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23 July 2024

Reference: Chinese Pharmacopeial Annex: Draft of Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products (First)

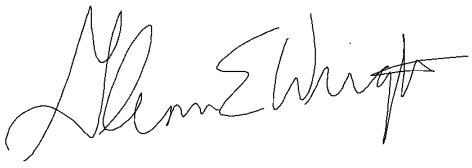
Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the Chinese Pharmacopeia on Annex: Draft of Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products (First). In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important Annex.

PDA is a non-profit international professional association with over 10,000 individual members, including scientists, industry professionals, and consultants who have an interest in pharmaceuticals, biologics, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,



Glenn E. Wright
President and CEO

cc. Josh Eaton, PDA; Carrie Horton, PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

PDA Comments to Chinese Pharmacopoeia Guidance: Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-Sterile Products

General Comments about the Guidance		
Comment	**Proposed Change**	**Rationale**
In multiple places in the document, the term "strain" is used, while the term "species" is used in Table 1. Recommend standardizing the language to species.	Replace references to "strain" with "species as described below. <u>Line 11 (translated version):</u> "The present Guidelines stipulate common **species** of objectionable organisms in.." <u>Section I. Header:</u> "Common **Species** of Objectionable Microorganisms" <u>Line 66 (translated version):</u> "appropriate method is selected to identify the microorganisms to **the species** level,". <u>Line 107 (translated version):</u> "If necessary, detected microbial **species** can be selected…"	Updated language will harmonize with those found in other current industry and regulatory documents and it is not critical to reference use the sub-species hierarchy of strain versus species level.

Introduction				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
6-9	"Objectionable microorganisms are potentially hazardous microorganisms that can survive or reproduce in non-sterile products, adversely affect the physical and chemical properties of the product, destroy the functions and effects, or cause damage to the health of patients through specific routes of administration."	PDA recommends clarifying the scope of the guideline in terms of the range of non-sterile products.	"Objectionable microorganisms are potentially hazardous microorganisms that can survive or reproduce in non-sterile products, adversely affect the physical and chemical properties of the product, destroy the functions and effects, or cause damage to the health of patients through specific routes of administration. **Non-sterile products include pharmaceutical drug products, over-the-counter consumer health products, dietary supplements, enteral nutrition products, medical devices, and traditional Chinese medicines**."	It is unclear if the guideline is limited to pharmaceutical drug products or is extended to over-the-counter consumer health products, dietary supplements, medical devices, and traditional Chinese medicines. By adding this statement, the scope of the guideline will be clarified.

Section I: Common Strains of Objectionable Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
17-18	"A microorganism is judged as objectionable microorganism in a particular non-sterile product, but may be acceptable for other products."	PDA proposes adding a statement regarding inherent non-objectionable organisms.	"A microorganism is judged as objectionable microorganism in a particular non-sterile product, but may be acceptable for other **non-sterile** products. **By definition, non-sterile products may contain, non-hazardous bioburden derived from materials present in the formulation and should be assessed for the risk to the consumer or product quality**."	By providing this statement, it will address the presence of inherent non-objectionable organisms and clarify scope of being for non-sterile products only.
18-21	"In determination of objectionable microorganisms of non-sterile products, it should comprehensively evaluate relevant factors such as the characteristics of the microorganism, product characteristics, route of administration, drug users, and production process."	PDA recommends adding "dosage form" as a product characteristic example.	"In determination of objectionable microorganisms of non-sterile products, it should comprehensively evaluate relevant factors such as the characteristics of the microorganism, product characteristics **(e.g., dosage form)**, route of administration, drug users, and production process."	By providing an example of a product characteristic it provides clarity for the reader and dosage form is a critical factor for consideration.
29 - 32	"Non-fermentative gram-negative bacteria, such as *Burkholderia cepacia complex*, *Ralstonia spp.,* *Stenotrophomonas spp.*,	PDA recommends removing the term "objectionable" from the statement.	"Non-fermentative gram-negative bacteria, such as *Burkholderia cepacia complex*, *Ralstonia spp.,* *Stenotrophomonas spp.*,	While the organisms listed are routinely associated with water systems, the organisms may not be categorized as "objectionable" as this

Section I: Common Strains of Objectionable Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
	Sphingomonas spp., etc., usually have strong tolerance to the antibacterial system of non-sterile products in water matrix, and are common objectionable microorganisms in pharmaceutical water system**."**		*Sphingomonas spp.*, etc., usually have strong tolerance to the antibacterial system of non-sterile products in water matrix, and are **commonly found ~~objectionable~~** microorganisms in pharmaceutical water systems."	determination is dependent on how/where the water is used. This concept aligns with the previous statement that a microorganism may be labeled as "objectionable" for a particular non-sterile product but may be acceptable for other products.

Section II: Risk Identification Strategy for Objectionable Microorganisms in Non-sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
38-39	"The identification and analysis of microorganisms detected in non-sterile products is the key to the risk assessment of objectionable microorganisms."	PDA proposes adding "accurate" to the sentence.	"The **accurate** identification and analysis of microorganisms detected in non-sterile products is the key to the risk assessment of objectionable microorganisms."	The accuracy of genotypic vs proteotypic vs phenotypic systems vary. By adding "accurate" to the beginning of the sentence, it will stress that the accuracy of the system selected for microorganism identification is relevant for proper root cause assignment and effective Corrective and Preventative (CAPA) resolution.

Section II: Risk Identification Strategy for Objectionable Microorganisms in Non-sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
39-44	"Compliant with the microbial limit standards for non-sterile products (General Chapter 1107), appropriate risk assessment methods should be used, such as Failure Mode and Effects Analysis (FMEA) or risk decision matrix, etc., in combination with the formulation, production process, route of administration, drug users and dosage form of different products to determine whether identification and analysis should be performed for the microorganisms detected in non-sterile products."	PDA suggests removing reference to Failure Mode and Effects Analysis (FMEA), and any specific tool recommendation for this application.	"Compliant with the microbial limit standards for non-sterile products (General Chapter 1107), appropriate risk assessment methods should be used **based on the nature of the situation.** ~~**such as Failure Mode and Effects Analysis (FMEA) or risk decision matrix, etc.,**~~ **Some considerations for the risk assessment include but are not limited to** formulation, production process, route of administration, drug users and dosage form of different products to determine whether identification and analysis should be performed for the microorganisms detected in non-sterile products."	By making this change, it allows for the selection of proactive or reactive assessments, as appropriate to the unique situation. If reference for reader is wanted, could refer to ICH Q9(R1) and other appropriate Quality Risk Management (QRM) guidance for tool usage and selection.
45-46	"Referring to Table 1, identification and analysis of microorganisms detected in different types of non-sterile products can be performed."	PDA recommends adding a statement regarding the use of Alternative Microbial Methods (AMM) and guidance that situations where an ID is not available to be considered as part of the risk assessment.	**"**Referring to Table 1, identification and analysis of microorganisms detected in different types of non-sterile products can be performed. **Situations where an ID is not available should be considered**	Section II largely focusses on traditional culture methods as a source of bioburden analysis which allows for culturable microorganisms. Alternative Microbial Methods (AMM's) may provide data which shows

Section II: Risk Identification Strategy for Objectionable Microorganisms in Non-sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
			as part of the risk assessment. This consideration is important with increased acceptance of Alternative Microbial Methods which can determine presence of viable organisms that may or may not be culturable. Where possible, should sufficient cells be harvested from the product, sequencing can be used to confirm the identity of contaminating organisms for risk categorization."	the presence of microorganisms which may or may not be culturable. The updated language provides consideration of this factor along with guidance.
47-55	"Table 1. Risk decision matrix for identification of microbial species detected in non-sterile products"	PDA encourages that Table 1. Risk decision matrix for identification of microbial species detected in non-sterile products be removed from this guidance.	"~~Table 1. Risk decision matrix for identification of microbial species detected in non-sterile products~~"	The Table does not fit all the variations for all products and could add more confusion for the reader.
57-62	"For example, when the microbial count results exceed the action limit or alert limit stipulated in the standard; suspicious hazardous microorganisms detected on the selective plate are tested using specified microorganisms; or	PDA recommends removing "alert limits" as part of the statement regarding their stipulation in "the standard" and adding "or an internal alert level" to clarify the intent of the statement. PDA also	"For example, when the microbial count results exceed the action limit **~~or alert limit~~** stipulated in the standard **or an internal alert level** suspicious hazardous microorganisms detected on the selective plate **of a test for ~~are tested using~~**	As currently written, it is implied that there are "alert limits" specified in guidance standards. The PDA is not aware of alert limits being specified in any standard.

