2018推動藥廠GMP國際化業者說明會

藥廠GMP國際法規新訊

2017-11 ~ Present

107-11-05 & 09

By

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PIC/S Guide to GMP

PIC/S GMP Guide New/Revised (PIC/S--PE 009-14 GMP Guide)

PIC/S--PE 009-14 GMP Guide - New

PE 009-14_GMP Guide Introduction
PE 009-14_GMP Guide Part I - Basic Requirements for Medicinal Products
PE 009-14_GMP Guide Part II - Basic Requirements for APIs
PE 009-14_GMP Guide Annexes

PIC/S--PE 009-14 GMP Guide - Revision

Revision of Chapters 3, 5 & 8 (Part I)
Revision of Annex 17 - Real Time Release & Parametric Release

PIC/S--PE 009-14 GMP Guide - Adoption & Entry into force

Adoption by the Committee on **17-18 April 2018**
Entry into force on **1 July 2018**

PIC/S GMP Guide New/Revised (PIC/S--PE 009-14 GMP Guide)

The PIC/S GMP Guide (**PE 009-14**)**:**

has been **revised** according to the EU GMP Guide and are now **in alignment with** the principles of Quality Risk Management (**ICH Q9**).

Chapters 3, 5 and 8 of the PIC/S GMP guide have been **revised** and have entered into force on **1 July 2018**.

The **revised** Chapters 3, 5 & 8 of the PIC/S GMP Guide are **based on** the equivalent Chapters of the EU GMP Guide with **some minor differences** in terms of language.

These Chapters of the PIC/S GMP Guide **have now been aligned with** principles of Quality Risk Management.

Chapter 3 and 5 have been **revised to include requirements to prevent cross-contamination**.

Expectations with regard to quality management system for the **evaluation of quality defects in relation to product recalls have been expanded in Chapter 8**, which has been **entirely revised**.

PIC/S GMP Document New/Revised

PIC/S-- PI 043-1 Aide-Memoire (稽查員用備忘錄**) -** Cross-Contamination in Shared Facilities - **New**

PIC/S-- PI 043-1 Aide-Memoire - Adoption & Entry into force
Adoption by the PIC/S Committee on **17-18 April 2018**
Entry into force on **1 July 2018**

PIC/S– PI 045-1 Guidelines on the Formalised Risk Assessment for ascertaining the appropriate GMP for Excipients of Medicinal Products for Human Use – **New**

PIC/S– PI 045-1 Guidelines on Excipient GMP Risk Assessment –
Transposition, Adoption & Entry into force轉換,採用&生效/實施
Transposed轉換 from EC document 2015/C 95/02 by PIC/S SCH in June 2015 ~ **September 2017**
Adoption by the PIC/S Committee on **17-18 April 2018**
Entry into force on **1 July 2018**

PIC/S GMP Document New/Revised (continued)

PIC/S-- PI 046-1 Guideline (Annex) on Setting Health Based Exposure Limits for use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities - **New**

PIC/S-- PI 046-1 Guideline - Adaption, Adoption & Entry into force

Adapted by SCC from EMA/CHMP/CVMP/SWP/169430/2012 in September 2015 – **September 2016** 接納/改編

Adoption by the PIC/S Committee on **17-18 April 2018**

Entry into force on **1 July 2018**

PIC/S– PI 047-1 Guidelines (Annex) on the Principle of GDP of Active Substances for Medicinal Products for Human Use– **New**

PIC/S– PI 047-1 Guidelines - **Transposition, Adoption & Entry into force**

Transposed by SCH from EC document 2015/C 95/01 in November 2015 – **September 2016**

Adoption by the PIC/S Committee on **17-18 April 2018**

Entry into force on **1 July 2018**

PIC/S GMP Document New/Revised (continued)

PIC/S-- PI 048-1 New PIC/S guidance on GMP inspection reliance, 2018-06 (PI 048-1 新的**PIC/S GMP**檢查/稽查依據指引**, 2018-06**)

This **guidance** is **based on** a **draft by ICMRA** (International Coalition of Medicines Regulatory Authorities(ICMRA(藥品監管機關的國際聯盟)) **GMP Inspection Reliance Framework**, **with the aim to maximise inspection resources** for **GMP compliance of overseas facilities**.

