109年 推動藥品GMP國際化
業者說明會

藥廠GMP國際法規新訊

GMP News_108-11 ~ 109-10

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PIC/S

PIC/S Documents - Recommendation (2019-11-28)

- **PI 054-1 (Draft 1) - Recommendation (2019-11-28)**

  How to Evaluate / Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management.

- Practical Guidance for GMP inspectors when seeking to evaluate the effectiveness of a company's pharmaceutical quality system (PQS) in relation to risk-based change management.
- It covers all relevant steps in the change management process – change proposal, change assessment, change planning and implementation, change review and effectiveness checks.

PIC/S Documents on HBELs (2020-06-01)

- PIC/S PI 046 **Guideline** on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities (**HBEL Guide**)
- PI 052-1 **Aide Memoire** Inspection of Health Based Exposure Limit (HBEL) Assessments and Use in Quality Risk Management (**HBEL Assessment**)
- PI 053-1 **Questions and Answers** on Implementation of Risk-based Prevention of Cross-Contamination in Production and 'Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities' (**HBEL Q&A**)

ICH

ICH Plans to harmonize with PIC/S and WHO

Include new details on the following interesting projects for the GMP area:

- A closer collaboration with PIC/S on guidelines with relevance to both Regulatory Assessor and Inspector disciplines is being planned.
- On her part, the WHO is planning to cooperate with the ICH.
- The Concept Paper outline on the revision of *ICH Q9: Quality Risk Management* was approved. Both, the ICH Assembly and Management Committee noted capacity constraints in the quality topic area. The starting time for the Q9(R1) guideline will therefore be delayed.
- The Q3C(R8) Maintenance EWG continues its work on the development of *Permitted Daily Exposure (PDE) levels for the solvents 2-methyltetrahydrofuran, cyclopentylmethylether and tert-butanol*. Q3C(R8) is expected to reach Steps 1 and 2a/b by early 2020.
- The Q3D(R2) Maintenance EWG continues its work on the draft Addendum on cutaneous and transdermal routes of administration. Steps 1 and 2a/b of the Q3D(R2) revision for the cutaneous and transdermal products are expected by early 2020.

ICH Q3C(R8) with three new PDES for comments

- The ICH Q3C(R8) draft Guideline on Impurities: Guideline for Residual Solvents contains the Permitted Daily Exposure (PDE) levels for:
  - 2-Methyltetrahydrofuran (proposed is a PDE of 50 mg/day and a placement in Class 3 solvents)
  - Cyclopentyl Methyl Ether (proposed is a PDE of 15 mg/day and a placement in Class 2 solvents)
  - Tertiary Butyl Alcohol (proposed is a PDE of 35 mg/day and a placement in Class 2 solvents).

EDQM

EDQM

- **Ph. Eur.—launches(發布) New general text (5.26) on implementation of Pharmacopoeial Procedures (for public consultation).**
- **Validation is not required**
- **2-Step Implementation Process**

  1) Assessment: Identification of critical factors

  2) Evaluation of method performance characteristics, such as accuracy and precision

EDQM - European Pharmacopoeia

- Sartan monographs of the European Pharmacopoeia revised due to nitrosamine impurities, concerned:
  - Candesartancilexetil (2573)
  - Irbesartan (2465)
  - Losartan potassium (2232)
  - Olmesartanmedoxomil (2600)
  - Valsartan (2423)
- Important changes:
  - "Manufacturing" section: N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) are classified as suspected carcinogens. Manufacturers must ensure that these impurities do not arise in their processes. A transitional period of two years is granted to adapt manufacturing processes. Meanwhile, strict limit values apply.
  - A test for nitrosamine impurities and set limit values can now be found in the "Purity testing" section.

EU/EMA

Update of Q&A on EU-US MRA(EMA)

- **Updated question 1:**
  - How does the EU-USA Mutual Recognition Agreement (MRA) affect Marketing Authorisation Applications or Variations?
  - Lists all available documents that have to be submitted as proof of GMP compliance for US manufacturing sites that have previously been inspected by the US FDA.