Section II: Risk Identification Strategy for Objectionable Microorganisms in Non-sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
	based on analyzed trends of historical data from microbial monitoring, such as three out of five consecutive test samples exceeding the alert limit or other abnormal trends, identification of microorganisms on microbial limit test plate is required."	recommends clarifying wording in last sentence.	specified microorganisms; or based on analyzed trends of historical data from microbial monitoring, such as three out of five consecutive test samples exceeding the alert limit or other abnormal trends, identification of **representative colonies** ~~**microorganisms**~~ on microbial limit test plate is required."	The current proposal clarifies for the reader that internal alert levels should be set by each manufacturer. This update will eliminate confusion regarding alert levels for the reader. Clarified wording that the organisms were from tests conducted for specified microorganisms. Clarified identification requirements.

Section 3.1: Potential Hazards of Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
78-81	"After the potential hazard characteristics of the detected microorganisms are clarified, further evaluation can be carried out in combination with factors such as the microbial load of non-sterile product, drug	PDA proposes adding a drug characteristic example to the sentence.	"After the potential hazard characteristics of the detected microorganisms are clarified, further evaluation can be carried out in combination with factors such as the microbial load of non-sterile product,	By providing an example of a product characteristic it provides clarity for the reader and dosage form is a critical factor for consideration.

Section 3.1: Potential Hazards of Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
	characteristics, drug users, and route of administration."		drug characteristics **(e.g., dosage form),** drug users, and route of administration."	

3.2: Water Activity				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
92-96	"For non-sterile products with low water activity, such as solid preparations and liquid preparations with non-aqueous matrix, microorganisms are usually not easy to grow and reproduce, but the bioburden of API and excipients and production process should be reasonably controlled, and attention should be paid to storage conditions and packaging system that affect water activity of products."	PDA recommends adding a clarifying statement regarding water activity and its use as an environmental moisture indicator.	"For non-sterile products with low water activity, such as solid preparations and liquid preparations with non-aqueous matrix, microorganisms are usually not easy to grow and reproduce, but the bioburden of API and excipients and production process should be reasonably controlled, and attention should be paid to storage conditions and packaging system that affect water activity of products. **Water activity for well controlled packaging and storage can be used as a guide especially where systems such**	Water activity can be used as an indicator when present in a moisture controlled environment (e.g. non toxic desiccant or hygroscopic chemistry/product) which controls water mobility. Where these conditions don't exist, water mobility can result in condensation where organisms can survive and grow.

3.2: Water Activity				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
			as non-toxic desiccants or hygroscopic product forms are present. The stability of the system should be assessed to ensure that condensate does not form enabling the conditions for growth within the stored or packed product."	

3.2 Product Formula				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
100-102	"In the drug research and development stage, characteristic parameters such as formula and pH should be reasonably optimized to effectively control the growth and reproduction of contaminating microorganisms in products."	PDA proposes adding "antimicrobial effectiveness of the drug formulation" as a characteristic parameter in place of "formula" for consideration in the control of microorganism growth and reproduction.	"In the drug research and development stage, characteristic parameters such ~~**formula**~~ as **antimicrobial effectiveness of the drug formulation** and pH should be reasonably optimized to effectively control the growth and reproduction of contaminating microorganisms in products."	Updated wording clarifies the aspect of formulation (solvent and antimicrobial preservatives) that play an important role in controlling microbial growth. It would be helpful for the reader to discuss this in the guidance.

3.3 Route of Administration or Intended Use				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
115-116	"Attention should be focused on whether the administration site is damaged, such as skin, respiratory tract, gastrointestinal tract or urinary tract."	PDA recommends removing "urinary tract" from the administration site listing and replacing with "genitourinary tract".	"Attention should be focused on whether the administration site is damaged, such as skin, respiratory tract, gastrointestinal tract or ~~**urinary**~~ **genitourinary** tract."	Unsure of what non-sterile product is applied to the urinary tract. Suggest changing to "genitourinary tract" to avoid reader confusion and cover drug formulations such as vaginal tablets, pessaries and intravaginal gels.
122-124	"Table 2. Risk level classification of dosage forms of non-sterile products High (Aw ≥0.6) Low (Aw<0.6) Note: Water activity A_w < 0.6 usually does not support the growth and reproduction of most microorganisms"	PDA suggests changing the Water Activity (A_w) value to <0.75.	"Table 2. Risk level classification of dosage forms of non-sterile products High (Aw **≥0.75**) Low (Aw**<0.75**) Note: Water activity A_w **<0.75** usually does not support the growth and reproduction of most microorganisms"	The water activity cut-off of 0.6 is too stringent when bacteria found in non-sterile products do not grow below 0.85 and most fungi do not grow below 0.75. An A_w of <0.6 does not support the growth of most microorganisms. Specialized microorganisms that grow below 0.75 are not isolated on compendial media. By making this update, it will align the guidance with other current industry and regulatory documents.

3.4 Drug Users				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
126-127	"The risk of adverse drug reactions and microbial pathogenicity is different among different drug users."	PDA suggests removing "adverse drug reactions".	"The risk of ~~**adverse drug reactions and**~~ microbial pathogenicity is different among different drug users."	An adverse drug reaction is a physiological response to the administration of a drug that may not be directly related to the presence of an objectionable microorganism which is the scope of this guidance. Removal of adverse drug reaction will ensure focus remains as to scope of this guideline.

3.5 Product Process				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
132-133	"Specific production links or processes have a greater impact on the effective control of bioburden."	PDA recommends expanding the statement to provide examples of bioburden reducing and/or eliminating processes. PDA also recommends directing the reader to consider processes that can be a source of contamination.	"Specific production links or processes have a greater impact on the effective control of bioburden. **Processes that reduce or eliminate the bioburden (e.g., heat extrusion, tablet compression, fluid bed drying, hot fills, etc.), as well as processes with the potential for contaminating**	Updated language provides consideration of processes that reduce/eliminate bioburden as current language only focuses on processes that can introduce contaminant or allow for microbial growth/reproduction.

3.5 Product Process				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
			the product, should be considered."	
133-136	"For production processes with microorganism contamination or high risk of growth and reproduction, such as high water activity (water system, liquid preparation, coating solution preparation, etc.) or long process operation time, it should focus on evaluating the effectiveness of production processes such as cleaning, disinfection, and sterilization."	PDA proposes adding "process hold times" and "microbial challenge studies and periodic process monitoring" to the statement.	"For production processes with microorganism contamination or high risk of growth and reproduction, such as high water activity (water system, liquid preparation, coating solution preparation, etc.) or long process operation time, **or process hold times**, it should focus on evaluating the effectiveness of production processes **(such as cleaning, disinfection, and sterilization) through microbial challenge studies and periodic process monitoring.**"	The current text highlights many design and operation parameters. By incorporating the proposal, it will highlight considerations regarding hold times of production steps and the value of microbial challenge studies and periodic process monitoring for determination of process effectiveness.
136-138	"Defects in equipment cleaning process, environment and personnel monitoring may lead to an increased risk of microbial contamination."	PDA recommends updating the statement to include other factors.	"Defects in **equipment design, equipment cleaning and sanitization**, environment **monitoring** and personnel **gowning and behavior** ~~**monitoring**~~ may lead to an increased risk of microbial contamination."	By rewriting the statement, it will clarify the importance of equipment design and equipment cleaning/sanitization. Sanitization is directly related to control of microorganisms and ineffective cleaning can increase the risk of ineffective sanitization.

3.5 Product Process				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
				By changing “personnel monitoring” to “personnel gowning and behavior”, it will emphasis the importance of ensuring proper control practices verses monitoring, which may or may not be in place for non-sterile operations.

