2016 藥廠 GMP 品質管理人員制度說明會

國際醫藥法規新知

Pharmaceutical Regulation Updates

105-04-19 & 20

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GMP/Quality related News

2015/12 ~ Present

Content

- WHO
- USP
- US FDA
- ICH
- EU
- EU Pharmaceutical Legislation Update (**New Safety Measures**) **-** The most serious fake medicine fraud in the European Union & subsequent measures taken by EU

WHO

WHO GMP for Biological Products

3rd Draft, Version 2_2015-02-18

- The draft guidance document was proposed to replace WHO TRS 822 (1992), Annex 1 – WHO-GMPs for Biological Products.
- Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives(*), immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA), and diagnostic agents for in vitro use, gene therapy, cell therapy, etc.
- The 33-pages guideline applies to the manufacture, control and testing of biological products for human use, from starting materials and preparations, including seed lots, cell banks, to the finished product.
- Manufacturing procedures within the scope of the guideline include:
  - Growth of strains of microorganisms and eukaryotic cells;
  - Extraction of substances from biological tissues, including human, animal and plant tissues, and fungi;
  - Recombinant DNA (rDNA) techniques;
  - Hybridoma techniques; and
  - Propagation of microorganisms in embryos or animals.

USP

USP - Draft to Water for Pharmaceutical Purposes

- **Changes**:
  - Updating the chapter to improve the organization and clarity of the information and remove redundant discussion text. This includes the organization into nine specific sections.
  - Removing wording redundant to referenced monograph wording.
  - Adding a detailed Outline/Table of Contents to improve user's topic discussion findability (topics will be hyperlinked in future electronic USP versions).

- **The nine specific sections**:
  1. Introduction
  2. Source Water Considerations
  3. Waters Used for Pharmaceutical Manufacturing and Testing Purposes
  4. Validation and Qualification of Water Purification, Storage, and Distribution Systems
  5. Design and Operation of Purified Water and Water for Injection Systems
  6. Sampling
  7. Chemical Evaluations
  8. Microbial Considerations
  9. Alert and Action Levels and Specifications

- USP chapter ＜1＞ on

  “Injections and Implanted Drug Products (Parenterals)-Product Quality Tests”

  - has been revised, and

  - will become official May 1, 2016.

US FDA

CDER List for 2016 Guidance Documents

- Three documents are listed under the category **"Pharmaceutical Quality/Manufacturing Standards (CGMP)"**:
  - CGMP Data Integrity Questions and Answers (already listed 2015)
  - Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products; Revised Draft
  - Repackaging of Certain Drug Products by Pharmacies and Outsourcing Facilities (already listed 2015)
- The related category **"Pharmaceutical Quality/CMC"** lists 16 additional guidances, inter alia on Microbiological Quality Considerations in Non-sterile Drug Product Manufacturing or a Technical Conformance Guide for Quality Metrics.

US FDA--Guidance for Industry

- FDA--Guidance for Industry--Immunogenicity-Related Considerations for Low Molecular Weight Heparin--2016-02
- FDA--Guidance for Industry--Completeness Assessments for Type II API DMFs Under GDUFA--2016-02
- FDA--Guidance for Industry, draft--Labeling for Biosimilar Products--2016-03-31
- FDA--Guidance for Industry--Safety Considerations for Product Design to Minimize Medication Errors--2016-04

FDA--Guidance for Industry

Contents of a Complete Submission for the Evaluation of Proprietary Names--2016-04

- The Institute of Medicine (IOM) recommended that FDA:
  1. "develop and enforce standards for the design of drug packaging and labeling that will **maximize safety** in use" and
  2. "require pharmaceutical companies to test proposed drug names to **identify and remedy** potential sound-alike and look-alike **confusion with existing drug names**.

     FDA要求製藥公司，需測試所提出(擬議)的藥品名稱，找出並解決(識別和補救)潛在有與現有的藥品名稱「聽起來相似/相同 與 看起來相似/ 相同」的混淆問題。

ICH

Training Modules for Q3D Elemental Impurities

- Regarding the complexity of the requirements of ICH Q3D, the modules should serve as a tool to provide clarity on the key aspects of the ICHQ3D guideline.
- They shall ensure a proper interpretation by industry and regulators. Following are the eight modules at a glance:
  - Module 0: Overview of Training Modules
  - Module 1: How to Apply Q3D Concepts to Routes of Administration, not addressed in Q3D
  - Module 2: Justification for Elemental Impurity Levels Higher than an Established PDE
  - Module 3: Developing an Acceptable Level for a Elemental Impurity not in Q3D
  - Module 4: Considerations for Parenteral Products
  - Module 5: General Approaches to Product Risk Assessment
  - Module 6: Control of Elemental Impurities
  - Module 7: Converting between PDEs and Concentration Limits
- Two more modules are still to come and will be published at a later date:
  - Module 8: Case Studies Illustrating an Approach to Presenting Risk Assessment
  - Module 9: FAQs

EU

Delegated Regulation on Safety Features

(Delegated Regulation 2016/161)

- **Two elements placed on the packaging** of a medicinal product should guarantee medicine authenticity and secure the medicine supply chain:
  - **A unique identifier**(獨特的識別碼), a unique sequence carried by a two-dimensional barcode allowing the **identification** and **authentication** of the individual pack on which it is printed; and
  - A device allowing the verification of whether the packaging of the medicinal product has been tampered with (**anti-tampering device**).
- The Commission has prepared a "Questions and Answers" document which sets out 46 frequently asked questions and answers regarding the implementation of the rules on the safety features for medicinal products for human use.
- The European Medicines Agency (EMA) has published an implementation plan that includes the regulatory requirements to be followed to notify the EMA of the placing of the unique identifier and/or the anti-tampering device on centrally authorized products.