It is a **non-binding** (i.e. applicable on a voluntary basis) **high-level guidance** for ICMRA and PIC/S Participating Authorities (PA) alike.

ICH Guidelines

ICH Membership Update

The International Council for Harmonisation (**ICH**) met in **Kobe**, **Japan** on 2 – 7 June **2018:**

1. The Assembly elected additional members to the Association's Management Committee: The Founding and Standing Members are now joined on the Management Committee by **five newer ICH Members**. CFDA, China, HSA, Singapore and MFDS, South Korea join the current regulatory members and BIO and IGBA join the current industry members..

2. The Assembly approved TFDA, Chinese Taipei as a new Regulatory Member. The Assembly also approved MMDA, Moldova, NPRA, Malaysia, SCDMTE, Armenia and TİTCK, Turkey as new Observers. With these new parties, **there are now 16 ICH Members** and **27 Observers**.

ICH Guideline & Status Update

ICH Harmonized Guidelines:

ICH S5(R3) - Detection of Toxicity to Reproduction for Human Pharmaceuticals, Draft Guideline, dated 5 July 2017

ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, **Draft Guideline**, Endorsed by the Members of the ICH Assembly on 16 November 2017

ICH Q12 (Annex) - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (**Annex**), **Draft Guideline**, Endorsed on 16 November 2017

ICH Q12 (Core Guideline) - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, **Draft Guideline**, Endorsed簽名認可 on 16 November 2017

ICH Guideline & Status Update

ICH Harmonized Guidelines (continued)**:**

ICH Q12 - Draft Guideline (Overall): The aim of the **new ICH Q12 guideline** is to **enable** full realization of more flexible regulatory approaches to post-approval CMC changes.(本**新的ICH Q12指引宗旨為**，**使**更具彈性/靈活的監管方法**能夠**充分實現於，(藥品)獲准(上市)後(申請)**CMC變更**之審批。) The draft guideline applies to **pharmaceutical drug substances**, **pharmaceutical drug products**, including **combination products**, and **analytical methods**.

ICH Q11 - Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)— **Q&As**, **Guidance for Industry**, February **2018**

ICH Q3D(R1) – Guideline for Elemental Impurities, Draft Guideline, (Revision to Cadmium inhalation Permitted Daily Exposures) Endorsed on 12 July **2018**

ICH Guideline & Status Update

Other guidance documents adopted by the Assembly at the Kobe meeting *(Step 4 or Step 2)*:

ICH E2B(R3) - Revision of Q&As for the Electronic Submission of Individual Case Study Reports;

ICH M8 - eCTD v3.2.2 Q&A and Specification Change Request Document v1.31;

ICH M8 - eCTD v4.0 Implementation Package v1.2;

ICH M8 - eCTD v4 Q&A and Specification Change Request Document v1.2;

ICH M8 - Specification for Submission Formats for CTD v1.2;

ICH S9 - Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals were adopted through written procedure in April 2018.

ICH M9 - Biopharmaceutics Classification System-based Biowaivers

EU/EMA Regulatory Update

EU Commission Directive on Good Manufacturing Practices for Medicines

- **EU--Commission Directives 2017-1572** - Regards the **principles & guidelines of GMP** for **MP** (**manufacture** or **import**) for Human Use--2017-09-15. (**Transposition by 2018-03-31** at the latest)
- **EU--GMP Guide** - **New Annex 1** (draft), 2017-12 consultation document
- **EU--ECA News** (**2018-10-17**) - **Expectations of the British MHRA** on **Decontamination with Vapour Hydrogen Peroxide**
- **EU--EBE Concept Paper** - Management & Control of **Raw Materials** Used in the **Manufacture of Biological Medicinal Products**-final--2017-11-29
- **EU--Brexit--EMA (2018-06-19) Practical guidance for procedures related to Brexit - Centralised Procedure**.
- **EU--Brexit--EMA (2018-06-19) Q&As related to the United Kingdom's withdrawal from the European Union - Centralised Procedure**.

