Updates on ICH Q

Center for Drug Evaluation, NMPA

QDG EWG

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China-Japan ICH Regional Joint Open Conference

保护和促进公众健康

ICH Quality and Multidisciplinary (CMC) Guidelines

No.	Code	Name	Time of Publication	Status
1	Q1A（R2）-Q1E	Q1A(R2): Stability Testing of New Drug Substances and Products	2003.2.6	Implemented (endorsed to be revised)
		Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products	1996.11.6	
		Q1C: Stability Testing for New Dosage Forms		
		Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	1996.11.6	
			2002.2.7	
		Q1E: Evaluation for Stability Data	2003.2.6	
2	Q2 （R1）	Q2(R1): Validation of Analytical Procedures Text and Methodology	2005.11	Under revision
3	Q3A（R2）	Q3A(R2): Impurities in New Drug Substances	2006.10.25	Implemented
4	Q3B（R2）	Q3B(R2): Impurities in New Drug Products	2006.6.2	Implemented
5	Q3C（R7）	Q3C(R7): Impurities：Guideline for Residual Solvents	2018.10.15	Under revision
6	Q3D（R1）	Q3D(R1): Guideline for Elemental Impurities	2019.3.22	Under revision
7	Q3E	Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics	/	Under development
8	Q4B	Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions/Q4B Frequently Asked Questions	2007.11.1	Implemented
9	Q5A（R1）	Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	1999.9.23	Under revision

ICH Quality and Multidisciplinary (CMC) Guidelines

No.	Code	Name	Time of Publication	Status
10	Q5B	Q5B: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products	1995.11.30	Implemented
11	Q5C	Q5C: Stability Testing of Biotechnological/Biological Products	1995.11.30	Implemented
12	Q5D	Q5D: Derivation and Characterisation of Cell Substrates Used for Production of BiotechnologicalBiological Products	1997.7.16	Implemented
13	Q5E	Q5E: Comparability of BiotechnologicalBiological Products Subject to Changes in their Manufacturing Process	2004.11.18	Implemented
14	Q6A	Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	1999.10.6	Implemented (endorsed to be revised)
15	Q6B	Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	1993.3.10	
16	Q7	Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients/Q&As	2000.11.10	Implemented
17	Q8(R2):	Q8(R2): Pharmaceutical Development	2009.8	Implemented
18	Q9	Q9: Quality Risk Management	2005.11.09	Under revision
19	Q10	Q10: Pharmaceutical Quality System	2008.6.4	Implemented
20	Q11	Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) /Q&As	2012.5.1	Implemented

ICH Quality and Multidisciplinary (CMC) Guidelines

No.	Code	Name	Time of Publication	Status
21	Q12	Q12：Technical And Regulatory Considerations For Pharmaceutical Product Lifecycle Management	2019.11.20	Implemented
22	Q13	Continuous Manufacturing of Drug Substances and Drug Products	/	Under development
23	Q14	Analytical Procedure Development and Revision of Q2(R1) Analytical Validation	/	Under development
24	M7（R1）	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	2017.3.31	Under revision
25	M4	Common Technical Document (CTD)	2016.6.15	Implemented
26	M8	Electronic Common Technical Document (eCTD)	2008.7.16	Implemented
27	M9	M9 Biopharmaceutics Classification System-based Biowaivers/Q&As	2019.11.20	Implemented

6 under revision, 3 under development, 3 endorsed to be revised

ICH Quality and Multidisciplinary (CMC) Guidelines

Published Q guidelines and related M guidelines	24
Adequately implemented in China	14 2 Tier 1 guidelines (Q1 and Q7) 1 Tier 2 guidelines (M4) 11 Tier 3 guidelines (Q2(R1),Q3A(R2), Q3B（R2），Q3C（R7），Q3D（R1），Q5A（R1），Q5B，Q5C，Q5E，Q6A，M7)
Implementation is encouraged in China	4 Q8（R2），Q9，Q10，Q11及问答
In implementation process	2 Q5D ,M9

Overview

- **Background – CM is an emergent technology getting a lot of interest from pharmaceutical and biotechnological companies. However, one identified barrier to adoption is a lack of harmonisation of regulatory expectations internationally.**