EU Pharmaceutical Legislation Update

New Safety Measures

The most serious fake medicine fraud in the European Union & subsequent measures taken by EU

BBC News (2011-04-08)

The most serious fake medicine fraud in the European Union & subsequent measures taken by EU.

(發生在歐盟最嚴重的偽劣藥品詐騙事件 及 歐盟後續所採取的預防措施)

Peter Gillespie was prosecuted successfully for a **£4.7m plot** to bring two million doses of counterfeit drugs from **China** to the **UK**, and sentenced to 8 years imprisonment.

BBC News (2011-04-08)

1. **Peter Gillespie** (a former wholesaler / parallel importer), 64, from Hertfordshire, was prosecuted successfully for a **£4.7m plot** to bring two million doses of counterfeit drugs (prescription drugs for conditions ncluding prostate cancer, heart disease and schizophrenia) from C**hina** to the **UK,** and sentenced to 8 years imprisonment. (**Peter Gillespie** 因涉及從中國大陸進口零售價高達四百七十萬英鎊之偽藥到英國的陰謀,被成功地**告發**起訴並**被**判處八年有期徒刑)。

2. **Peter Gillespie** and other 4 are accused of conspiring together to defraud (被控告共謀欺詐) pharmaceutical wholesalers, pharmacists, members of the public and holders of intellectual property rights in pharmaceuticals between January 1, 2006 and June 30, 2007.

BBC News (2011-04-08)

continued

3. The case arose from a £750,000 / three-and-a-half-year investigation by **MHRA**.
4. 72,000 packs of counterfeit medicine - with a retail value of £4.7m - penetrated the UK supply chain between December 2006 and May 2007.
5. Some 25,000 of these packs reached pharmacies and were given to patients. The MHRA was able to seize (扣押) 40,000 before they got to pharmacies, and 7,000 were recovered following recalls.
6. The counterfeit drugs contained just **50% to 80%** of the correct ingredients.

EU Pharmaceutical Legislation Update

New Safety Measures

1. **BBC News (2011-04-08): The most serious fake medicine fraud in the European Union.**
   發生在歐盟最嚴重的偽劣藥品詐騙事件**(2011-04-08)**。
2. **EU--Directive 2011-62-EU--2011-06-08: amending Directive 2001-83-EC - Prevention of falsified medicinal products get into the legal supply chain.**
   歐盟修訂其人用藥品監管法規**Directive 2001/83/EC** 增列防止偽/禁**(**仿冒**)**藥條款。
3. **EU--Consolidated Directive 2001/83/EC_2012_en: on the Community code relating to medicinal products for human use.** 歐盟**2012-**整併之人用藥品監管法規。
4. **EU—other Acts—Guidelines of 7 March, 2013 on Good Distribution Practice of Medicinal Products for Human Use.**
   歐盟公告其新人用藥**GDP**指引。
5. **EU—EC Guidelines of 2013-11-05 on GDP of Medicinal Products for Human Use.** 修訂之歐盟新人用藥**GDP**指引。
6. **EU--Commission Delegated Regulation(EU)-2016-161: Rules for the safety features--2015-10-02-en.** 生效日 **2019-02-09**
   訂定有關藥品標示與包裝應具備安全特徵之規定**(**規則**)**。

EU--Consolidated Directive 2001-83-EC

(2012) - TITLE I - DEFINITIONS 定義

- **Article 1-33. Falsified medicinal product 偽/禁(仿冒)藥:**

  Any medicinal product with a false representation of:

  任何具有下列不實陳述之藥品:

  (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

  藥品的識別，包括其包裝及標示、名稱或關於任何成分的組成，包括賦形劑及這些成分的效力;

  (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

  其來源，包括其製造商、製造國家、其原產國或販賣許可持有者或

  (c) its history, including the records and documents relating to the distribution channels used.

  其紀錄，包括與運銷途徑相關的紀錄與文件。

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:

  — 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 (確認是否被篡改/篡開過裝置).

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

- 5.2. Qualification of suppliers供應商之資格認可:

  Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation, or who are in possession of a manufacturing authorisation which covers the product in question.

  批發運銷商必須從符合國內法令要求之供應者取得藥品。

- 5.3. Qualification of customers客戶的認可:

  Wholesale distributors must ensure they supply medicinal products only to persons who are themselves in possession of a wholesale distribution authorisation or who are authorised or entitled to supply medicinal products to the public.

  批發運銷商須確保其藥品只能供應給符合國內法令要求之對象。

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 of the unique identifier
  Two-dimensional barcode
- 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.

END

謝謝大家

Thank you for your attention

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Article 4: Composition of the unique identifier (獨特的識別碼)

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.

數據要件

(b) The unique identifier shall consist of the following **data elements**:

(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** 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).