Revised Q&A on Nitrosamine Contamination(EMA)

- **The 10-page updated document lists potential sources of nitrosamine contamination that have been identified so far and includes four new Q&As.**
  - 4. How should tests be conducted by MAHs and manufacturers? (UPDATED) deals with the development of analytical methods for the determination of nitrosamines and is mentioned as a supplement for Step 2.
  - 5. When should MAHs report to competent authorities? (UPDATED) mentioned as a further source of information for Step 1. It explains in detail how the results of the risk assessments can be submitted.
  - 6. What limits will apply for nitrosamines detected in any products? (UPDATED, See also Q&A 16)
    deals with interim limits. With the substantial number of APIs and finished products involved, final limits of nitrosamines for non-sartan products are still under consideration.
  - 13. What is the approach for new and ongoing marketing authorization applications (MAA)? (UPDATED)
    takes up the approach for new and ongoing applications for authorisation.

New Q&A on nitrosamine impurities for Marketing Authorisation Holders (EMA) (1)

- **They are intended to**
  - design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of N-nitrosamines in their API and FP(s);
  - assess the risk of presence nitrosamine impurities in their API(s) and FP(s) and introduce any resultant changes to the dossier as needed (e.g. changes to their manufacturing processes);
  - ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.
- **Biological APIs must now also be reviewed:**
  - biologicals containing chemically synthesised fragments, where risk factors similar to chemically synthesised active substances are present;
  - biologicals using processes where nitrosating reagents are deliberately added;
  - biologicals packaged in certain primary packaging material, such as blister packs containing nitrocellulose.

New Q&A on nitrosamine impurities for Marketing Authorisation Holders (EMA) (2)

- "Call for Review" is divided into three steps:
  - Step 1: Risk evaluation
  - Step 2: If a risk exists, confirmatory tests must be performed and the results must be reported immediately
  - Step 3: If the presence of nitrosamines is confirmed, variations to reduce the risk should be submitted
- Important deadlines for marketing authorisation holders to submit the results from step 1:
  - for products containing chemically synthesised APIs: until 31 March 2021
  - for products containing biological APIs: until 1 July 2021

New Q&A on nitrosamine impurities for Marketing Authorisation Holders (EMA) (3)

- **Q&A on the following points:**
  - Currently known causes for the presence of nitrosamines
  - Procedure after completion of steps 1 and 2 if new information becomes available
  - Prioritization of certain factors in the risk assessment
  - Performance of the risk assessment
  - Conduction of the confirmatory tests
  - Requirements for the analytical methods
  - Limits for nitrosamines
  - What-To-Do after detection of nitrosamine contamination
  - Mitigation measures
  - Changes required for marketing authorisations
  - Procedure for new and existing marketing authorisation applications
  - Information on the time of inclusion of a test for nitrosamines in the authorisation dossier
  - Responsibilities of marketing authorisation holders for active substances with Certificates of Suitability (CEPs) and Active Substance Master Files (ASMFs)

Reflection Paper on GMP-related responsibilities of MAHs(EMA)

- To clarify in a single document what the different responsibilities are and what they mean for MAHs at a practical level.
- Addresses the legal provisions in European Directives and other Directives that relate to GMP and also affect marketing authorisation holders.
- Summarize all these aspects for MAHs at a practical level:
  - Outsourcing and technical agreements
  - Audits and qualification activities
  - Communication with manufacturing sites (e.g. MA dossier information, variations, regulatory 269 commitments, etc.)
  - Product Quality Reviews
  - Quality defects, complaints and product recalls
  - Maintenance of supply of medicinal products
  - Continual improvement activities.

Information on Brexit (EMA)

- Great Britain is considered a third country for the EU after 31 January 2020.
- The EU pharmaceutical law will continue to apply during the agreed transition period from 1 February to 31 December 2020.
- Pharmaceutical companies and medical device manufacturers can resume their activities until the end of the year (2020).
- At the end of the transitional period, all necessary changes to authorised medicinal products must have been made. It must therefore be ensured that they comply with EU law.

