Overall introduction on ICH

ICH’s mission is to HARMONIZE global regulatory requirements to ensure safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

Objectives

- Harmonize criteria and documents required for approval and authorization of new medicinal products across different regions
- Improve efficiency of new drug development and facilitate faster patient access to new, safe, and effective drugs
- Create venue for involvement of both regulatory and industry stakeholders in harmonization work

Intended Benefits

- Prevent clinical trial duplication
- Minimize use of animal testing without compromising safety and effectiveness
- Streamline submission preparation and regulatory processes, providing better use of limited resources
- Share industry/regulatory experience and knowledge

Harmonisation does not mean loss of national sovereignty/autonomy

Provides platform for better communication between industry and regulator to provide faster access to safe and effective medicines to patients

Source: Health Advances analysis, ICH website, FDA 2017 Overview of ICH, Kuhnert 2011 DIA Global Forum, Brennan 2016 RAPS.
Overall introduction on ICH
ICH framework facilitates paradigm shift

- Providing common technical language for industry and regulators
- Global drug development
- Exchange of knowledge and information

Faster access of Safe and Effective good quality medicines for PATIENTS

ICH Stakeholders
Members of ICH represent the major regulatory and industry stakeholders, both domestically and internationally.

**Founding Members**
- Regulatory Members
  - FDA, US
  - European Commission, Europe
  - PMDA, Japan
- Industry Members
  - PhRMA
  - EFPIA
  - JPM

**Observers**
- Standing Observers
  - IFPMA
- Legislative or Administrative Authorities
  - CDSCO, India
  - CECMED, Cuba
  - COFEPRIS, Mexico
  - HSA, Singapore
  - MCC, South Africa
  - National Center, Kazakhstan
  - Roszdravnadzor, Russia
  - TDA, Chinese Taipei
  - TGA, Australia
- Regional Harmonization Initiatives
  (e.g. APEC, ASEAN, EAC etc.)
- International Pharmaceutical Industry Organizations (APIC)
- International Organizations with an Interest in Pharmaceuticals (e.g. CIOMS, IPEC, USP, PIC/S etc.)

**Other Members**
- Regulatory Members
  - CFDA, China
  - Health Canada, Canada
  - Swissmedic, Switzerland
  - ANVISA, Brazil
  - MFDS, Republic of Korea
- Industry Members
  - BIO
  - IGBA
  - WSMI

Note: BIO = Biotechnology Innovation Organization, IGBA = International Generic and Biosimilar Medicines Association, WSMI = World Self-Medication Industry.
Source: Health Advances analysis, ICH website.
Overall introduction on ICH Governance of ICH Association

ICH and Q4B Pharmacopeias Harmonization – Beijing, 30th November

Governance of ICH Association

MedDRA: Medical Dictionary for Regulatory Activities

ICH New Topic Selection Process

Topics are submitted by ICH members and observers. All new topics, and their subsequent concept papers and business plans, must be endorsed by the ICH governing body to be selected for harmonization.

New Topic Proposed

- Proposed by any ICH member or observer, per annual New Topic selection process

Topic Endorsed

- ICH assembly endorses or rejects topics at annual meeting, by consensus agreement or majority vote

Working Group Established

- Informal Working Group established, typically led by member proposing topic

Concept Paper/Business Plan Development

- Concept Paper provides further context and scope
- Business Plan outlines, timelines, costs, impact and benefits of harmonization

Endorsement and EWG Established

- Final Concept Paper and Business Plan submitted
- EWG established for development new guideline or revision to existing guidelines, or other ICH work product

Note: EWG = Expert Working Group
Source: Health Advances analysis, ICH website, ICH 2017 SOP of the ICH Working Groups.

ICH and Q4B Pharmacopeias Harmonization – Beijing, 30th November
Formal ICH Procedure

ICH WG decisions during the formal ICH Procedure should be made by consensus, if consensus cannot be achieved, the MC should be consulted.