4.2 Carry Out Continuous and Effective Microbial Monitoring of Pharmaceutical Water				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
166-167	“Good water system design and control, appropriate microbial alert limit and action limit, and daily water quality testing are crucial for effective control of contamination by potentially objectionable microorganisms.”	PDA suggests changing recommendation of “daily monitoring” to “routine monitoring.	“Good water system design and control, appropriate microbial alert limit and action limit, and **routine** water quality testing are crucial for effective control of contamination by potentially objectionable microorganisms.”	By making this language change, it will harmonize recommendations with current industry and regulatory documents and allow companies the flexibility to determine monitoring frequency based on the system and associated risks.

4.3 Develop a List of Objectionable Microorganisms that Comply with Specific Non-Sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
171-179	*"Develop a list of objectionable microorganisms that comply with specific non-sterile products.* The establishment of a database of contamination microorganisms in specific non-sterile products is beneficial for effective risk identification and control of objectionable microorganisms. Product dosage forms with higher risks should pass effective risk assessment, formulate a list of objectionable microorganisms that meet the risk control requirements of enterprises' products and production processes, which is adjusted in a timely manner according to changes in contaminating microbial populations and production processes. Reliable and sufficient historical data analysis can effectively improve the efficiency of risk identification and investigation	PDA recommends updating the section title and verbiage to replace "list" with "database". PDA also recommends updating the statement to clarify for the reader the importance of the database utilization.	*"Develop a* ***database*** *of* ~~***objectionable***~~ *microorganisms* ~~***that comply with***~~ ***typically recovered in*** *specific non-sterile products.* The establishment of a database of ~~**contamination**~~ microorganisms **typically recovered** in specific non-sterile products **may be** beneficial for effective risk identification and control of objectionable microorganisms. ~~**Product dosage forms with higher risks should pass effective risk assessment, formulate a list of objectionable microorganisms that meet the risk control requirements of enterprises' products and production processes, which is adjusted in a timely manner according to changes in contaminating microbial populations and production processes.**~~ **The database can allow for**	By changing the verbiage, it is clarified for the reader that emphasis should be placed on risk assessment and on the development of an evolving database that can be used to monitor microbial populations (i.e., tracking changes over time) and identify the appropriate response.

4.3 Develop a List of Objectionable Microorganisms that Comply with Specific Non-Sterile Products				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
	of objectionable microorganisms.”		**detection of changes in contaminating microbial populations and production processes.** Reliable and sufficient historical data analysis can effectively improve the efficiency of risk identification and investigation of objectionable microorganisms.”	

4.4 Establish Reliable Strategies and Methods for the Detection of Objectionable Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
183-185	“Establish and validate detection methods of objectionable microorganisms in non-sterile products to ensure that the performance of the method meets the requirements.”	PDA recommends clarifying the statement to be applicable to non-compendial tests.	**“If tests beyond those described in ChP General Chapter 1106 are required,** establish and validate detection methods of objectionable microorganisms in non-sterile products to ensure that the performance of the method meets the requirements.”	Updated language clarifies the circumstances where the test method requires validation. Compendial methods do not require validation and instead require method suitability verification for the non-sterile product.

4.5 Establish Risk Assessment and Control Measures for Objectionable Microorganisms				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
190-196	"In addition to the daily prescribed microbial count and specified microorganism inspection standards for non-sterile products, manufacturers should identify risks of potentially objectionable microorganisms through scientific risk analysis and assessment, and establish written microbial contamination control procedures and product internal control and release standards including unacceptable microbial inspection standards, hazard identification, risk analysis, risk assessment and risk control, so as to actively detect potential risk microorganisms that may affect the quality and safety of non-sterile products."	PDA proposes changing "daily" to "routinely".	"In addition to the ~~**daily**~~ **routinely** prescribed microbial count and specified microorganism inspection standards for non-sterile products, manufacturers should identify risks of potentially objectionable microorganisms through scientific risk analysis and assessment, and establish written microbial contamination control procedures and product internal control and release standards including unacceptable microbial inspection standards, hazard identification, risk analysis, risk assessment and risk control, so as to actively detect potential risk microorganisms that may affect the quality and safety of non-sterile products."	By making this language change, it will harmonize recommendations with current industry and regulatory documents and allow companies the flexibility to determine monitoring frequency based on the system and associated risks.

Ⅴ**. Risk Decision Tree of Objectionable Microorganisms**				
Line Numbers-Translation	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
222-233	“Figure 1. Risk decision tree for objectionable microorganisms in non-sterile products”	PDA proposes removing Figure 1. Risk decision tree for objectionable microorganisms in non-sterile products from the guidance.	----------	The decision tree does not fit all the variations for all products and could add more confusion for the reader.

附件：非无菌产品不可接受微生物风险评估与控制指导原则草案公示稿（第一次）

非无菌产品不可接受微生物风险评估与控制指导原则

不可接受微生物(objectionable microorganisms)是指能够在非无菌产品中生存或繁殖，对产品理化特性产生不利影响、破坏其功能及疗效，或经特定给药途径对患者健康造成损害的潜在危害微生物。本指导原则涉及的不可接受微生物，一般指细菌、真菌等微生物。

本指导原则对非无菌产品中不可接受微生物常见菌种、风险识别策略、风险评估特征因素、风险控制要点，以及风险决策树等予以规定，为不可接受微生物的风险评估和控制提供指导，以降低或消除非无菌产品中不可接受微生物的污染风险。

一. 常见的不可接受微生物菌种

一种微生物在特定的非无菌产品中被判定为不可接受微生物，但对于其他产品可能是可接受的。判定非无菌产品不可接受微生物时，需综合评估微生物自身特性、产品特征、给药途径、用药人群和生产工艺等相关因素。

动植物、矿物成分等天然来源原辅料，易被肠杆菌和芽孢杆菌污染，是非无菌产品不可接受微生物污染的主要来源。此外，水系统、生产设备、生产环境、生产人员、包装材料和容器等也会引入潜在危害微生物的污染，若生产过程微生物负载控制工艺存在缺陷或实施措施不当，易导致终产品污染不可接受微生物。非发酵型革兰阴性菌，如洋葱伯克霍尔德菌群（*Burkholderia cepacia complex*）、罗尔斯通菌（*Ralstonia spp.*）、寡氧单胞菌(*Stenotrophomonas spp.*)、鞘氨醇单胞菌(*Sphingomonas spp.*)等，通常对水基质非无菌产品抑菌体系具有较强的耐受性，是制药用水系统中常见的不可接受微生物。此外，粘质沙雷菌（*Serratia marcescens*）、肺炎克雷伯菌（*Klebsiella pneumoniae*）、蜡样芽孢杆菌 (*Bacillus cereus*) 、阴沟肠杆菌（*Enterobacter cloacae*）、不动杆菌（*Acinetobacter spp.*）以及某些丝状真菌（*Filamentous fungi*）等也是非无菌产品中常见的不可接受微生物。

二. 非无菌产品不可接受微生物风险识别策略

非无菌产品中检出微生物的鉴定分析是开展不可接受微生物风险评估的关键。在符合非无菌产品微生物限度标准（通则 1107）要求下，应进一步结合不同产品的处方、生产工艺、给药途径、用药人群以及产品剂型等因素，采用适宜的风险评估方法，如：失效模型和影响分析（Failure Mode and Effects Analysis，FMEA）或风险决策矩阵等，判定是否需要对非无菌产品检出的微生物开展菌种鉴定分析。可参考表 1，开展不同类型非无菌产品检出微生物的鉴定分析。