EU GMP Annex 1: Second Draft on Sterile Manufacture

- The new title Annex 1: Manufacture of Sterile Products (formerly Manufacture of Sterile Medicinal Products) clarifies the extended scope of application also for :
  - active substances
  - sterile excipients
  - primary packaging materials and
  - finished dosage forms, packed sizes from single to multiple units,
  - processes (from highly automated systems to manual processes) and
  - technologies such as biotechnology, classical manufacturing of small molecules and closed systems.
- The application of the principles of quality risk management (QRM) are further emphasized.
- Quality assurance: all critical control points must be defined and the effectiveness of all controls
- Contamination Control Strategy: should be continuously updated with the aim of continuously improving the manufacturing and control methods over the entire life cycle of the product.

Draft EU GMP Annex 21: Import of medicinal products published (1)

- **The draft is divided into seven chapters:**
  - ***Scope***
  - ***Principles***
    for the physical transfer from a third country and certification by a Qualified Person (QP).
  - ***Pharmaceutical Quality System***,
    according to Chapter 1 of the EU-GMP Guide: This includes product quality reviews, which should be performed by the site performing QP certification for the products imported, including products imported for export.Written agreements on the responsibilities of all parties involved should be in place, along with reliable sampling practices in the third country, verification of transport deviations or a comparison of the analysis results from the third country and the import inspection on site.
  - ***Premises and equipment***
    at the manufacturing site should be adequate. A quarantine area for storage should be available until their further processing after QP release.

Draft EU GMP Annex 21: Import of medicinal products published (2)

- ***Documentation***
  should be set up according to Annex 16.There should be documentary evidence that the site performing QP certification has qualified the third country manufacturer and regularly monitors its performanceby periodic on-site audits, to ensure that the imported products are manufactured in accordance with EU GMP or equivalent requirements and the MA.
- ***Operations***
  should be subject to an ongoing stability programme, as described in Chapter 6. This can also be carried out as an outsourced activity in the third country, provided the QP receives all necessary information. Protocols, results and reports, should be available for inspection at the MIA holder responsible for QP certification. The QP is also responsible for checking the security features. The QP is responsible for reference and retained samples.
- ***Complaints, quality defects and product recalls***
  should be made in accordance to Chapter 8. Contractual agreements should be defined between the importing site, the third country manufacturer and the MAH.

Updated Version 17 of the Q&A on safety features for medicinal products for human use

EU--Commission Delegated Regulation - Safety Features

- Question 5.11 is new:
  Clarifies whether wholesalers should be connected to the national repositories or to the European hub.
  - Wholesalers physically holding products or performing activities according to the Articles 20–23 of the Commission Delegated Regulation (EU) 2016/161 should be connected to the national repository where the acitivities take place.
- Question 1.22 received additions:
  Deals with the handling of safety features by parallel traders.
  - If a new, equivalent safety feature is placed by parallel traders, it should meet the requirements of the Member State in which the medicinal product is intended to be placed on the market.
  - Centrally authorised products from which parallel traders remove or cover safety features are expected to display the original manufacturer's batch number.
  - Traceability in the repository must be maintained in all cases.

Updated Version 18 of Q&A on safety features for medicinal products for human use (1)

- Q&A 4.6:
  A manufacturer may outsource the application of safety features to a packaged medicinal product to another manufacturer, provided this is done in accordance with the requirements of the EU GMP Guide Part I, Chapter 7 and the manufacturer has a manufacturing authorization. The contracted manufacturer must be included in the marketing authorization.
- Q&A 5.12:
  A wholesaler with multiple locations must be clearly identifiable from any location and therefore must not use a single access to the NMVS system for verification and deactivation of security features.
- Q&A 5.13:
  Medicinal products purchased from a third party do not need to be verified according to Article 20(b) of the Commission Delegated Regulation (EU) 2016/161 based on the unique identifier if they are shipped directly from the manufacturer, marketing authorisation holder or a designated wholesaler.
- Q&A 6.9:
  see question 5.12, here with reference to the pharmacy chain and the verification and deactivation of security features before dispensing medicinal products. The pharmacy branch must also be clearly identifiable when connecting to the NMVS system.

