Impurity Control Strategy

杂质控制策略

Elemental impurities (ICH Q3D) and nitrosamine risk assessment and control strategy.
元素杂质（ICH Q3D）与亚硝胺风险评估与控制策略。

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Product 产品	Polyethylene Oxide (PEO) · Benzalkonium Chloride (BKC) · Trehalose Dihydrate, injectable grade 聚环氧乙烷 · 苯扎氯铵 · 海藻糖二水合物（注射级）
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1 Elemental impurities — ICH Q3D risk assessment 元素杂质 —— ICH Q3D 风险评估

The risk assessment follows the ICH Q3D(R2) guideline and the corresponding general chapter on elemental impurities. Each element is assessed against its source, the probability of introduction and the ability of the process to remove it. Where no risk of introduction exists, periodic or skip testing is justified; where risk exists, routine testing with a validated ICP-MS method is applied.
风险评估依据 ICH Q3D(R2) 及相应元素杂质通则。逐元素评估其引入来源、引入可能性及工艺去除能力。 不存在引入风险的，采用定期检测或免检；存在风险的，采用经验证的 ICP-MS 方法逐批检验。

Class 类别	Element 元素	PDE oral 口服 PDE	PDE parenteral 注射 PDE	Assessment 评估	Control 控制
1	Cd	5 µg/day	2 µg/day	无有意添加；来源于设备、水与包装的潜在引入	**[to be confirmed]**
1	Pb	5 µg/day	5 µg/day		
1	As	15 µg/day	15 µg/day		
1	Hg	3 µg/day	3 µg/day		
2A	Co	50 µg/day	5 µg/day	催化剂与合金设备残留可能性	**[to be confirmed]**
2A	V	100 µg/day	10 µg/day		

Class 类别	Element 元素	PDE oral 口服 PDE	PDE parenteral 注射 PDE	Assessment 评估	Control 控制
2A	Ni	200 µg/day	20 µg/day		
2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl	按需评估		非有意添加；仅在存在合理来源时评估	[to be confirmed]
3	Ba, Cr, Cu, Li, Mo, Sb, Sn	按需评估		口服 PDE 较高；注射剂需额外评估	[to be confirmed]

PDE values are quoted from ICH Q3D(R2) for reference only and must be verified against the current guideline edition and the applicable route of administration before use in a filing.
PDE 值引自 ICH Q3D(R2)，仅供参考；用于注册申报前请核对现行指南版本及适用给药途径。

Test method and limits 检测方法与限度

Method 方法	ICP-MS, validated per USP <233> / Ph. Eur. 2.4.20 ICP-MS，按 USP <233> / 欧洲药典 2.4.20 验证
Target elements 目标元素	[to be confirmed] （建议至少覆盖 Class 1 与 Class 2A）
Frequency 频次	[to be confirmed] （每批 / 定期 / 免检，按风险结论确定）
Conclusion 结论	[to be confirmed] （风险等级：低 / 中 / 高）

2 Nitrosamine risk assessment and control strategy 亚硝胺风险评估与控制策略

The assessment follows the current FDA and EMA guidance on nitrosamine impurities in human medicines, and covers every potential source of secondary or tertiary amines together with nitrosating agents. Where a risk of formation or carry-over cannot be excluded by design, a validated LC-MS/MS method with a limit of quantitation of [to be confirmed] ppm, or lower, is applied.
本评估依据现行 FDA 与 EMA 关于人用药品亚硝胺杂质的指南，覆盖仲胺或叔胺与亚硝化试剂的所有潜在来源。 凡不能通过设计排除形成或携带风险的，采用经验证的 LC-MS/MS 方法，定量限 [待确认] ppm 或更低。

Risk source 风险来源	Assessment 评估	Control measure 控制措施
Raw materials 起始物料与原料	是否存在胺类结构或亚硝酸盐残留	[to be confirmed]
Solvents and reagents 溶剂与试剂	是否使用仲胺、叔胺或亚硝酸盐类试剂	[to be confirmed]
Catalysts 催化剂	是否含胺类配体	[to be confirmed]
Equipment and utilities 设备与公用工程	橡胶件、密封件、脱模剂、蒸汽与水的交叉污染可能性	[to be confirmed]
Packaging 包装材料	内包材是否含胺类助剂或亚硝化前体	[to be confirmed]
Cross-contamination 交叉污染	共线产品与清洁验证覆盖情况	[to be confirmed]
Storage and transport 贮存与运输	是否可能生成亚硝胺	[to be confirmed]

Control strategy summary 控制策略概要

Element 要素	Statement 说明
Overall risk conclusion **总体风险结论**	**[to be confirmed]**
Testing frequency **检测频次**	**[to be confirmed]**
Acceptance limit **可接受限度**	**[to be confirmed]** （按适用法规与剂型确定）
OOS handling **超标处理**	书面调查、批次隔离、通知客户
Change notification **变更通知**	原料、工艺或供应商变更前评估亚硝胺影响并通知客户

Statement 声明

The risk assessments above are maintained by the manufacturing site's quality unit, reviewed at defined intervals, and re-assessed whenever a change is made to raw materials, process, equipment or packaging. The completed assessment report, including raw data, is available under a confidentiality agreement.

上述风险评估由生产场地质量部门维护，按规定周期复审；原料、工艺、设备或包装发生变更时重新评估。 完整评估报告（含原始数据）可在签署保密协议后提供。

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Checked by 审核	Name 姓名:	Signature 签名:	Date 日期:
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