  背景：连续制造作为一个新兴技术，得到制药公司（包括生物制药）越来越多的关注。然而，国际层面监管预期缺乏协调统一，成为阻碍该技术的一个明显障碍。

- **Objective – Develop a new guideline to provide harmonisation on technical and regulatory aspects unique to CM of drug substances and drug products for small and large molecules. Main guideline covers fundamental CM aspects and annexes cover special topics with examples**

  目标：形成一个新的指导原则，期望在原料药和制剂（包括小分子和大分子）的技术和监管方面进行协调统一。其中，正文将介绍连续制造的基本原则，附录将提供特定示例。

Progress of Q13

Date	Milestone
Nov. 2018	Concept Paper and Business Plan Endorsement 形成概念文件和商业计划
Jun. 2019	Face-to-Face Meeting in support of consensus building, outline finalization 面对面会议，达成共识&确认提纲
Nov. 2019	Face-to-Face Meeting in support of development of the technical document 面对面会议，起草技术文件
Apr. 2020	Completed draft distributed to individual organizations for feedback (first internal consultation) 完成技术文件草稿征求意见（第1次）
May 2020	Virtual Meeting in support of revisions of the technical document 虚拟会议，技术文件修改
Sep. – Oct. 2020	Three virtual CM site visits 3次虚拟工厂参观
Nov. 2020	Virtual Meeting to continue revisions of the technical document and plan training materials 虚拟会议，技术文件修改，计划培训材料
Dec. 2020	Completed draft distributed to individual organizations for feedback (second internal consultation) 完成技术文件草稿征求意见（第2次）
May 2021	Incheon Virtual Meeting （May 24 – 27, 2021）develoment of step 1 sign-off version 仁川虚拟会议，2021年5月24-27日, 形成第一阶段签署文件版本

Conclusions for Incheon Meeting

- **Draft for Step 1 sign off completed**

  起草完成第1阶段签署文件

- **Ready to begin Step 1 sign off and Step 2 a/b endorsement process and initiate public consultation period**

  准备进行第1阶段签署、第2a/2b阶段推荐、启动公开征求意见

- **Ready to begin discussing development of training materials**

  着手准备讨论培训材料

Work plan: Expected future Key Milestones

Expected Completion date	Deliverable
June 2021 **2021年6月**	• **Step 1 sign-off and Step 2 a/b endorsement** 第1阶段签署、第2a/2b阶段推荐 • **Initiate regional public consultation period** 启动公开征求意见
November 2021 **2021年11月**	• **Virtual Face to Face Meeting for developing training materials** 召开虚拟面对面会议起草培训材料
June 2022 **2022年6月**	• **Face to Face Meeting** 面对面会议 • **Review and resolve public comments** 研究解决公开意见
November 2022 **2022年11月**	• **Step 3 sign-off and Step 4 Adoption of final guideline** 第3阶段签署、第4阶段采纳

Overview

- **Q2(R1) revision includes validation principles that cover analytical use of spectroscopic data some of which often require multivariate statistical analyses. The guideline will continue to provide a general framework applicable to products mostly in the scope of Q6A and Q6B.**

  Q2(R1) 修订版，涵盖分析使用光谱数据的验证原则，有些光谱数据通常需要多变量统计分析。该指 南将继续提供对Q6A、Q6B 范围内大部分产品适用的一般框架。

- **Q14 is to provide the principles relating to the description of Analytical Procedure Development process. Applying this guideline will improve regulatory communication between industry and regulators and facilitate more efficient approval as well as post-approval change.**

  Q14 是提供与分析方法开发过程描述相关的原则。应用该指南将改善业界与监管机构之间的监管沟通，并促进更有效的审批和审批后变更。

Progress of Q14

Date	Milestone
Jun. 2018	*Topic was endorsed* 该提议正式采纳
Nov. 2018	*Final Concept Paper and Business Plan endorsed* 议题概念文件和工作计划正式通过审核
Jun. 2019	Second EWG Meeting
Nov. 2019	Third EWG Meeting
Q2. 2020	First intra-constituent review conducted 形成第一稿
May 2020	Fourth EWG Meeting 审议第一稿
Nov. 2020	Fifth EWG Meeting
Q1. 2021	Second intra-constituent review conducted **形成第二稿**
June 2021	Sixth EWG Meeting 审议第二稿