EU--Brexit--EMA (ECA News - 2018-10-17)

- The **European Medicines Agency** (**EMA**) **has to face challenges** like the **relocation** to Amsterdam and the **loss of personnel**. Because of this, EMA needs to temporarily **scale back** or **suspend additional activities**. **EMA has** now published a press release and announced the next phase of its **Brexit preparedness business continuity plan** (**BCP**), which entered into its **third phase**.
- **Despite** the necessary temporary **suspension/scaling back of activities**, **EMA has defined seven guidelines**, **which will exceptionally continue during BCP phase 3:**
  - **Revision of Annex 1 of the EU GMP Guide** (H/V) - **Manufacture of sterile medicinal products**.
  - **New Annex 21** of the **EU GMP Guide** (H/V) - **Guidance for importers** of medicinal products.
  - **Reflection Paper of Good Manufacturing Practice** and Marketing Authorisation Holders.
  - Guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product.
  - Good Pharmacovigilance Practice: Pregnancy and Breast Feeding.
  - Revision 6 of Note for Guidance on the evaluation of anticancer medicinal products in man.
  - Guideline on the use of minimal residual disease as a clinical endpoint in Multiple Myeloma trials.

EU's other GMP related Guidances

2018-10-15

- MHRA--**'GXP' Data Integrity Guidance and Definitions—2018-03**
- **EU--EC**--**Safety Feature** for Medicinal Products for Human Use_Q&As Ver 11_en – **GDP related**

EU's other GMP related Guidances

continued

MHRA--**'GXP' Data Integrity Guidance and Definitions—2018-03**

1. Follow the WHO and EMA(Q&A), the final version of this document had been published on March 9, 2018.
2. Over 1300 comments from industry during the consultation process, and the comments received have all been taken into consideration.
3. Some content amendments:
   - A new chapter 3 covers the principles of data integrity. The topics range from organisational culture and the need to take responsibility up to the ALCOA-principle.
   - As the title suggests, chapter 6 comprehensively defines and explains more than 20 terms and requirements to assure data integrity. From "recording and collection of data" to "data transfer/migration" to "IT suppliers and service providers (including cloud providers and virtual service/platforms)" chapter 6 forms the core element of the guideline.
   - Point 6.19 Validation of computerised systems refers to Annex 11 and Annex 15 of the EU GMP Guide. The MHRA states that "These should be validated for their intended purpose which requires an understanding of the computerised system's function within a process. The acceptance of vendor-supplied validation data in isolation of system configuration and users intended use is not acceptable. Validation for intended purpose ensures that the steps reflect the data checking SOP.
   - Under Point 6.20 (new) cloud or virtual services are addressed. It is emphasised that the understanding of services, ownership, retrieval, retention and security of data is a must.

Regulatory Guidance on Brexit
for the Pharmaceutical Industry

- All Union **primary** and **secondary law** ceases to apply to The **United Kingdom** since The United Kingdom withdraw from the EU.
- EMA and the European Commission have now released a Q&A document regarding the withdrawal of the UK from the European Union:
  - What if I am a marketing authorisation holder (MAH) established in the UK?
    如果我是在英國建立的上市許可持有者(MAH)，(我應該)怎麼辦？
  - What if I am an orphan designation holder established in the UK? (for medicines for human use)
  - What if I am a UK company with a MUMS (Minor Use Minor Species/limited market) status for my product? (for veterinary medicines)
  - What if my Qualified Person for Pharmacovigilance (QPPV) resides and carries out his/her tasks in the UK?
  - What if my Pharmacovigilance System Master File is located in the UK (PSMF)? (for medicines for human use)
  - What if my manufacturing site of the active substance is located in the UK?
  - What if my manufacturing site of the finished product is located in the UK?
  - What if my batch release site is located in the UK?
  - I am a UK based SME (small to medium-sized enterprise), would I still have access to financial and administrative assistance in accordance with Commission Regulation (EC) No 2049/2005 (the 'SME Regulation')?