**Step 1: Consensus Building Technical document**
- An ICH WG will work to develop a consensus draft Technical Document
- Sign-off on the Step 1 Technical Document

**Step 2: Confirmation of consensus and endorsement of a draft guideline**
- Regional Regulatory are consulted and invited to discuss comments received in each region and revise the draft Guideline
- Finalization of Step 3 Experts Draft Guideline sign-off

**Step 3: Regulatory consultation and discussion**
- Assembly adopts a harmonized Guideline based on a recommendation from the MC and consensus of the ICH Regulatory Members

**Step 4: Adoption of an ICH harmonized guideline**
- The ICH Guideline is implemented by each Regulatory Member in their respective region

**Step 5: Implementation**

---

Overall introduction on ICH
Overview of ICH topics implemented under Discussion/Development (as of Sept 2018)

1. Continuous Manufacturing (Q13)
2. Analytical development and validation (Q7A, Q14)
3. Lifecycle Management (Q12, Q7, Q9)
4. Specifications (Q6A, Q6B)
5. QA/QC (Q10, Q11)
6. GMP and Change Management (Q7, Q8)
7. Development and Manufacture of DS (Q11, Q14, Q6A)
8. Stability (Q2, Q3A, Q3B)
9. Quality Risk Management (Q10, Q9)
10. Impurities DS/DP (Q1A-Q1E)
11. Elemental Impurities (Q1F)
12. Residual Solvents (Q3C)
13. Quality of Biotech products (Q4B)
14. Maintenance procedure (Q30, Q4B, Q5A-Q5E, Annexe 1-14)
The harmonization of specific compendial test chapters has been considered as critical by the ICH steering Committee to achieve full relevance of the ICH Q6A & Q6B guidelines. As mentioned in the following statement extracted from ICH Q6A:

**2.8 Pharmacopoeial Tests and Acceptance Criteria**

The full utility of this Guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products...

...To signify the harmonized status of these procedures, the pharmacopoeias have agreed to include a statement in their respective texts which indicates that the procedures and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable.

---

**Q4B Harmonization**

**Issues / Challenges**

PDG harmonization text on General method can still report some differences between PhEur./USP/JP

**Example**

Same electrode system is described combining a glass electrode and a reference electrode, different characteristic requirements:

- **JP**: Reproducibility n=5 within 0.05 pH unit
- **USP**: capable of reproducing pH
- **PhEur.**: sensitivity

The operational pH corresponds to the theoretical pH. The composition of common buffers is basically the same:

- **JP**: Two buffers within 0.02 pH unit (amongst a selection of 6 buffers)
- **PhEur.**: Two buffers and the intermediate buffer testing must not differ by more than 0.05 pH unit (amongst a selection of 9 buffers)
- **USP**: Two buffers not exceed 4 pH units and The pH of the second buffer solution is within ±0.07 pH unit of the tabulated value (amongst a selection of 5 buffers)

Recommendation on temperature for measurement is different among JP, Ph.Eur. and USP as follows:

- **JP**: 20 °C / the temperature of a sample solution must be controlled to be the same as that of the pH standard solutions (within 2 °C)
- **PhEur.**: 20-25 °C / all measurements are made at the same temperature
- **USP**: 25±2 °C / Buffer Solutions for Standardization at the temperature at which the test material is to be measured

Do these methods can be nevertheless considered equivalent / interchangeable?

Do differences impact on the ability to achieve a result with the same accept and reject capability?
Q4B Harmonization

Consequences

Representative from Industries request ICH SC to create an EWG to address Regulatory Acceptance (3 regions) of harmonized pharmacopeial methods from Ph.Eur./JP/USP (PDG)

Considering the following pre-requisites

• Develop a Regulatory, Industry, and Pharmacopoeial FORUM
• Resolve potential regulatory issues resulting from PDG harmonization efforts to judge if the remaining text differences don’t jeopardise the harmonisation status
• Try to speed up and ensure consistent harmonization by implementing a process
Q4B Harmonization

What is Q4B?

Official denomination of the Expert Working Group (EWG):
Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions

Composition of EWG

Q4B Harmonization

Why is Q4B needed?