Q2(R2)/Q14

Progress made at the meeting

Common topics 共同议题

- Clarified shared scope 明确适用范围

ICH Q2(R2)

- Refined range content 细化“范围”内容
- Aligned on additional definitions related to validation 统一解释再验证,交叉验证 ,共同验证
  Revalidation, cross-validation, co-validation
- Agreed that the guidance should not be prescriptive on regulatory submission content
  同意该指南不再规定监管提交的内容
- Deep dive into robustness 深入研究耐用性

ICH Q14

- Reviewed case studies on ECs for analytical procedures and change management; agreed to form subteam to elaborate on the topic
  审查了基于EC 研究的分析方法和变更管理案例；确定成立亚组详细阐述该主题
- Deep dive into parameter range evaluation, risk assessment, and analytical procedure control strategy topics
  深入探讨了参数范围评估、风险评估及分析方法控制策略等主题
- Discussion of opportunity to restructure document based on development and post-approval lifecycle management
  基于分析方法开发和批准后生命周期管理，讨论重新调整文件结构的可能性

Next Steps

ICH Q2(R2)

- Finalize Introduction, Tables, TAE　　最终确定“介绍”、表格及“TAE”等内容
- Update Annex 1 & 2　　更新附录1和2

ICH Q14

- Key concepts require further work, i.e., ECs and Change Management　进一步明晰关键概念
- Evaluate opportunity to restructure for clarity, including update of introduction　进一步梳理结构
- Revise Robustness chapter　　修订耐用性章节
- Revision of Annex B (Risk Assessment) & Annex E (Multivariate MLC)
  修订附录B (风险评估) & 附录E (多变量模型生命周期构成案例MLC)
- Draft Annex D (Change Management)　起草附录D (变更管理)

Work Plan: Expected Future Key Milestones

Expected Completion Date	Deliverable
Sep 2021	• Complete revisions of draft Q2(R2) and Q14 based on priorities agreed at Incheon meeting
Sep/Oct 2021	• Interim EWG plenary meetings to finalize draft text
Vancouver Nov 2021	• *Step 1* sign off
Dec 2021	• *Step 2a/b* endorsement
Jan – Jun 2022	• Public consultation period
Nov 2022	• *Step 3* • *Step 4*

Overview

- **Background – ICH has developed guidelines covering many aspects of impurities, including process and product related substances (Q3A, Q3B), residual solvents (Q3C) , elemental (Q3D) and mutagenic (M7) impurities. However, there is no internationally harmonized guidance on extractables and leachables (E&L) impurities, which are related to drug manufacturing systems, container-closure systems and drug delivery device components.**

背景：ICH协调制定了一系列杂质相关的指导原则，包括原料药和制剂的有关物质（**Q3A, Q3B** ）、残留溶剂（ **Q3C**） 、元素杂质（ **Q3D**）和遗传毒性杂质（ **M7** ）。然而对于从药品生产系统、包装系统和给药装置中引入的杂质—可提取杂质和浸出杂质，尚缺少协调一致的指导原则。

- **Objective – Develop a new guideline on the assessment and control of extractables and leachables (E&L), mainly including aligned framework, safety assessment and thresholds, chemical testing and lifecycle management, etc.**

目标：将形成一个新的指导原则，以协调可提取杂质和浸出杂质的评估和控制，主要包括：统一的E&L杂质评估流程、杂质安全性评估及阈值、化学测试以及上市后变更管理等内容。

Progress of Q3E

Past completion date	Milestone
Jun. 2019 ***2019年6月***	*Topic was endorsed* 该提议正式采纳
Jul. 2020 ***2020年7月***	*Final Concept Paper and Business Plan endorsed* 议题概念文件和工作计划正式通过审核
Nov. 2020 ***2020年11月***	*First EWG Meeting* 首次EWG会议 • Discussion of the table of contents and four main topics of Q3E, including quality assessment, safety assessment, chemical testing and lifecycle management. 讨论指导原则目录以及指导原则所涵盖的四大模块，包括质量评估、安全性评估、化学测试、上市后变更。
June 2021 ***2021年2月***	*Second EWG Meeting* 第二次EWG会议 • Discussion of the scope and four main flowcharts of Q3E. 讨论指导原则适用范围以及四大模块的流程图。
June 2021 ***2021年6月***	*Third EWG Meeting* 第三次EWG会议