表 1. 非无菌产品检出微生物菌种鉴定风险决策矩阵

用药人群风险等级	非无菌产品剂型 [a]		
	气雾剂、喷雾剂、鼻喷剂	**阴道用栓剂、软膏剂和乳剂，局部用洗剂、软膏剂和乳剂，口服液（水溶液）**	**口服片剂、胶囊剂，口服液（非水溶液），直肠用栓剂或软膏剂**
高风险（如免疫抑制、免疫力低下、侵入性治疗人群）	对微生物限度检查平板上所有菌落进行鉴定分析	对微生物限度检查平板上所有菌落进行鉴定分析	对选择性平板可疑菌落和超内控可接受限度计数平板典型特征菌落进行鉴定分析
中风险（通常为老人和儿童）	对微生物限度检查平板上所有菌落进行鉴定分析	对选择性平板可疑菌落 [b] 和计数平板上典型特征菌落 [c] 进行鉴定分析	对选择性平板可疑菌落和超内控可接受限度计数平板典型特征菌落进行鉴定分析
低风险（一般为成年人群）	对微生物限度检查平板上所有菌落进行鉴定分析	对选择性平板可疑菌落和超内控可接受限度计数平板典型特征菌落进行鉴定分析	对选择性平板可疑菌落进行鉴定分析

注：

a 本表所列剂型未涵盖所有非无菌产品，应根据风险评估结果进行不可接受微生物的鉴定；

b 可疑菌落是指疑似控制菌或其他特征明确的危害微生物菌落；

c 典型特征菌落是指根据评估，平板上具有不同菌落形态特征的菌落。

非无菌产品中检出微生物的菌种鉴定也可与微生物限度检测结果或历史数据趋势分析相结合。例如, 当微生物计数结果超过标准规定纠偏限或警戒限；控制菌检查选择性平板上检出可疑危害微生物；或基于微生物监测的历史数据分析趋势，例如连续五个测试样本中有三个超过警戒限或其他异常趋势，

需要对微生物限度检查平板上的微生物进行菌种鉴定。

应制定非无菌产品潜在不可接受微生物菌种鉴定策略。可参考微生物鉴定指导原则（通则 9204）分离培养可疑微生物，选择适宜的方法将待检微生物鉴定到菌种水平，以有效评估和发现潜在不可接受微生物。

三. 不可接受微生物风险评估主要特征因素

非无菌产品中检出微生物进行菌种鉴定分析后，应基于质量风险管理原则进行不可接受微生物的风险评估，以判定其是否属于不可接受微生物，考察因素包括但不限于微生物的潜在危害、药品特性、给药途径或预期用途、用药人群、生产工艺等多方面。

3.1 微生物的潜在危害

可从国内外非无菌产品召回事件、警告信、临床及疾病爆发调查、权威专著或学术文献等来源获取微生物的潜在危害性。特别是在同类产品中曾被报道为不可接受微生物时，该微生物可能具有较高的风险。检出微生物在明确潜在危害特性后，可结合非无菌产品的微生物负载、药品特性、用药人群、给药途径等因素进一步开展评估。

3.2 药品特性

检出微生物是否能在非无菌产品中生存或繁殖、产生有毒有害物质、破坏药品的理化性质及功能疗效也是判定不可接受微生物的关键因素。与不可接受微生物风险评估相关的产品特征因素主要包括水分活度、产品配方、包装形式等。

水分活度

水分活度与微生物生长繁殖密切相关。液体制剂和半固体制剂，一般具有更高的水分活度，微生物能够生长繁殖的风险较高，例如：溶液剂、混悬剂、洗剂、乳膏剂、软膏剂和凝胶剂等。固体制剂、非水性基质液体制剂等水分活度较低的非无菌产品，微生物通常不易生长繁殖，但应合理控制原辅料和生产过程的生物负载，关注储存条件、包装系统等对产品水分活度的影响。

产品的配方

微生物可利用产品组分作为物质代谢的基础，产生有毒物质或导致产品物理、化学特征改变进而影响临床疗效和功能。在药品研发阶段应合理优化

配方、pH 等特征参数，有效控制产品中污染微生物的生长繁殖。由于天然组分（如植物或动物来源成分）可能携带较高的生物负载，需要监测和控制生产过程的生物负载和特定风险微生物污染。产品能否有效抑制目标微生物的生长是判定不可接受微生物的重要特征因素。必要时，可选择检出微生物菌株，通过抑菌效力挑战试验评估产品抑菌性。

包装形式

应确保产品的包装能有效阻隔外源性微生物污染。多剂量、高水分活度的产品较易引入外源性微生物污染，而单剂量独立包装的形式通常具有较低的风险。

3.3 给药途径或预期用途

应重点关注给药部位是否破损，如皮肤、呼吸道、胃肠道或泌尿道等。一般经口腔、直肠、未破损皮肤等给药途径的风险较低，经有损伤的皮肤、耳、鼻和呼吸道等给药途径则更易引起用药风险。当目标微生物的危害途径与产品给药途径一致时，则该微生物具有较高风险。非无菌产品剂型的风险程度可参考表 2。

表 2. 非无菌产品剂型风险程度分类

给药途径风险等级	不同水分活度支持微生物生长的风险 [a]	
	高（Aw ≥0.6）	低(Aw<0.6)
高风险（如破损皮肤、鼻、呼吸道等）	凝胶剂、洗剂、鼻喷雾剂	气雾剂、干粉吸入剂、散剂
中风险（如耳、阴道、透皮治疗等）	乳膏剂、阴道软膏剂、洗剂	栓剂、贴膏剂、贴剂
低风险（如口腔、直肠、未破损皮肤给药等）	口服液体制剂、糖浆剂	栓剂、胶囊剂、片剂、颗粒剂、丸剂

注：当水分活度 Aw <0.6 通常不支持大多数微生物的生长繁殖

3.4 用药人群

不同用药人群发生药物不良反应和微生物致病的风险不同。对于外伤、手术、疾病或慢性病等导致的免疫力低下患者，以及婴儿和老人等特殊高风险用药人群，使用被微生物污染的非无菌产品时一般具有较高的风险，应建立更严格的不可接受微生物风险控制要求。

3.5 生产工艺

特定生产环节或工艺在有效控制生物负载方面有较大影响。对生产中存在微生物污染或生长繁殖风险较高的过程，如高水分活度（水系统、配液、制备包衣液等）或工艺操作时间较长。应重点评估清洁、消毒、除菌、灭菌等生产工艺的有效性。若设备清洁工艺、环境及人员监控存在缺陷，可能导致微生物污染风险增加。

3.6 其他因素

除上述关键风险特征因素外，非无菌产品中微生物污染率、耐药性、生物被膜形成能力、感染剂量、检测方法及产品摄入剂量等，也可作为不可接受微生物评估的风险特征因素。

四. 不可接受微生物的风险控制

应对非无菌产品及其生产、储存、运输等全生命周期中的潜在危害微生物进行有效识别、监测、预防和控制，建立系统、清晰的不可接受微生物风险识别和控制策略。可根据非无菌产品制剂特征和生产工艺，制定包括不可接受微生物检查方法和控制措施在内的产品质量标准，实施全面的微生物质量风险管理，有效防范不可接受微生物的污染风险。

4.1. 建立非无菌产品全过程微生物负载控制措施。应建立涵盖非无菌制剂、原辅料、设备和设施、工艺设计、维护和清洁、生产和储存、以及生产环境等非无菌产品全过程污染微生物控制措施和程序，加强生产过程微生物质量控制与监督，确保微生物污染可控，防止引入不可接受微生物风险。需特别关注易形成生物被膜的工艺步骤、关键控制点和趋势分析，如阀门和管道等不易清洁的位置及微生物检测结果的不良趋势。

4.2 开展持续有效的制药用水微生物监控。制药用水系统是不可接受微生物的重要污染来源，应设计、控制和维护稳健的制药用水系统。良好的水系统设计和控制、恰当的微生物警戒限和纠偏限、以及日常水质量检测对于有效控制潜在不可接受微生物污染至关重要。持续对制药用水系统开展常规微生物计数和菌种鉴定分析，确保和维持水系统持续可控。

4.3 制定符合特定非无菌产品的不可接受微生物清单。建立特定非无菌产

品污染微生物数据库，对于有效开展不可接受微生物的风险识别和控制是有益的。风险较高的产品剂型应通过有效的风险评估，制定符合企业产品和生产工艺风险控制要求的不可接受微生物清单，并根据污染微生物种群和生产工艺的变化适时调整。可靠和充分的历史数据分析可有效提高不可接受微生物的风险识别与调查效率。