Intended Objective

- Promote harmonization by making a recommendation on the interchangeability of the ICH regional compendium (USP/JP/Ph.Eur.) based on well advanced PDG-harmonized texts
- Ultimate aiming is to avoid multiple testing by giving ability to generate analytical data by a single test method which is acceptable in each region, despite differences in the Harmonisation text.
Q4B Harmonization
Benefice for StakeHolders

Savings in time, effort and cost

Regulatory Agencies
- To reduce or eliminate the need to go through a justification procedure as to the use of other compendial methods (done one time to eliminate repetitive justifications) – interchangeability

PDG
- To increase value and further legitimate their harmonization work and outcomes

Industries
- To avoid uncertainty of rejection by investigating the similarity or differences among pharmacopoeia and judge the interchangeability by themselves.
- Globally unify testing strategies [for applications and other regulatory (compliance) needs] one test rather than three to avoid
  - Duplicate testing without added value for the patient
  - Additional validation or equivalence studies (Cross-validation)
  - Multiple version of Marketing application
Q4B Harmonization
Scope & Status

- ICH SC establishes Q4 EWG scope
- Only general chapters were concerned (excluded excipients, API or products monographs)
- Initial scope, address 11 General Test Chapters mentioned in guideline Q6A
- Scope was expanded with 5 new chapters coming from Q6A & Q6B

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<td>2</td>
<td>Extractable Volume</td>
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<td>3</td>
<td>Particulate Contamination</td>
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<td>Microbial Enumeration Tests</td>
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<td>Tests for Specified Microorganisms</td>
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<td>4C</td>
<td>Microbiological Acceptance Criteria</td>
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<td>Disintegration Test</td>
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<td>6</td>
<td>Uniformity of Dosage Units</td>
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<td>8</td>
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<td>13</td>
<td>Bulk Density and Tapped Density</td>
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<td>14</td>
<td>Bacterial Endotoxins</td>
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Q4B Harmonization
Historical Story

- SC approves Q4B Work Plan
- Apr. 2003: Q4B EWG begins evaluating PDG harmonized text
- Nov. 2003: 1st Annex approved (Residue on ignition/sulphated Ash)
- Jun. 2006: Completion of the scope of 11+5 General Test Chapters
Q4B Working Mechanism
Process of Harmonisation

PDG Process
Stage 1: Identification
Stage 5B: Sign-off: sign-off ends PDG process
Stage 7: Inter-Regional Implementation (in each Pharmacopeia)

Q4B Process
Step 1: Evaluation of the documents for regulatory impact prior to sign-off the Draft Topic-specific Annex
Step 2: Steering Committee review
Step 3: Regulatory consultation in the three regions
Step 4: The ICH Steering Committee adoption
Step 5: Regional regulatory implementation

Q4B Process steps
Process of Harmonisation - Activities in Step 1

1. PDG provide to Q4B EWG:
   - PDG harmonized text
   - JP/EP/USP draft version of the text is intended to be published
   - Briefing note to delineate any local differences or potential issues and appropriate supporting data
   - Printing timelines to move each pharmacopeia to official status

2. Q4B member parties bring the documents back to their constituents for independent evaluation

3. Q4B EWG reviews the evaluations

4. Issues discussed within Q4B EWG for possible resolution

5. Evaluation results and possible resolution mechanisms conveyed back to and/or discussed with PDG

6. Once issues are resolved, Q4B EWG recommends approval (ICH Step 2) to the ICH SC – start of Annex process
Q4B Harmonization

**Interchangeability Declaration**

The status means that any of the official texts from JP, Ph. Eur., or USP can be substituted one for the other (appropriately referenced) in the ICH regions for purposes of the pharmaceutical registration/approval process.

Using any of the interchangeable methods, an analyst will reach the same accept or reject decisions.

**Example**

**Endotoxin Methods**

- Turbidimetric Tech.
- Chromogenic Tech.
- Gel Clot Tech.

**Comparison of the following parameters:**
- Limit of detection and inhibition/enhancement
- Sensitivity (spiked samples & positive samples)
- Variability

**Assessment of Interchangeability**

- Recombinant Horseshoe Crab Factor C Assay
- Monocyte Activation Type Pyrogen Test
Q4B Harmonization
Annex Content

Each topic-specific Annex indicates whether and how the regulatory authorities will accept the chapters as interchangeable when the Annex is implemented in each region.