ICH Q3E

- **Table of Content of Q3E 大纲**

1、INTRODUCTION 引言

2、**ENHANCED QUALITY BY DESIGN FRAMEWORK** ***Quality Assessment subteam 质量评估亚组***
E&L杂质评估整体框架/流程

3、**SAFETY ASSESSMENT AND THRESHOLDS** ***Safety Assessment subteam 安全性评估亚组***
安全性评估和阈值

4、RISK ASSESSMENT风险评估
- **Prior knowledge 先验知识**
- **Chemical testing 化学测试** ***Chemical Testing subteam （NMPA）化学测试亚组***

5、RISK CONTROL风险控制

6、DOCUMENTATION AND COMPLIANCE文件和合规

7、RISK REVIEW风险回顾
- **Lifecycle Management 生命周期管理** ***Lifecycle Management subteam (NMPA) 生命周期管理亚组***

Conclusions for Incheon Meeting
仁川会议总结

- **Discussion of the scope of Q3E (herbal products)**

  讨论Q3E适用范围 （植物提取类药物）

- **Discussion of the drafts written by four subteams based on the established flowcharts, including Quality Assessment Subteam, Safety Assessment Subteam, Chemical Testing Subteam and Lifecycle Management Subteam.**

  讨论四个工作亚组基于先前确定的流程图撰写的初稿，包括质量评估亚组、安全性评估亚组、化学测试亚组和全生命周期管理亚组。

ICH Q3E

➢ Discuss the Scope of Q3E (need further discussion)

讨论指南适用范围

- **Medical Devices/医疗器械** **Exclude /不包括**

  The definition of MD is different among regions. 各国定义不同，建议不包括。

- **Herbals/ 植物提取药物** **Silent /无明确结论**

  The definition of herbal products is different among regions. However, when liquid excipients are contained in DP, the principle may apply. 各国定义不同，部分含液体辅料的植物提取药可参考。

- **Excipients/辅料** **Exclude/不包括**

- **Products in Clinical Development/临床开发期间产品** **The principle of M7 approach can be used.** 可参考ICH M7思路

- **Marketed Products /已上市产品** **The principle of M7 approach can be used.** 可参考ICH M7思路

Quality Assessment draft　质量评估部分初稿

➢ *referring to ICH Q9 current revisions 参考ICH Q9当前修订版本*

- Introduction

简介

- Scope

范围

- General Principles

一般原则

Hazard Identification

危害物识别

Risk Analysis

风险分析

Risk Evaluation

风险评价

- Risk Assessment and Risk Control

风险评估及风险控制

	Knowledge impacting severity scoring
Knowledge Types: Studies	Extractable studies data, e.g., qualitative understanding of substances present from instrumental analysis or total amount of substances present via non-volatile residue (NVR) and/or total organic carbon (TOC)
Knowledge Types: Material Compliance (Direct Relevance)	Toxicological study data including biocompatibility assessments e.g. ISO10993-1 compliance[8] USP <87>, USP <88> [9, 10]
	Material compliance statements with direct relevance to severity term, e.g., USP <660>,[11] USP <661>,[12] USP <661.1>,[13] USP <661.2>,[14] USP <381>,[15] USP <232>[16] Ph.Eur. 3.1 and Ph.Eur. 3.2[17, 18]
Knowledge Types: Material Compliance (In-Direct Relevance)	Material compliance statements with in-direct relevance to severity term, e.g., Food compliance (USA), food compliance (EU) REACH declarations
Knowledge Types: Product Knowledge	Compositional information, supplier information (non-study or compliance) such as absence statements