WHO GMP Update

Technical Report Series 1010 published (1)

The following guidelines were adopted and recommended for use

WHO_TRS_1010 (2018)—Annexes:

- Annex 1 - WHO guidelines on good herbal processing practices for herbal medicines.
- Annex 2 - WHO good manufacturing practices for herbal medicines (revision).
- Annex 4 - WHO model certificate of analysis (revision).
- Annex 5 - WHO guidance on testing of "suspect" **falsified medicines**.
- Annex 8 – WHO guidelines (**draft**) on GMP for **heating, ventilation and air-conditioning systems** (**revision**).
- Annex 9 – WHO guidance on good practices for **desk assessment** of compliance with **GMP**, **GLP** and **GCP** for medical products regulatory decisions.
- Annex 10 – WHO **stability testing** of active pharmaceutical ingredients and finished pharmaceutical products (**revision**).

Annex 8 – WHO guidelines on GMP for heating, ventilation and air-conditioning systems (revision)

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Annex 10 – WHO stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision)

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- **1. Introduction**
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- 2.1.10 Statements and labelling
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Annex 10 – WHO stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision)

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Annex 10 – WHO stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision)

Contents (continued)

US FDA

Guidance Documents published in 2018

FDA: CGMP Inspection & Guidance Agenda

- **FDA--MAPP 5014.1**--Office of Pharmaceutical Quality - **Understanding CDER's Risk-Based Site Selection Model for CGMP Inspections--2018**-09-26
- **FDA--Guidance Agenda - New & Revised Draft Guidances CDER Plans to Publish During Calendar Year 2018--2018-01-19**
- **FDA--Guidance Agenda - Guidance Documents CBER is Planning to Publish During Calendar Year 2018**

Drug Development & NDA, ANDA related:

- **FDA--Guidance for Industry, draft--Postapproval Changes** to **Drug Substances--2018-09**
- **FDA--Guidance for Industry, draft--Insanitary Conditions** at Compounding Facilities**--2018-09**
- **FDA--Guidance for Industry & Review Staff, draft**--Good Review Management Principles & Practices for NDA & BLA--**2018-09**

Guidance Documents published in 2018

Drug Development & NDA, ANDA related (continued):

- **FDA--Guidance for Industry, draft--Microbiology Data** for Systemic Antibacterial Drugs - Development, Analysis, & Presentation--Revision 1**--2018-01**
- **FDA--Guidance for Industry, draft--Good ANDA Submission Practices--2018-01**
- **FDA--Guidance for Industry, draft--Assessing the Irritation & Sensitization Potential of** Generic Transdermal & Topical Delivery Systems for **ANDAs--2018-10**
- **FDA--Guidance for Industry, draft--Assessing Adhesion** With Transdermal & Topical Delivery Systems for **ANDAs--2018-10**
- **FDA--Guidance for Industry, draft-- Long Term Follow-Up After Administration of Human Gene Therupy Products--2018-07**
- **FDA--Guidance for Industry--ANDA Submissions - Content and Format--2018-09**
- **FDA--Guidance for Industry--Bioanalytical Method Validation--2018-05**

Guidance Documents published in 2018

Drug Development & NDA, ANDA related (continued):

- **FDA--Guidance for Industry--Dissolution Testing & Acceptance Criteria for IR Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances--2018-08**
- **FDA--Guidance for Industry--Elemental Impurities in Drug Products--2018-08**
- **FDA--Guidance for Industry--Liposome Drug Products - CMC, Human PK & BA, & Labeling Documentation--2018-04**
- **FDA--Guidance for Industry--Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients - Q&As--2018-04**
- **FDA--Guidance for Industry--Quality Attribute Considerations for Chewable Tablets--2018-08**
- **FDA--Guidance for Industry--Regulatory Classification of Pharmaceutical Co-Crystals--2018-02**