Updated Version 18 of Q&A on safety features for medicinal products for human use (2)

- Q&A 1.8:
  The information has been added that the importer of a medicinal product who imports a product into a Member State according to Article 5(1) of Directive 2001/83/EC does not have to upload the unique identifiers into the national database of the country of destination.
- Q&A 2.14:
  If the application of the unique identifier on the packaging of a medicinal product is outsourced to third parties, this must be done in accordance with the principles described in the EU-GMP Guideline Part I Chapter 7.
- Q&A 4.4:
  A manufacturer may use packaging that carries a unique identifier applied by a packaging manufacturer. If pre-printed cartons are used, a written agreement is required that defines the respective responsibilities. The supplier of the packaging materials must be audited and qualified. It is expected that the manufacturer of the finished medicinal product will carry out appropriate checks on the quantity and quality of the unique identifiers in accordance with EU GMP principles.

New guideline on the quality of water for pharmaceutical use (EMA) (1)

- On 1 February 2021, the guideline replaces:
  - *Note for guidance on quality of water for pharmaceutical* (from 1 May 2002)
  - *CPMP Position Statement on the quality of water used in the production of vaccines for parenteral* (from 20 October 2003)
- Following interim changes to the European Pharmacopoeia:
  - the revised monograph on Water for Injection (0169), which offers the possibility of using processes other than distillation for WFI (Water for Injection), e. g. reverse osmosis
  - new monograph on water for the production of extracts (2249) and
  - the suppression of the monograph for HPW, highly purified water (1927)
- Reflects the expectations for the minimum acceptable water quality in the manufacture of active ingredients and medicinal products for human and veterinary use.

New guideline on the quality of water for pharmaceutical use (EMA) (2)

- Chapter 5 "Quality of Water for Pharmaceutical Use" contains tables with examples for different water qualities such as
  - Water present as an excipient in the final formulation
  - Water used during manufacture of active substances and medicinal products excluding water present as an excipient in the final formulation
  - Water used for cleaning/rinsing of equipment, containers and closures
- Read together with the corresponding Q&A paper *"Questions and answers on production of water for injections by nondistillation methods – reverse osmosis and biofilms and control strategies"* (2017).

EN 17141:2020 Cleanrooms and associated controlled environments – Biocontamination Control

- Has been issued on 12 August 2020 and will replace the DIN EN ISO 14698 (Parts 1 and 2) of the year 2003.
- based on a quality risk management approach and defines the modern principles and basic methodology of an operational system for the control of biocontamination in cleanrooms and all associated controlled areas.
- Specifies methods for a consistent assessment of the risk areas to be monitored and the application of control measures according to the existing level of risk.
- New ways of evaluating and verifying microbiological sampling equipment are identified.
- Annexes of the document containing checklists, flowcharts, tables on cleanliness levels and application examples.

WHO

WHO - Technical Report Series No. 1025, 2020

- **Quality Assurance – GMP**
  - **Production of water for injection by means other than distillation (Annex 3)**
  - **The Expert Committee noted that the document should be integrated into WHO's existing guideline on Water for pharmaceutical use.**
  - **Good chromatography practices (Annex 4)**
  - **Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance (Annex 6)**
- **Quality Assurance – distribution and supply chain**
  - **Good storage and distribution practices for medical products (Annex 7)**
  - **Points to consider for setting the remaining shelf-life medical products upon delivery (Annex 8)**

WHO - New draft guidelines for commentary (1)