4.4 建立可靠的不可接受微生物检验策略和方法。建立科学合理的不可接受微生物检测策略，确保有效控制药品原辅料和成品制剂中不可接受微生物的污染。建立并验证非无菌产品不可接受微生物检测方法，确保方法的性能满足要求。如果非无菌产品存在不可接受微生物污染的风险，则应在每批产品放行前进行不可接受微生物检测，确保产品中没有不可接受微生物污染。

4.5 建立不可接受微生物风险评估和控制措施。除日常规定的非无菌产品微生物计数和控制菌检查标准外，生产企业应通过科学的风险分析及评估识别潜在的不可接受微生物风险，建立包含不可接受微生物检查标准、危害识别、风险分析、风险评估和风险控制在内的微生物污染控制书面程序和产品内控、放行标准，以主动发现可能影响非无菌产品质量安全的潜在风险微生物。若原辅料和生产过程中发现终产品已明确的不可接受微生物菌种，则应采取有效措施消除污染风险。加强员工微生物知识和操作技能培训，提高员工对微生物污染风险的识别和控制能力。

4.6 制定有效的不可接受微生物风险消除和回顾措施。应调查任何不符合非无菌产品微生物质量控制标准的情况，包括同一产品的其他批次以及可能相关的其他生产环节、原辅料、人员等，根据检查结果有效识别风险来源，迅速实施适当的纠正和预防措施，有效降低或消除不可接受微生物污染风险，并将相关风险控制措施形成具体操作文件，定期回顾和落实，保障非无菌产品中不可接受微生物的风险可控。

五. 不可接受微生物的风险判定决策树

应对非无菌产品不可接受微生物风险特征因素进行充分研究，积累足够的历史数据。参考 ICH Q9《质量风险管理》推荐的风险评估工具或其他适宜的方法，对非无菌产品中潜在不可接受微生物进行风险评估。评估人员应经过微生物学和统计分析等方面的培训，充分了解产品工艺，确保评估准确性。

本指导原则提供了用于非无菌产品不可接受微生物风险判定的决策树，见图1。决策树仅为评估不可接受微生物风险的一种方法，可能并不全面，可结合其他适宜的方法开展不可接受微生物风险评估。

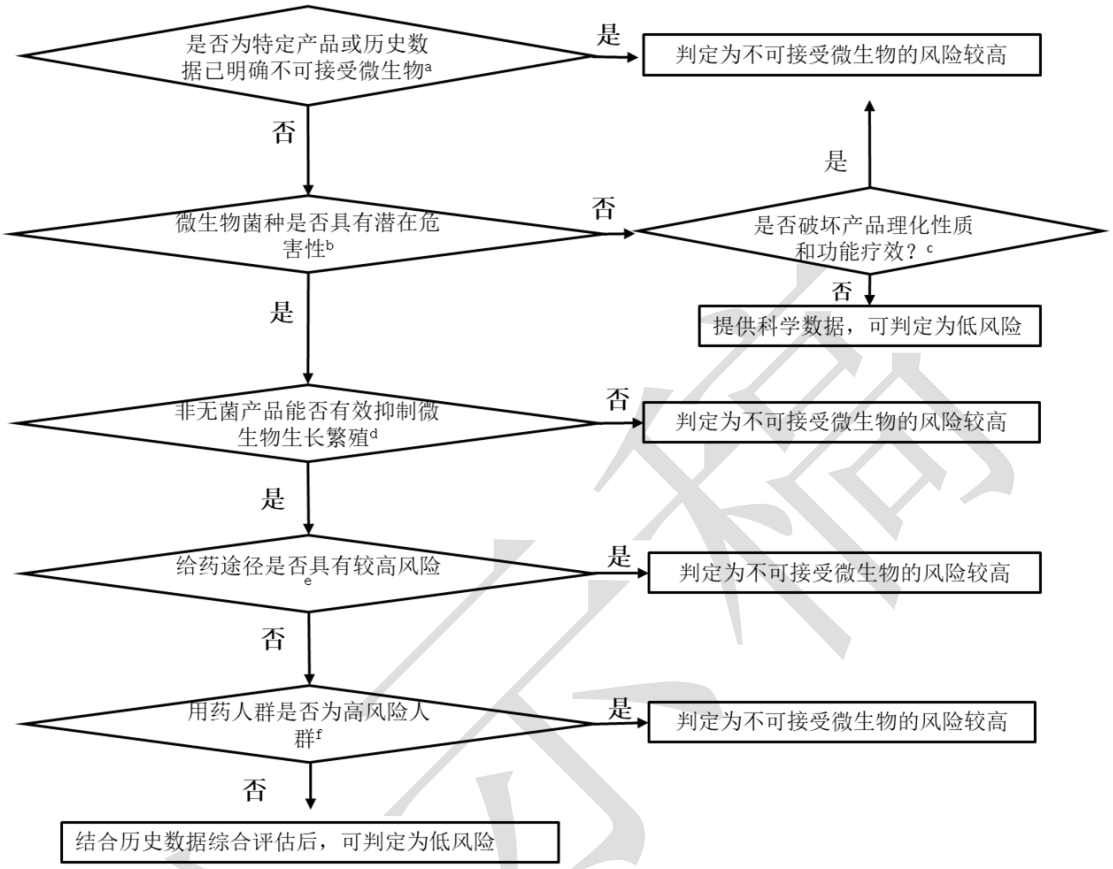


图 1. 非无菌产品中不可接受微生物的风险决策树

注：

a：与历史数据或已报道的不可接受微生物进行比对。

b：判定检出微生物是否具有潜在危害性。

c：提供科学数据评价污染微生物对产品理化性质和功能疗效的影响。

d：可通过挑战实验，提供科学数据评价产品是否能有效抑制目标微生物的生长繁殖。

e：结合不同产品的给药途径和危害微生物的传染途径判定潜在风险程度。

f：判定用药人群是否为儿童老人以及免疫力低下等高风险人群。

起草单位：上海市食品药品检验研究院　　联系电话：18001677839

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非无菌产品不可接受微生物风险评估与控制指导原则起草说明

一、制订的目的意义

《中国药典》2020 版通则 1107 指出：本标准所列控制菌对于某些药品的微生物质量控制可能并不全面，因此，对于原料、辅料及某些特定的制剂，根据原辅料及其制剂的特性和用途、制剂的生产工艺等因素，可能还需检查其他具有潜在危害的微生物。非无菌产品剂型多样，污染微生物种群复杂，特别是临床数据表明通过非无菌药品途径导致的院内感染中，药典规定“控制菌”外的其他潜在危害微生物占比高达 82.6%。因此，对于非无菌药品“控制菌”外的其他潜在危害微生物亟需重视和加强监管。

国际标准法规中，如《美国药典》、美国 cGMP、澳大利亚法规以及 PDA 技术报告等均以“不可接受微生物”来描述非无菌药品中的“其他潜在危害微生物”。但如何判定哪些微生物属于“不可接受微生物”，如何评估其风险，采取哪些措施控制其风险，现行国内外药典标准则缺乏明确的技术指导，导致无法排除潜在不可接受微生物的安全隐患。因此，国家药典委员会微生物专业委员组织起草了《非无菌产品不可接受微生物风险评估与控制指导原则》，旨在明确不可接受微生物的定义、风险评估程序和方法策略，为非无菌产品中不可接受微生物的风险评估和控制提供指导，以降低或消除潜在危害微生物的风险，保障产品的安全、有效。

二、起草过程

《非无菌产品不可接受微生物风险评估与控制指导原则》是在 2022 年国家药典会课题（2022Y21）的支持下，由上海市食品药品检验研究院牵头，浙江省食品药品检验研究院、辽宁省药品检验检测院、陕西省食品药品检验研究院、山东省食品药品检验研究院、内蒙古自治区药品检验研究院、广州市药品检验所以及杭州微数生物科技有限公司，以及部分制药企业代表共同参与起草拟订的。通过本课题的研究明确“不可接受微生物”的定义，拟定“非无菌药品不可接受微生物风险评估与控制指导原则”，解决非无菌产品中“不可接受微生物”定义缺乏、风险控制策略和相关标准缺失等问题，为制药企业和监管机构提供系统、清晰、可操作性的不可接受微生物风险识别和控制技术