Section 2

• Contain the Q4B recommendation of interchangeability, and may include specific considerations regarding the pharmacopoeial chapters
• Include in drug product registrations, as well as information needed by testing laboratories to enable use of the harmonized chapters.

Section 4

• For existing product registration: Any change related to the Annex should be subject to notification/variation in accordance with established regional regulatory mechanism pertaining to compendial changes.
• For new product registration, provide reference in the application dossier to pharmacopoeial text(s) declared interchangeable

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   2.2 Acceptance Criteria
3. TIMING OF ANNEX IMPLEMENTATION
4. CONSIDERATIONS FOR IMPLEMENTATION
   4.1 General Consideration
   4.2 FDA Consideration
   4.3 EU Consideration
   4.4 MHLW Consideration
   4.5 Health Canada Consideration
5. REFERENCES USED FOR THE Q4B EVALUATION
At the beginning there was only PDG (Q4A)

- Pharmacopoeial Discussion Group (PDG) created in 1990
- Associated to ICH but not really an ICH EWG
- composed of EP, JP, and USP representatives
- Aim of PDG: harmonisation of excipients monographs and general chapters within the 3 pharmacopoeias
- But PDG process is slow
- Even after the harmonisation step, differences remain between the 3 pharmacopoeias, and as regulators are not part of PDG there is no absolute certainty that one text will be accepted by the regulators of the two other regions
ICH and Q4B Pharmacopoeia Uniform Coordination

Lionel Randon

Beijing, 2018 November 30th

Overall Introduction

ICH’s mission is to coordinate global pharmaceutical regulatory requirements to ensure the most effective use of resources to develop and register safe, effective, and high-quality drugs.

- ICH Human Medicinal Products International Coordination Committee

**Objectives**

- Coordinate standards and documents required for the approval and authorization of new drugs in different regions
- Improve the efficiency of new drug development and increase patient access to safe and effective new drugs
- Create a platform for coordination work involving regulatory authorities and industry stakeholders

**Expected Benefits**

- Prevent repetitive clinical trials
- Minimize animal testing while ensuring safety and efficacy assessments
- Standardize submission preparation and regulatory approval processes to better utilize limited resources
- Share industry organizations/pharmacopoeia experience and knowledge

- Coordination does not mean the loss of national sovereignty/autonomy

For industry organizations and regulatory authorities to better communicate, thereby enhancing patient access to safe and effective drugs.

Source: Health Advances, ICH website, FDA 2017 ICH profile, Kuhnert 2011 DIA Global Forum, Brennan 2016 RAPS.
ICH整体介绍
ICH框架促进以往模式转变

- 为行业组织和监管机构提供通用技术语言
- 全球药物研发
- 知识和信息交流

患者更快地获得安全有效的高质量药品

ICH利益相关者
ICH成员代表着国内和国际主要监管机构和行业组织的利益相关者。

创始人

<table>
<thead>
<tr>
<th>创始成员</th>
<th>观察员</th>
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<tr>
<td>监管机构成员</td>
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<td>- FDA, 美国</td>
<td>- WHO</td>
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<td>- CIBM，印度</td>
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<td>- PMDA，日本</td>
<td>- CECH，古巴</td>
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<td>行业组织成员</td>
<td>- CEFPRIS，墨西哥</td>
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<td>- 药品医疗器械及社会国家中心，哈萨克斯坦</td>
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<td>- 俄罗斯药品局，俄罗斯</td>
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其他成员

- 监管机构成员
  - GIPA，中国
  - 加拿大卫生部，加拿大
  - 瑞士卫生部，瑞士
  - ANVISA，巴西
  - MFSIS，大韩民国
- 行业组织成员
  - BIO
  - IGBA
  - WSMI

注：ICH创始成员包括：WHO国际药物非临床非生物研究协会、IUPHAR生物制药研究学会协会、ICH研究和开发协会、ICH成员。
ICH整体介绍
ICH协会的管理组织架构

ICH新题目选择程序
ICH成员和观察员提交题目。所有新选题目及其后续概念文件和业务计划均必须获得从事协调统一的ICH管理机构背书。

• 由任何ICH成员或观察员按照年度新题目选择程序提出
• ICH大会通过达成一致
• 通常由提出题目的成员领导成立一个非正式工作组
• 概念文件提供进一步的背景和范围
• 业务计划纲要、时间表、成本、影响和统一协调获益
• 提交的最终概念文件和业务计划
• 为制定新的指导原则或修订现有指导原则、或其他ICH工作文件而成立EWG