- *Good reliance practices in regulatory decision-making: high-level principles and recommendations* (May 2020)
  - promote a more efficient approach to the regulation of medicinal products
  - strengthen the overarching principles in the field of pharmacovigilance
  - a guideline for the harmonisation of the regulatory landscape and provides definitions and key concepts
- *Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities*
  - offers several possible approaches to limit the carryover during manufacture in shared facilities
  - concerns health-based exposure limits (HBEL)
  - clarification on cleaning validation is given as well as important points to be considered when reviewing the current status and the approaches to cleaning validation in multiproduct facilities
  - should be applied to the manufacturing of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs)

WHO - New draft guidelines for commentary (2)

- ***Good manufacturing practices: water for pharmaceutical use***
  - deals with the production, storage and distribution of water for pharmaceutical purposes (WPU) in bulk form
  - provides guidance on the quality management of water systems, water storage and distribution systems, water treatment systems as well as on qualification and validation, sampling, testing and routine monitoring of water
  - "Production of water for injection by means other than distillation" (Annex 3) from the Technical Report Series No. 1025 will also be included in this guideline

WHO - New draft guidelines published

- *Good regulatory practices for regulatory oversight of medical products*
  - is intended to reflect Member States with widely-recognized principles of Good Regulation Practice (GRP)
- *Good manufacturing practices: water for pharmaceutical use*, the following changes were made:
  - The chapter on "Highly Purified Water (HPW)" was omitted.
  - The chapter on "Biocontamination control techniques" is also no longer available.
  - The chapter on "System Sanitisation and bioburden control" is more comprehensive now,
  - as well as the chapter "Bulk water for injections".
  - The chapter "Good practices for water systems" now distinguishes between drinking water and purified water/WFI.
- *Guideline on data integrity* 2nd draft
  - will replace the *WHO Guidance on good data and record management practices (Annex 5, WHO Technical Report Series, No 996, 2016) (1)*
  - has been harmonised with existing DI guidelines, e. g. the US FDA, as far as possible
  - the examples of quality risk management and data integrity assessments are well worth mentioning, as well as the ten examples of good documentation practices in data integrity.

WHO

WHO—Draft working document for comments:

- **WHO--Points to consider on the different approaches – including HBEL (Health-Based Exposure Limits) – to establish carryover limits in cleaning validation for identification of contamination risks when *manufacturing in shared facilities***
- **WHO--Guideline on Data Integrity (2020-06), Draft working document for comments (1)**

WHO TRS 1025 (2020)

- Annex 2 International Atomic Energy Agency and WHO guideline on GMP for Radiopharmaceutical Products
- Annex 3 Production of WFI by means other than distillation
- Annex 4 Good chromatography practices
- Annex 5 Quality management system requirements for national inspectorates
- Annex 7 Good storage and distribution practices for medical products - Appendix 1: Table A7.1
- Annex 8 Points to consider for setting the remaining shelf-life of medical products upon delivery - App. 1 Table A8.1
- Annex 13 WHO guideline on the implementation of quality management systems for national regulatory authorities

WHO TRS 1025, Annex 7--Appendix 1: Recommended storage conditions

Table A7.1 Recommended limits for descriptive storage conditions[a]

Label description	Recommended limits
Store at **controlled room temperature**	15 to 25 °C
Store in a **cold or cool place**	8 to 15 °C
Store in a **refrigerator**	5 ± 3 °C
Store in a **freezer**	–20 ± 5 °C
Store in **deep freezer**	–70 ± 10 °C
Store in a **dry place**	No more than 60% relative humidity
Protect from moisture	No more than 60% relative humidity
Store under **ambient conditions**	Store in well-ventilated premises at temperatures of between 15 °C and 30 °C and no more than 60% relative humidity. Extraneous odours, other indications of contamination and intense light must be excluded.
Protect from light	To be maintained in the original manufacturer's light-resistant containers.
Chilled	5 ± 3 °C

"a" These limits are recommended values and are based on pharmacopoeia limits and guidelines.