	Knowledge impacting probability scoring
Knowledge Types: Studies	Leachable studies (or simulation study) data Extractable studies data
Knowledge Types: Product Knowledge	Manufacture and/or processing steps with ability to affect material or leaching (e.g., sterilization, coating, dilution or purge points) Knowledge on limiting solubility and understanding of partitioning behavior between material and formulation (Direction and extent of migration) • Solubilization strength of pharmaceutical preparation (composition/polarity, surfactants / co-solvents (solubilizers)) • Differential solubility / solubilization of leachables in material versus drug solution Kinetics of leaching (i.e., time to equilibrium): • Diffusion behavior • Structure and morphology of material • Temperature • Contact time • Contact surface area to material volume ratio (SA/V_{mat})

Q1: Many items are regional standards/guidance, especially addressing in U.S & Eur., which may not be appropriate descripted in ICH. Furthermore, different region may have their own additional Compliance requirements.

问题1：很多项目引用区域性指南/标准，在ICH 文件中体现并不恰当，且区域性要求/标准也不尽相同。

Q2: The applicability of scoring system?

问题2：打分系统的可行性?

Safety assessment and thresholds 安全性评估部分 初稿

➢ A 'de-risking' strategy: 基于已有知识降低风险的策略

Toxicological knowledge on compound- 化合物的毒理学信息	**Step 步骤**	**Action required 评估**
Substance-specific data available including CoC 化合物存在自身毒理学信息时 包括**特殊关注队列杂质 (CoC)**		Use ST_{ss} 采用该化合物特定的安全性阈值STss进行评估
None 无	1	Check if compound is CoC compound 确认是否属于CoC
If compound has a CoC structural alert without substance-specific data 如化合物含CoC类警示结构，且没有自身毒理学信息	2a	SAR analysis/RaX; class-specific TTC. 构效关系分析、分类 根据分类进行TTC评估
Compound is not a CoC compound 如果化合物为非CoC的遗传毒性杂质	2b	Use ST_m; 1.5, 10, 20 or 120 µg/day 采用遗传毒性杂质阈值STm评估
Compound is not a mutagen 如果化合物非遗传毒性杂质	3	Use ST_{nm} 采用非遗传毒性杂质控制阈值

Chemical Testing 化学测试部分 初稿

- Gather information and compile prior knowledge
  收集先验知识
- Material/Component Selection and Characterization
  材料/组件的选择和表征
- Risk Assessment
  风险评估
- Extractable study (purpose)
  提取研究
- Leachable study (purpose)
  浸出研究
- Conclude, summarize and submit
- 结论以及申报资料提交

Q1：approach and tox assessment should be discussed with Safety Thresholds subteam.
问题1：AET的设定需与安全性评估阈值相结合。

Q2：Role of simulation studies and application.
问题2：模拟试验的作用和应用情形。

Q3：Correlation of E/L studies.
问题3：E/L研究的相关性。

Lifecycle Management 全生命周期管理 初稿

- Gather information and compile prior knowledge
  收集先验知识
- Instances where E&L re-assessment may be warranted in lifecycle management
  常见上市后变更示例
- Risk Categorization
  风险分类
- Assessing E/L for Low-Risk Materials and other Changes

  低风险材料相关变更 （符合药典标准/食品包装相关标准）

Q: The gap between regions for Phamacopoeia standards and Food Contact Material management systems and standands.

问题： 各国家地区间药典和食品包装的管理体系、执行标准存在差异。

- Assessing E/L for Medium/High Risk Materials and other Changes

  中、高风险材料相关变更 （开展提取/浸出研究）
- Assessing E/L for Novel Situations (typically would involve a new regulatory submission)

  新情况（往往涉及新产品申报，不应再按上市后变更管理）

ICH Q3E

Further Work Plan

Expected Completion
➢ Subteams continue to work. 四个亚组继续开展工作
➢ A harmonizing group be set up to work on the gaps between four subteams. 成立单独的协调小组，协调四个亚组之间的内容
➢ Cooperation with ICH Q9 group, maybe for some case studies. 与ICH Q9的合作，可能讨论案例合作
➢ Anticipated E/L Impurities List （to be considered） 常见E/L杂质清单（待定）

Thanks For Your Attention !

保护和促进公众健康