采纳和实施
ICH和Q4B药典统一协调
- 北京，11月30日
7正式的ICH程序
应通过达成共识作出正式ICH程序中的ICH WG决策，如果无法达成共识，应咨询MC

### 第一步：达成共识的技术文件
- ICH将致力于制定统一意见的技术文件草案
- 签署第一步技术文件

### 第二步：确认共识和背书指导原则草案

### 第三步：向监管机构协商与讨论
- ICH将邀请监管机构对第二步的意见进行讨论
- 对第三步专家签署的指导原则草稿

### 第四步：采纳一项ICH协调统一的指导原则
- 代表大会根据MC建议和ICH监管机构成员的共识
- ICH指导原则由相应地区的监管机构成员实施

### 第五步：采纳和实施

---

### ICH整体介绍

正在讨论/创建的ICH题目概述
（截至2018年09月）
ICH和Q4B药典统一协调

ICH指导委员会认为某些药典特定检测章节的协调统一对于充分实现ICH Q6A&Q6B指导原则的相关性至关重要，如从ICH Q6A中选取的以下声明所述。

2.8 药典检测和验收标准

本指导原则的充分应用取决于是否能够成功完成对新原料药或新制剂质量标准中通常考察的多个属性的药典检查方法的协调统一。为说明上述检查方法的协调统一状态，各药典会已同意在其相应章节中纳入一项声明，表明所有三个药典的检查方法和验收标准均视为等效，因此具有可互换性。

Q4B协调统一

问题/挑战

对通则检查方法的PDG协调报告仍然显示PhEur./USP./JP之间还存在某些差异。尽管如此，是否可视为这些方法具有等效性/可互换性？这些差异是否会影响到对于一种结果可以产生相同的接受和拒绝的能力？
Q4B协调统一
后果

行业组织代表要求ICH SC成立一个EWG，以处理对Ph. Eur./JP/USP/PDG药典方法协调统一后的监管机构认可（3个地区）

需考虑以下先决条件

• 创建一个药政监管、行业组织和药典论坛
• 解决PDG协调工作导致的潜在药政监管问题，以判断剩余的文字差异不会削弱整个协调统一状态
• 尝试通过实施来加快并确保协调一致
Q4B协调统一
什么是Q4B？

专家工作组（EWG）的官方名称：ICH地区使用的药典文字评价与建议

EWG的组成

- 药政监管部门
- 行业组织代表
- 观察员

Q4B协调统一
为什么需要Q4B？

预期目的

- 基于先进的PDG协调统一后的内容，通过对ICH地区药典（USP/JP/Ph. Eur.）的可互换性提出建议，促进协调统一
- 最终目的是通过能够生成采用单一检查方法获得在各地区均被接受的分析数据来避免多重检验，尽管协调一致的内容存在差异。
Q4B协调统一
利益相关者获益
节省时间、精力和成本

药政审批机构
- 减少或删除对使用其他药典方法时需提供依据步骤的要求（只进行一次，不需要多次提供依据）- 可互换性
- 提升价值并进一步合理协调其工作和成果

行业组织
- 通过考察药典的相似性或差异性来避免发生被拒绝的不确定因素，并自行判断可互换性。
- 全球统一的检查方法策略[对于申请和其他药政监管（合规性）要求]，采用一种检查方法，避免采用三种方法
  - 重复检查并未给患者带来附加值
  - 额外验证或等效性研究（交叉验证）
  - 多个版本的上市申请资料
**Q4B协调统一**

**范围和状态**

- ICH SC确立Q4 EWG范围
- 仅涉及通则（辅料、API或产品各论除外）
- 初始范围，说明指导原则Q6A中提及的11个一般检查章节
- 来自Q6A & Q6B的5个新章节内容范围扩大

