

Good Manufacturing Practices (GMPs)

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 previous years
<i>DIRECT INTERESTS:</i>				
1.1 Employment with a company: pharmaceutical company in an executive role	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> mandatory
1.3 Employment with a company: other activities	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
2. Consultancy for a company	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
3. Strategic advisory role for a company	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
4. Financial interests	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
5. Ownership of a patent	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
<i>INDIRECT INTERESTS:</i>				
6. Principal investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
7. Investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
8. Grant or other funding	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
9. Family members interests	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional

***Cristina Baccarelli**, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. < I am not receiving any compensation >



Agenda

- Importance of Good Manufacturing Practices
- EU GMP
- AIFA Inspections and Certifications Department
- Training and qualification of GMP Inspectors



Why is GMP important?

Poor quality medicines are not only a health hazard, but a waste of money for both governments and individual consumers.

Poor quality medicines can damage health: they may contain toxic substances that have been unintentionally (or intentionally, in case of counterfeiting) added. A medicine that contains little or none of the claimed ingredient will not have the intended therapeutic effect.

During the years there have been many cases showing that a poor control over quality of production and product can have serious consequences, including the death of the patient.



Good Manufacturing Practices

Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards appropriate to their intended use and as required by the product specification.

It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

The main risks are: unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects.



Good Manufacturing Practices

GMP covers all aspects of production, from the starting materials, premises and equipment to the training and personal hygiene of staff.

Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.



Good Manufacturing Practices

GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors.

This in turn, protects the consumer from purchasing a product which is not effective or even dangerous.

Failure of firms to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and jail time.



Good Manufacturing Practices

GMP defines quality measures for both production and quality control and defines general measures to ensure that processes necessary for production and testing are clearly defined, validated, reviewed, and documented, and that the personnel, premises and materials are suitable for the production of pharmaceuticals and biologicals including vaccines

GMP also has legal components, covering responsibilities for distribution, contract manufacturing and testing, and responses to product defects and complaints. Specific GMP requirements relevant to classes of products such as sterile pharmaceuticals or biological medicinal products are provided in a series of annexes to the general GMP requirements.



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Good Manufacturing Practices

Most GMP requirements are very general and open-ended, allowing each manufacturer to decide individually how to best implement the necessary controls.

This provides much flexibility, but also requires that the manufacturer interpret the requirements in a manner which makes sense for each individual business.



Good Manufacturing Practices

GMP is also sometimes referred to as "cGMP". The "c" stands for "current," reminding manufacturers that they must employ technologies and systems which are up-to-date in order to comply with the regulation.

Systems and equipment used to prevent contamination, mix-ups, and errors, which may have been "top-of-the-line" 20 years ago, may be less than adequate by today's standards.

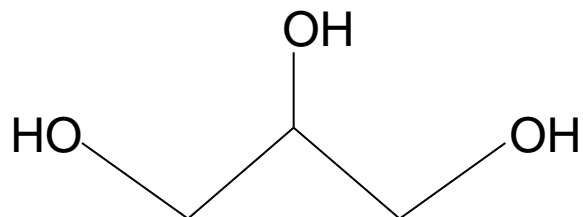


Example: supply chain is complicated

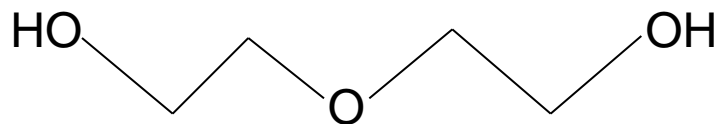


Glycerol & diethylene glycol impurity

- Diethylene glycol = structurally it is chemically similar



Glycerol
(C₃H₈O₃)



Diethylene glycol
(C₄H₁₀O₃)

- Physically similar
- Light coloured
- Sweet taste
- Slightly viscous at room temperature



Glycerol's tainted history

USA (1937)

More than 100 people died after ingesting contaminated Elixir Sulfanilamide (antibiotic). Resulted in enactment of the Federal Food, Drug, and Cosmetic Act (FDA).

Haiti (1995-96)

At least 80 children died due to contaminated Paracetamol syrup.