WHO TRS 1025, Annex 8--Appendix 1:
Example of *Minimum Remaining Shelf-life* of medical products

Table A8.1 Example of the Minimum Remaining Shelf-life (RSL; at the time of dispatch and upon delivery) of Medical Products[a], based on the outcome of risk assessment

Total shelf-life (TSL)	RSL at time of dispatch from manufacturer's premises	RSL at time of delivery at port of entry of country	RSL at time of delivery at end-user level
48 months < TSL ≤ 60 months	40 months	30 months	12 months
36 months < TSL ≤ 48 months	30 months	24 months	12 months
24 months < TSL ≤ 36 months	20 months	15 months	6 months
12 < TSL ≤ 24 months	9 months	7 months	3 months
TSL ≤ 12 months	Special arrangements and conditions apply		

"a" Medical Product: **Finished pharmaceutical products**, Medical devices, Vaccines and IVD products

FDA

FDA CDER - Guidelines planned for 2020 (1)

- **Pharmaceutical Quality/CMC**
  - ANDAs: Stability Testing of Drug Substances and Products Questions and Answers
  - Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research
  - Chemistry Manufacturing and Controls Considerations for Individualize Antisense Oligonucleotide (ASO) Therapies
  - Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations
  - ICH Q12, General Considerations for FDA Implementation
  - Inspection of Injectable Products for Visible Particulates

FDA CDER - Guidelines planned for 2020 (1)

- **Pharmaceutical Quality/CMC** (continued)
  - Quality Considerations for Topical Ophthalmic Drug Products
  - Quality and Stability Testing of Drug Substances and Drug Products for NDAs, ANDAs, and BLAs and Associated Labeling Statements for Drug Products
  - Risk Management Plans to Mitigate the Potential for Drug Shortages
  - Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biologics
  - The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

FDA CDER - Guidelines planned for 2020 (2)

- **Pharmaceutical Quality/CGMP**
  - PET (positron emission tomography) Drugs - Current Good Manufacturing Practice (CGMP); Revised Draft
- **Pharmaceutical Quality/Microbiology**
  - Microbiological Quality Considerations in Non-Sterile Drug Product Manufacturing
  - Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biologics

FDA - Guidance on Control of Nitrosamine Impurities

- Published by the US FDA on 1 September 2020
- Discusses potential causes for the formation of nitrosamines and presents a comprehensive risk assessment strategy to detect and prevent their presence.
- Acceptable intake (AI) limits for the nitrosamine impurities NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA are recommended.
- An external introduction of nitrosamines are described as possible sources of contamination.
- Provides a step by step instruction If a contamination is detected in a finished drug.

MHRA

MHRA - Guidelines for post-brexit period

- 2 documents on clinical trials
  containing information about registration of clinical trials and on how to deal with substantial amendments to a clinical trial.
- 1 document on the regulation of medical devices
  describing what to do to place a medical device on the Great Britain, Northern Ireland and European Union (EU) markets. The guidance is divided into sections on the different rules that will apply within those areas.
- 12 documents covering the area of licensing
  that show how the approval of pharmaceutical and biological products will work from 1.1.2020.
- 6 documents explaining the import and export scenario
  for medicinal products, active ingredients and investigational medicinal products. This includes a list of all countries approved for import and also guidelines for the import of QP-certified medicinal products from the EEA under the supervision of a Responsible Person Import (RPi).
- 2 general documents on IT systems
  dealing with the registration for submission of marketing authorization documents to the MHRA.

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

EU--Consolidated Directive 2001-83-EC (2012)

- TITLE V - LABELLING AND PACKAGE LEAFLET (標籤與包裝說明書)

- 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/篡開過的裝置**).

EU--Consolidated Directive 2001-83-EC (2012)

- TITLE V - LABELLING AND PACKAGE LEAFLET (標籤與包裝說明書)

- Article 54a-2-(e):

provisions on the establishment, management and accessibility of the **repositories system** (資料儲存庫系統的建立，管理與其(儲存資訊/資料之)易接近性/可獲取性(的建立)) 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.

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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**.

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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)**.

Anti-tampering Device, Safety Features & Unique Identifier

Anti-tampering device

Safety features

Unique Identifier

END

謝謝大家

Thank you for your attention