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<td>3</td>
<td>颗粒污染</td>
<td>第5步R1</td>
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<td>4A</td>
<td>微生物计数检查</td>
<td>第5步R1</td>
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<tr>
<td>4B</td>
<td>特定微生物检查</td>
<td>第5步R1</td>
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<td>4C</td>
<td>微生物学检查标准</td>
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<td>5</td>
<td>崩解试验</td>
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<td>6</td>
<td>重量单位均度</td>
<td>第5步R1</td>
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<td>7</td>
<td>溶出度检查</td>
<td>第5步R2</td>
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<td>8</td>
<td>无菌检查</td>
<td>第5步R1</td>
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<td>9</td>
<td>片剂硬度</td>
<td>第5步R1</td>
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<td>10</td>
<td>聚丙烯酰胺胶凝胶电泳</td>
<td>第5步R1</td>
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<tr>
<td>11</td>
<td>毛细管电泳</td>
<td>第5步R1</td>
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<td>12</td>
<td>分析筛选</td>
<td>第5步R1</td>
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<tr>
<td>13</td>
<td>松散堆积密度和振实堆积密度</td>
<td>第5步R1</td>
</tr>
<tr>
<td>14</td>
<td>细菌内毒素</td>
<td>第5步R1</td>
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</tbody>
</table>

**Q4B协调统一**

**发展史**

- 2003年04月 SC批准Q4B工作计划
- 2003年11月 Q4B EWG开始评价PDG协调后的内容
- 2006年06月 批准的首个附件（炽灼残渣/硫酸盐灰分）
- 2012年10月 完成11+5个一般检查章节的范围

**现状**

- 维持现有方法
Q4B工作机制
协调步骤

PDG步骤
阶段1：鉴定
步骤5B：签署
步骤6：签署PDG结束程序
步骤7：地区间实施（各药典）

Q4B步骤
步骤1：签署特定题目草案附件前，评价药政监管影响的文件
步骤2：指导委员会审查
步骤3：3个地区的监管机构协商
步骤4：ICH指导委员会采纳
步骤5：地区监管机构实施

Q4B程序步骤
协调程序-步骤1中的活动

1. PDG向Q4B EWG提供：
   - PDG协议后的内容
   - 各公布的JP/EP/USP正文草案
   - 对任何地方差异或潜在问题的意见说明和支持数据
   - 药典开始进入官方状态的时间表
2. 各Q4B成员将文件带回至其成员单位进行独立评价
3. Q4B EWG审查评价结果
4. Q4B EWG内部讨论可能解决的问题
5. PDG传达和/或PDG讨论的评价结果和潜在解决机制
6. 一旦问题得到解决，Q4B EWG建议ICH SC批准（ICH步骤2）-附件程序启动
Q4B协调统一
可互换性声明

该状态意味着ICH地区中JP、Ph.Eur.或USP的任一官方内容可替代另一种官方内容（适当参考），用于药品注册/批准程序。

分析员使用任何可互换的方法将作出相同的接受或拒绝决策

举例

内毒素方法

- 比浊法
- 显色法
- 重组鲎试剂因子C测定
- 单核细胞活化型热原试验

可互换性评估

比较以下参数：
- 检测限和抑制/增强作用
- 灵敏度（加标样品和阳性样品）
- 变化性
Q4B协调统一
附件内容

附件各特定题目说明当在各地区实施附件时，药政监管部门是否以及如何将接受可互换性章节内容。

第2节

- 包含可互换性的Q4B推荐内容，并可能包括有关药典章节的特殊考察因素
- 包括在制剂注册中，以及检测实验室所需的信息，以便使用协调统一的章节。

第4节

- 对于已有产品注册，对于附件相关的任何变更，均应按照当地政府建立的针对药典变更的药政管理制度进行备案/变更申请。
- 对于新产品注册，在申请注册资料中，提供申请可互换性药典正文的参考文献。
谢谢

备份
开始时仅存在PDG（Q4A）

- 1990年创建药典讨论组（PDG）
- 与ICH相关，但并非真正的ICH EWG
- 由EP、JP和USP代表组成
- PDG目的：协调统一3部药典中的辅料各论和通则
- 但PDG进展较慢
- 即使在完成协调步骤后，3部药典之间仍存在差异，由于监管机构不是PDG的成员，因此无法绝对保证另外两个地区的监管机构将接受同一版本内容