USP--Intended Revision of chapter <797> "Sterile Compounding"

Several major changes:

- Definition of the scope of the chapter to include sterile compounding activities and exclude administration of medication (e.g., withdrawing doses for administration).
- Simplified compounded sterile preparation (CSP) microbial risk levels from three (low, medium, and high) to two—Category 1 CSPs and Category 2 CSPs. Category 1 and 2 CSPs are distinguished primarily by the facility in which they are made and the time period within which they must be used, i.e., the beyond-use date (BUD).
- **Addition of guidance** on use and storage of opened or needle-punctured conventionally manufactured products and CSPs.
- Addition of information on notification and recall of CSPs that have out-of-specification results.
- Clarification of requirements for compounding allergenic extract prescription sets.
- Removal of information related to handling of hazardous drugs and addition of references to Hazardous Drugs—Handling in Healthcare Settings ⟨800⟩.
- Removal of the section on radiopharmaceuticals as CSPs and addition of a reference to Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repac

PDA Technical Reports Update

PDA published two Technical Reports in 2018

- **PDA--Technical Report No. 79**, **2018**--Particulate Matter Control in Difficult to Inspect Parenterals
- **PDA--Technical Report No. 80**, **2018**--Data Integrity Management System for Pharmaceutical Laboratories

Pharmaceutical Product Serialisation & Authentication

藥品 序列化 與 真實性的確認/證明

USA versus EU

USA--The Drug Supply Chain Security Act

The **DSCSA** was signed into law on November 27, 2013. The DSCSA outlines critical steps to build an electronic, interoperable system by November 27, 2023, that will identify and trace certain prescription drugs as they are distributed within the United States. Section 202 of the DSCSA, which added new sections 581 and 582 to the FD&C Act, sets forth new definitions and **requirements** related to product tracing, product identifier, and verification requirements for manufacturers, repackagers, wholesale distributors, and dispensers to facilitate the tracing of product through the pharmaceutical distribution supply chain. Failure to comply with the requirements of section 582 is prohibited and subject to enforcement action under the FD&C Act.

Product identifier *(藥品識別碼)* **is defined under section 581(14) of the FD&C Act as a standardized graphic** (標準化的文字圖形) **that includes, in both human-readable form and on a machine-readable data carrier** (‘**2-dimensional data matrix barcode**’) **that conforms to the standards developed by a widely recognized international standards development organization, the standardized numerical identifier, lot number, and expiration date of the product.**

FDA Guidance Documents published in 2018

GDP & DSCSA related:

- **FDA--Guidance for Industry, draft**--Waivers, Exceptions, & Exemptions from the Requirements of Section 582 of FD&C Act (traceability and security requirements for certain prescription drugs)**--2018-05--GDP related**
- **FDA--Guidance for Industry, draft**--Standardization of Data and Documentation Practices for Product Tracing--**2018-03--GDP related**
- **FDA--Guidance for Industry, draft--Product Identifiers** Under the Drug Supply Chain Security Act - **Q&As--2018-09--GDP related**
- **FDA--Guidance for Industry, draft--Verification Systems Under DSCSA for Certain Prescription Drugs--2018-10--GDP related**
- **FDA--DSCSA Decision Tree** for determining **drug package or case** that needs **Product Identifier under DSCSA--2018-10-09--GDP related**
- **FDA--Guidance for Industry, draft--Definitions of Suspect Product and Illegitimate Product** for Verification Obligations Under **DSCSA--2018-03--GDP related**

FDA postpones DSCSA compliance for one year - 2017-06-30

- **The Original Deadline Day for pharmaceutical package serialization – *November 27, 2017*.**
- **The operative FDA statement (FDA的有效聲明): *FDA does not intend to take action against manufacturers who do not affix or imprint a product identifier to their packages and homogenous cases of product that are intended to be introduced in a transaction into commerce between November 27, 2017, and November 26, 2018*.**
- ***November 27, 2018* becomes the Deadline Day for Serializing Pharmaceutical Packages.**

FDA – Draft Guidance for Industry Identifying Trading Partners Under the Drug Supply Chain Security Act - 2017-08

- **Definitions of Drug Supply Chain Entities Under DSCSA**

  DSCSA identifies and defines five types of entities in the prescription drug supply chain: Manufacturers, Repackagers, Dispensers, Wholesale distributors, and 3PLs.

