characteristics of the solution prepared will be analyzed prior to filling and a complete set of analyses will be done at the end of the manufacturing for release of the lots. 在灌装前对配制溶液的化学和微生物特性进行分析，产品放行前进行全项检验。
			Incompatibility issues can modify the chemical profile of the solution. 不相容问题可改变溶液的化学组成	3	2	2	12	The compatibility of the system with all the materials used along the process will be performed with the SU. If there are no data available or in case of doubt, appropriate compatibility studies can be agreed on with the SU. 和转让方一起进行工艺使用的所有物料与系统的相容性研究。如果没有相关数据或存在疑问，应同转让方商定适当的相容性研究
		Particle matter 可见异物	Material released from the gasket material can modify the particle matter profile of the solution 垫圈释放的物质可改变溶液可见异物组成	3	1	1	3	No further actions are needed. Regarding the release from the gaskets used in the solution preparation grade C area, the solution is filtered 0.22/0.2 µm before the acquasant (or surge tank) of the filling machine. Moreover a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.

API attributes API特性	API appearance API外观	Appearance 外观	Anomalous appearance of the API can modify solution appearance. API外观异常可改变溶液外观	3	1	1	3	无需进一步措施。针对C级区配液使用的垫圈的物质释放问题，可在灌装机缓冲罐前将溶液通过0.22/0.2 μm过滤。而且还进行最终产品的100%目检。剔除有可见异物缺陷的瓶子
	API particle matter API颗粒性物质	Particle matter 可见异物	Insoluble matter in the API can impact the solution's particle matter level. API中不溶性物质可影响溶液中可见异物的水平	3	1	2	6	
	API density, pH, and osmolality API的密度、pH和渗透压	pH, density, and osmolality pH、密度和渗透压	Anomalous pH, density, or osmolality can impact the chemical characteristics of the solution pH、密度或渗透压异常可影响溶液的化学特性	3	1	1	3	An internal API specification will be issued with well-defined range for each test. 建立API内控标准，确定每一测试项目的适当接受范围 Each lot will be analyzed and released prior to its use in production. 在放行用于生产前，对每批API进行检验。
	API bioburden API生物负载	Sterility 无菌	High bioburden of the API can impact the overall bioburden prefiltration of the compounded solution API生物负载偏高可影响配制溶液过滤前生物负载水平	3	1	2	6	
	Excipient's attributes 辅料特性	pH, density, osmolality, appearance, and particle matter,sterility pH、密度、渗透压、外观、颗粒性物质、无菌	Each excipient characteristics can impact the final product quality. 每一辅料特性均可影响最终产品质量	1	2	2	4	Internal specifications will be issued with well-defined ranges for each excipient test. 建立辅料内控标准，确定每一测试项目的适当接受范围 Each lot of each excipient will be analyzed and released prior to its use in production. 在放行投入生产前对每批辅料进行检验

Reference: PDA TR 65