Argentina, Bangladesh, India, and Nigeria (1990 to 1998)

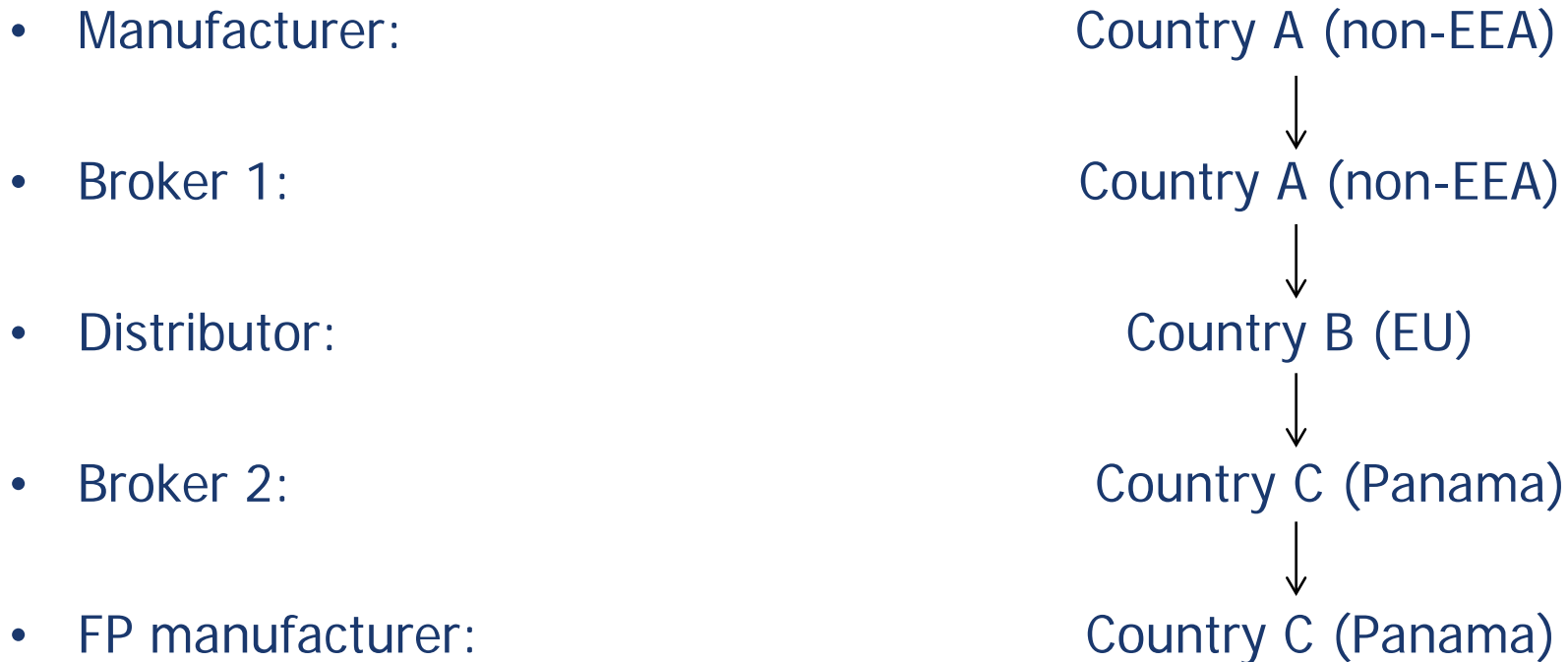
Similar incidents of poisoning occurred resulting in hundreds of deaths.

Panama(September 2006)

Contaminated cough syrup resulted in dozens of hospitalizations for serious injury and 46 deaths.



Glycerol supply chain in 2006 incident



Complicated – but not atypical!!

Activities performed at each stage

Manufacturer

- Substituted glycerol with diethylene glycol and labelled it as 'glycerine substitute'

Broker 1

- Removed manufacturer name from CoA
- Replaced CoA header with Broker company name
- 'Translated' into English



Activities (continued)

Distributor

- Removed Broker details on CoA and replaced with own

Broker 2

- Changed the expiry date of the material

Finished product manufacturer

- Manufactured cough syrup using wrong excipien.

Not one party tested the material once it left the raw material manufacturing site!!



EU GMP



EU GMP: Legal basis

EudraLex Volume 1 - Pharmaceutical Legislation

http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm

EudraLex Volume 4 - Good manufacturing practice (GMP) Guidelines

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Compilation of Community Procedures on Inspections and Exchange of Information

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000156.jsp&mid=WC0b01ac05800296cb



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EU GMP: Legal basis

Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary medicinal products



EU GMP: Legal basis

The last amendment of Directive 2001/83/EC is the so called "Falsified Medicines Directive":

➔ Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

This amendment is very important as it introduced more stringent controls over active substance manufacturers

➔ Italian system was only partially affected as Italy has been authorizing and inspecting active substance manufacturers since 1991.



EU GMP: Legal basis

The principles and guidelines for EU GMP are stated in two Directives and one Regulation:

- Directive 2003/94/EC for medicines and investigational medicines for human use
- Directive 91/412/EEC for medicines for veterinary use
- Commission Delegated Regulation (EU) No 1252/2014 for active substances for medicinal products for human use



EU GMP: Legal basis

GMP guidelines provide interpretation of these principles and guidelines, supplemented by a series of annexes that modify or augment the detailed guidelines for certain types of product, or provide more specific guidance on a particular topic.