标准指南。

三、制订的总体思路

课题组通过广泛调研及深入研究，明确了非无菌产品不可接受微生物的定义。通过对制药企业、临床感染数据、以及国内外非无菌药品召回事件以及警告信等的调研以及收集整理，基于真实世界数据分析，总结常见的潜在不可接受微生物种类，为制药企业判定不可接受微生物提供参比依据；开展了非无菌药品不可接受微生物风险特征因子及判定标准研究，建立了非无菌产品及原辅料中不可接受微生物风险决策树，为药品监管和制药企业提供具体方法路径和评估工具；最后从全生命周期控制出发，研究了非无菌产品不可接受微生物风险消除和风险接受等风险控制措施，形成不可接受微生物风险识别和风险控制的闭环，拟定“非无菌产品不可接受微生物风险评估与控制指导原则”。本标准文本涵盖了不可接受微生物的定义、适用范围、常见不可接受微生物的种类、不可接受微生物的风险识别策略、不可接受微生物风险评估的主要特征因素、不可接受微生物的风险控制要点、不可接受微生物的判定决策树等方面的内容。“非无菌产品不可接受微生物风险评估与控制指导原则”的起草，进一步完善了非无菌产品中微生物质量控制技术标准，填补了药典领域相关标准的空白。

Annex: Announcement Draft of Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products (First)

Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products

Objectionable microorganisms are potentially hazardous microorganisms that can survive or reproduce in non-sterile products, adversely affect the physical and chemical properties of the product, destroy the functions and effects, or cause damage to the health of patients through specific routes of administration. The objectionable microorganisms involved in the present Guidelines generally refer to microorganisms such as bacteria and fungi.

The present Guidelines stipulate common strains of objectionable microorganisms in non-sterile products, risk identification strategies, risk assessment characteristic factors, risk control points, and risk decision tree, etc., and provide guidance for risk assessment and control of objectionable microorganisms to reduce or eliminate the risk of contamination by objectionable microorganisms in non-sterile products.

I. Common Strains of Objectionable Microorganisms

A microorganism is judged as objectionable microorganism in a particular non-sterile product, but may be acceptable for other products. In determination of objectionable microorganisms of non-sterile products, it should comprehensively evaluate relevant factors such as the characteristics of the microorganism, product characteristics, route of administration, drug users, and production process.

API and excipients from natural sources such as animal, plant and mineral components are easily contaminated by enterobacteriaceae and bacillus, and are the main source of objectionable microorganism contamination in non-sterile products. In addition, water system, production equipment, production environment, production personnel, packaging materials and containers will also introduce contamination of potentially hazardous microorganisms. If there are defects in the microbial load control process or improper implementation measures during the production, it easily causes the final product contaminated with objectionable microorganisms. Non-fermentative gram-negative bacteria, such as *Burkholderia cepacia complex*, *Ralstonia spp., Stenotrophomonas spp.*, *Sphingomonas spp.*, etc., usually have strong tolerance to the antibacterial system of non-sterile products in water matrix, and are common objectionable microorganisms in pharmaceutical water system. In addition, *Serratia marcescens*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Enterobacter cloacae, Acinetobacter spp.*, and certain *Filamentous fungi* are also objectionable microorganisms commonly found in non-sterile products.

II. Risk Identification Strategy for Objectionable Microorganisms in Non-sterile Products

The identification and analysis of microorganisms detected in non-sterile products is the key to the risk assessment of objectionable microorganisms. Compliant with the microbial limit standards for non-sterile products (General Chapter 1107), appropriate risk assessment methods should be used, such as Failure Mode and Effects Analysis (FMEA) or risk decision

matrix, etc., in combination with the formulation, production process, route of administration, drug users and dosage form of different products to determine whether identification and analysis should be performed for the microorganisms detected in non-sterile products. Referring to Table 1, identification and analysis of microorganisms detected in different types of non-sterile products can be performed.

Table 1. Risk decision matrix for identification of microbial species detected in non-sterile products

Risk level of drug users	Dosage form of non-sterile product[a]		
	Aerosols, sprays, nasal sprays	Suppositories, ointments and emulsions for vagina, lotions, ointments and emulsions for topical use, oral liquids (aqueous solutions)	Oral tablets, capsules, oral liquids (non-aqueous solutions), rectal suppositories or ointments
High risk (e.g., immunosuppressed, immunocompromised, invasive treatment populations);	All colonies on microbial limit test plate are identified and analyzed	All colonies on microbial limit test plate are identified and analyzed	The suspicious colonies on selective plates and typical characteristic colonies on plates exceeding internal control acceptable limit count are identified and analyzed
Moderate risk (usually the elderly and children)	All colonies on microbial limit test plate are identified and analyzed	The suspicious colonies[b] on selective plates and typical characteristic colonies[c] on the counting plate are identified and analyzed	The suspicious colonies on selective plates and typical characteristic colonies on plates exceeding internal control acceptable limit count are identified and analyzed
Low risk (generally adult population)	All colonies on microbial limit test plate are identified and analyzed	The suspicious colonies on selective plates and typical characteristic colonies on plates exceeding internal control acceptable limit count are identified and analyzed	The suspicious colonies on selective plates are identified and analyzed

Notes:
a The dosage forms listed in this table may not cover all non-sterile products, and objectionable microorganisms should be identified based on the results of risk assessment;
b Suspicious colonies refer to suspected specified microorganisms or other hazardous microbial colonies with clear characteristics;
c Typical characteristic colonies refer to colonies with different morphological characteristics on plates as assessed.

Identification of microorganisms detected in non-sterile products can also be combined with the results of microbial limit test or trend analysis of historical data. For example, when the microbial count results exceed the action limit or alert limit stipulated in the standard; suspicious hazardous microorganisms detected on the selective plate are tested using specified microorganisms; or based on analyzed trends of historical data from microbial monitoring,

such as three out of five consecutive test samples exceeding the alert limit or other abnormal trends, identification of microorganisms on microbial limit test plate is required.

Strategies for the identification of potentially objectionable microorganisms in non-sterile products should be developed. Suspicious microorganisms can be isolated and cultivated with reference to the guidelines for microbial identification (General Chapter 9204), and an appropriate method is selected to identify the microorganisms to be tested to the strain level, so as to effectively evaluate and detect potentially objectionable microorganisms.

III. Main Characteristic Factors of Risk Assessment of Objectionable Microorganisms

After the microorganisms detected in non-sterile products are identified and analyzed, the risk assessment of objectionable microorganisms should be carried out based on the principles of quality risk management to determine whether they are objectionable microorganisms. The investigated factors include but are not limited to the potential hazards of microorganisms, drug characteristics, route of administration or intended use, users, and production process.

3.1 Potential Hazards of Microorganisms

The potential hazards of microorganisms can be obtained from sources such as domestic and foreign non-sterile product recalls, warning letters, clinical and disease outbreak investigations, authoritative monographs or academic literature. The microorganism may have a higher risk, particularly when it has been reported as objectionable in similar products. After the potential hazard characteristics of the detected microorganisms are clarified, further evaluation can be carried out in combination with factors such as the microbial load of non-sterile product, drug characteristics, drug users, and route of administration.

3.2 Drug Characteristics

Detecting whether microorganisms can survive or reproduce in non-sterile product, produce toxic and hazardous substances, destroy the physical and chemical properties, function and efficacy of drugs is also a key factor to determine objectionable microorganisms. The product characteristics related to the risk assessment of objectionable microorganisms mainly include water activity, product formula, packaging form, etc.

Water activity

Water activity is closely associated with the growth and reproduction of microorganisms. Liquid preparations and semi-solid preparations generally have higher water activity and higher risk of microbial growth and reproduction, such as solutions, suspensions, lotions, creams, ointments and gels, etc. For non-sterile products with low water activity, such as solid preparations and liquid preparations with non-aqueous matrix, microorganisms are usually not easy to grow and reproduce, but the bioburden of API and excipients and production process should be reasonably controlled, and attention should be paid to storage conditions and packaging system that affect water activity of products.