- **Identifying Who is a Trading Partner:**

  A. *Manufacturers* as Trading Partners Under DSCSA

  B. *Repackagers* as Trading Partners Under DSCSA

  C. *WDDs* as Trading Partners Under DSCSA

  D. *3PLs* as Trading Partners Under DSCSA

  E. *Dispensers* as Trading Partners Under DSCSA

EU--EC Guidelines of 2013-11-05 on GDP of Medicinal Products for Human Use

- **Introduction (paragraph 4):**

  These Guidelines lay down appropriate tools to assist wholesale distributors in conducting their activities and to prevent falsified medicines from entering the legal supply chain. Compliance with these Guidelines will ensure control of the distribution chain and consequently maintain the quality and the integrity of medicinal products.

  本指引制定適當的工具以協助批發運銷商進行其活動 ，並預防**偽/禁(仿冒)藥**流入合法供應鏈中。遵循這些指引可確保運銷鏈的管制，進而**維護藥品的品質**與完整性。

EU--Consolidated Directive 2001-83-EC

(2012) - TITLE V - LABELLING AND PACKAGE LEAFLET

- **Article 54(o):**

for medicinal products other than radiopharmaceuticals referred to in Article 54a(1), **safety features** (安全特徵) enabling **wholesale distributors** and **persons authorised** or **entitled to supply medicinal products to the public** to (使...能夠):

— verify the **authenticity** of the medicinal product 確認真實性 , and

— **identify** individual packs 識別個別包裝, as well as

— identify **a device** allowing verification of whether the outer packaging has been tampered with (識別具有允許(能夠)確認外包裝是否已被篡改/篡開過之**裝置**).

EU--Consolidated Directive 2001-83-EC

(2012) - TITLE V - LABELLING AND PACKAGE LEAFLET

- **Article 54a-2-(e):**

provisions on the establishment, management and accessibility of the **repositories system** (資料存儲庫系統) in which information on the safety features (安全特徵), enabling the verification of the authenticity and identification of medicinal products, as provided for in point (o) of Article 54, shall be contained. The costs of the repositories system shall be borne by the manufacturing authorisation holders of medicinal products bearing the safety features.

EU--Commission Delegated Regulation(EU) -2016-161

Rules for the safety features--2015-10-02-en.

- **Article 4: Composition of the unique identifier** (獨特的識別碼)
- **Article 5: Carrier** (載體) **of the unique identifier** Two-dimensional barcode (**Machine-readable**)
- **Article 7: (unique identifier) Human-readable format**
- **Article 31 ~ 39: Establishment, Management & Accessibility of the repositories system**
- **Article 50: This Regulation shall enter into force on February 9, 2019.**

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Composition of the unique identifier (獨特的識別碼)

- **A unique identifier** which complies with the following **technical specifications**:

(a) The unique identifier shall be **a sequence of numeric or alphanumeric characters** that is unique to a given pack of a medicinal product.

(b) The **unique identifier** shall consist of the following **data elements** (獨特的識別碼，應由下列數據要項組成):

(i) **a code** allowing the identification of at least the name, the common name, the pharmaceutical form, the strength, the pack size and the pack type of the medicinal product bearing the unique identifier (**'product code** 產品代碼**'**);

(ii) a numeric or alphanumeric sequence of maximum 20 characters, generated by a deterministic or a non-deterministic randomisation algorithm (**'serial number** 序列號**'**);

(iii) **a national reimbursement number** 國家保險給付碼 or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market;

(iv) the **batch number (**批號**)**;

(v) the **expiry date (**末效日期**)**.

END

謝謝大家

Thank you for your attention