Product formula

Microorganisms can use product components as the basis of substance metabolism to produce toxic substances or cause changes in physical and chemical characteristics of products, thereby affecting clinical efficacy and function. In the drug research and development stage, characteristic parameters such as formula and pH should be reasonably optimized to effectively

control the growth and reproduction of contaminating microorganisms in products. Because natural components, such as those of plant or animal origin, may carry high bioburden, bioburden and contamination with specific risk microorganisms should be monitored and controlled during the production. Whether the product can effectively inhibit the growth of target microorganisms is an important characteristic factor for judging objectionable microorganisms. If necessary, detected microbial strains can be selected to evaluate the bacteriostasis of the product by bacteriostasis challenge test.

Packaging form

It should be ensured that the packaging of products can effectively block exogenous microbial contamination. Products with multiple doses and high water activity are more likely to introduce exogenous microbial contamination, while single-dose individually packaged form usually has a lower risk.

3.3 Route of Administration or Intended Use

Attention should be focused on whether the administration site is damaged, such as skin, respiratory tract, gastrointestinal tract or urinary tract. Generally, the risk of administration via the oral cavity, rectum, and undamaged skin is low, while administration via damaged skin, ears, nose, and respiratory tract is more likely to cause medication risks. The microorganism has a higher risk when the hazard route of target microorganism is consistent with the product's administration route. The risk levels of dosage forms of non-sterile products can be referred to Table 2.

Table 2. Risk level classification of dosage forms of non-sterile products

Risk level of administration routes	Risk of different water activities to support microbial growth[a]	
	High (Aw ≥ 0.6)	Low (Aw < 0.6)
High risk (e.g., damaged skin, nose, respiratory tract, etc.)	Gels, lotions, nasal sprays	Aerosol, dry powder inhaler, powder
Moderate risk (e.g., ear, vagina, transdermal treatment, etc.)	Creams, vaginal ointments, lotions	Suppositories, plasters, patches
Low risk (e.g., oral, rectal, undamaged skin administration, etc.)	Oral liquid preparations, syrups	Suppositories, capsules, tablets, granules, pills

Note: Water activity Aw < 0.6 usually does not support the growth and reproduction of most microorganisms

3.4 Drug Users

The risk of adverse drug reactions and microbial pathogenicity is different among different drug users. For patients with low immunity caused by trauma, surgery, disease or chronic disease, as well as special high-risk groups such as infants and the elderly, use of non-sterile products contaminated by microorganisms generally has a higher risk, and stricter requirements for risk control of objectionable microorganisms should be developed.

3.5 Production Process

Specific production links or processes have a greater impact on the effective control of bioburden. For production processes with microorganism contamination or high risk of growth and reproduction, such as high water activity (water system, liquid preparation, coating solution preparation, etc.) or long process operation time, it should focus on evaluating the effectiveness

of production processes such as cleaning, disinfection, and sterilization. Defects in equipment cleaning process, environment and personnel monitoring may lead to an increased risk of microbial contamination.

3.6 Other Factors

In addition to the above key risk characteristic factors, microbial contamination rate in non-sterile products, drug resistance, biofilm formation ability, infective dose, detection method and product dose administered can also be used as risk characteristic factors for the assessment of objectionable microorganisms.

IV. Risk Control of Objectionable Microorganisms

Effective identification, monitoring, prevention and control of potentially hazardous microorganisms in the entire life cycle of non-sterile products and their production, storage, and transportation should be carried out, and a systematic and clear risk identification and control strategy for objectionable microorganisms should be established. According to the preparation characteristics and production process of non-sterile products, product specification including objectionable microbial inspection method and control measures can be formulated, and comprehensive microbial quality risk management can be implemented to effectively prevent the risk of contamination by objectionable microorganisms.

4.1. Establish control measures for microbial burden in the whole process of non-sterile products. Measures and procedures should be established to control the contamination of microorganisms in the whole process of non-sterile products, including non-sterile preparations, API and excipients, equipment and facilities, process design, maintenance and cleaning, production and storage, and production environment, and to strengthen the quality control and supervision of microorganisms in the production process to ensure that microbial contamination is controllable and prevent the risk of introducing objectionable microorganisms. Special attention should be paid to process steps, critical control points and trend analysis that are prone to biofilm formation, such as difficult-to-clean locations such as valves and pipes, and adverse trends in microbiology test results.

4.2. Carry out continuous and effective microbial monitoring of pharmaceutical water. Pharmaceutical water system is an important source of contamination by objectionable microorganisms, and a robust pharmaceutical water system should be designed, controlled and maintained. Good water system design and control, appropriate microbial alert limit and action limit, and daily water quality testing are crucial for effective control of contamination by potentially objectionable microorganisms. Continue to carry out routine microbial counting and identification and analysis of pharmaceutical water system to ensure and maintain the continuous controllability of water system.

4.3. Develop a list of objectionable microorganisms that comply with specific non-sterile products. The establishment of a database of contamination microorganisms in specific non-sterile products is beneficial for effective risk identification and control of objectionable microorganisms. Product dosage forms with higher risks should pass effective risk assessment, formulate a list of objectionable microorganisms that meet the risk control requirements of enterprises' products and production processes, which is adjusted in a timely manner according to changes in contaminating microbial populations and production processes. Reliable and sufficient historical data analysis can effectively improve the efficiency of risk identification and investigation of objectionable microorganisms.

4.4. Establish reliable strategies and methods for the detection of objectionable microorganisms. Establish a scientific and reasonable detection strategy for objectionable microorganisms to ensure effective control of objectionable microorganism contamination in API, excipients and finished drug products. Establish and validate detection methods of objectionable microorganisms in non-sterile products to ensure that the performance of the method meets the requirements. If there is a risk of objectionable microorganism contamination in non-sterile products, objectionable microorganism testing should be carried out before release of each batch of products to ensure that there is no objectionable microorganism contamination in the products.

4.5. Establish risk assessment and control measures for objectionable microorganisms. In addition to the daily prescribed microbial count and specified microorganism inspection standards for non-sterile products, manufacturers should identify risks of potentially objectionable microorganisms through scientific risk analysis and assessment, and establish written microbial contamination control procedures and product internal control and release standards including unacceptable microbial inspection standards, hazard identification, risk analysis, risk assessment and risk control, so as to actively detect potential risk microorganisms that may affect the quality and safety of non-sterile products. If objectionable microorganisms that have been identified in the final product are found in the API and excipients and production process, effective measures should be taken to eliminate the risk of contamination. Strengthen the employee training on microbial knowledge and operational skills, and improve employees' ability to identify and control the risk of microbial contamination.

4.6. Develop effective risk elimination and review measures for objectionable microorganisms. Any non-compliance with the microbial quality control standards for non-sterile products, including other batches of the same product and other production links, API and excipients, personnel, etc., should be investigated, and the source of risk should be effectively identified based on the inspection results, and appropriate corrective and preventive measures should be quickly implemented to effectively reduce or eliminate the risk of objectionable microbial contamination, and form relevant risk control measures into specific operating documents, regularly review and implement, to ensure that the risk of objectionable microorganisms in non-sterile products is controllable.

V. Risk Decision Tree of Objectionable Microorganisms

Adequate research should be conducted on the risk characteristics of objectionable microorganisms in non-sterile products, and sufficient historical data should be accumulated. Risk assessment is carried out for potentially objectionable microorganisms in non-sterile products with reference to the risk assessment tools recommended by ICH Q9 Quality Risk Management or other appropriate methods. Evaluators should be trained in microbiology and statistical analysis and fully understand the product process to ensure the accuracy of evaluation. The present Guidelines provide a decision tree for determining the risk of objectionable microorganisms for non-sterile products, as shown in Figure 1. Decision tree is only a method to assess the risk of objectionable microorganisms, and may not be comprehensive. It can be combined with other appropriate methods to carry out the risk assessment of objectionable microorganisms.

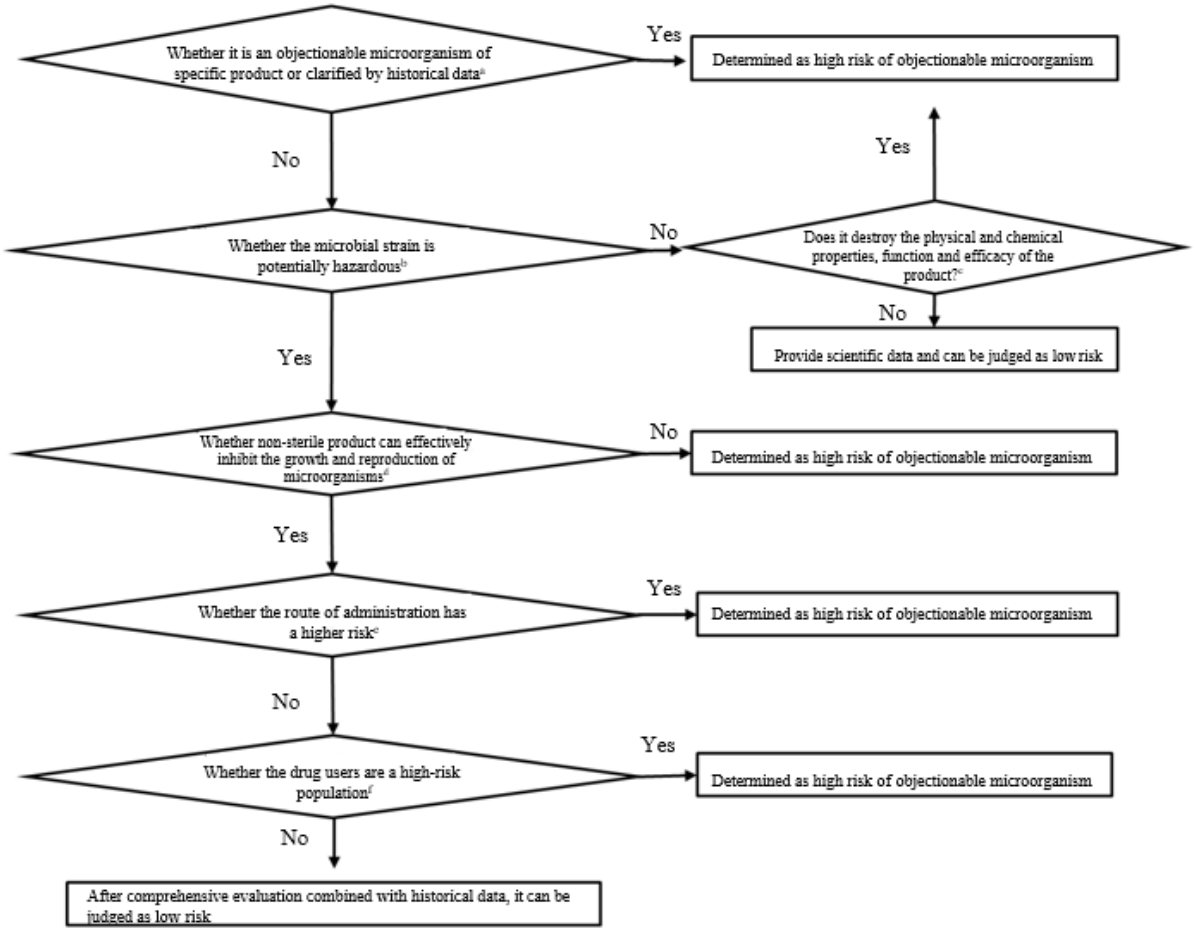

Figure 1. Risk decision tree for objectionable microorganisms in non-sterile products

Notes:
a: Comparison to historical data or reported objectionable microorganisms.
b: Determine whether the detected microorganism is potentially hazardous.
c: Provide scientific data to evaluate the impact of contaminating microorganisms on the physical and chemical properties, function and efficacy of products.
d: Through challenge experiment, scientific data can be provided to evaluate whether the product can effectively inhibit the growth and reproduction of target microorganisms.
e: Determine the degree of potential risk in combination with the route of administration of different products and the route of infection of hazardous microorganisms.
f: Determine whether the drug users are high-risk groups such as children, the elderly, and low immunity.

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Drafting Instruction for Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products

I. Objective and Significance of Formulation

The Chinese Pharmacopoeia 2020 General Chapter 1107 points out that the specified microorganisms listed in this standard are not necessarily exhaustive for microbial quality control of some drugs. Thus, API, excipients and some special preparations may be necessary to control other potential hazardous microbes depending on nature and usage of API, excipients and drug product, and manufacturing process of drug product. The dosage forms of non-sterile products are diverse, and the population of contaminating microorganisms is complex. In particular, clinical data shows that among nosocomial infections caused by non-sterile drugs, other potentially hazardous microorganisms other than “specified microorganisms” stipulated in the Pharmacopoeia account for up to 82.6%. Therefore, it is urgent to pay attention to and strengthen supervision of other potentially hazardous microorganisms other than “specified microorganisms” of non-sterile drugs.

In international standards and regulations, such as United States Pharmacopoeia, US cGMP, Australian regulations and PDA technical reports, etc., "objectionable microorganisms" are used to describe "other potentially hazardous microorganisms" in non-sterile drugs. However, how to determine which microorganisms are “objectionable microorganisms”, how to assess their risks, and what measures are taken to control their risks, the current domestic and foreign pharmacopoeia standards lack clear technical guidance, resulting in safety hazards of inability to rule out potentially objectionable microorganisms. Therefore, the Microbiology Members of National Pharmacopoeia Committee organized the drafting of the Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products, which aims to clarify the definition of objectionable microorganisms, risk assessment procedure and methodological strategies, and provide guidance for risk assessment and control of objectionable microorganisms in non-aseptic products, so as to reduce or eliminate the risk of potentially hazardous microorganisms and ensure the safe and effective products.

II. Drafting Process

Supported by the 2022 National Pharmacopoeia (2022Y21), the Shanghai Institute for Food and Drug Control led, and Zhejiang Institute for Food and Drug Control, Liaoning Institute for Drug Control, Shaanxi Institute for Food and Drug Control, Shandong Institute for Food and Drug Control, Inner Mongolia Institute for Drug Control, Guangzhou Institute for Drug Control, and Hangzhou Digital-Micro, and representatives of some pharmaceutical companies participated in the drafting of the Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products. The research in this project clarified the definition of "objectionable microorganisms”, drafted the Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products, and solved the problems of lack of definition of "objectionable microorganisms” in non-sterile products, lack of risk control strategies and related standards, providing pharmaceutical companies and regulatory agencies with systematic, clear and operable technical standards for risk identification and control of objectionable microorganisms.

III. Overall Concept of Establishment

Through extensive survey and in-depth research, the project group clarified the definition of objectionable microorganisms in non-sterile products. Through the research and collection of pharmaceutical companies, clinical infection data, domestic and foreign non-sterile drug recalls and warning letters, etc., based on real-world data analysis, common potentially objectionable microbial types are summarized, providing reference basis for determination of objectionable microorganisms for pharmaceutical companies; research on risk characteristic factors and judgment standards of objectionable microorganisms in non-sterile drugs is carried out, and a decision tree for risk of objectionable microorganisms in non-sterile products and API and excipients is established to provide specific method paths and evaluation tools for drug supervision and pharmaceutical companies; finally, starting from the whole life-cycle control, the risk control measures such as risk elimination and risk acceptance of objectionable microorganisms in non-sterile products are studied, forming a closed loop of risk identification and risk control for objectionable microorganisms, and formulating the Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products. This standard text covers the definition of objectionable microorganisms, scope of application, common types of objectionable microorganisms, risk identification strategies for objectionable microorganisms, main characteristic factors for risk assessment of objectionable microorganisms, key points for risk control of objectionable microorganisms, judgment decision tree for unacceptable microorganisms, etc. The drafting of the Guidelines for Risk Assessment and Control of Objectionable Microorganisms in Non-sterile Products has further improved the technical standards for microbial quality control in non-sterile products and filled the gap in relevant standards in the field of pharmacopoeia.

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