 Compliance with these principles and guidelines is mandatory within the EEA.



EudraGMDP database

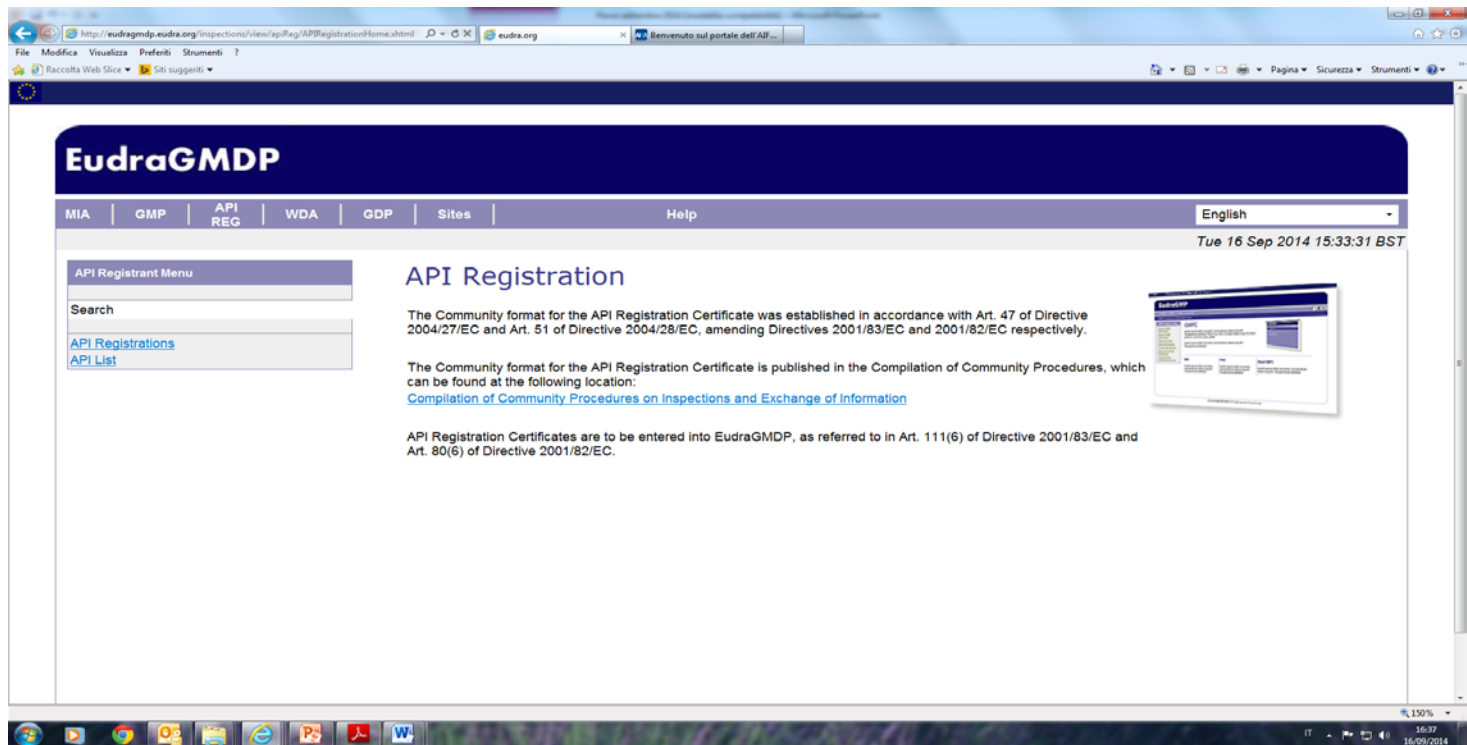
The EudraGMDP database is maintained and operated by the EMA (European Medicines Agency).

Access to the general public is granted in order to enhance availability of information related to the EMA mandate.

The content of the database is provided by the National Competent Authorities (NCA) of the EEA.

EudraGMDP database

Manufacturing sites authorizations/registrations



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EudraGMDP database

Public database of GMP Certificates and Non Compliance Reports

The screenshot shows a web browser window displaying the EudraGMDP search interface. The browser's address bar shows the URL: <http://eudragmdp.audra.org/inspections/gmpc/searchGMPCompliance.do>. The page title is "EudraGMDP".

The interface includes a navigation menu with links for MIA, GMP, API REG, WDA, GDP, and Sites. A "Help" link is also present. The date and time are displayed as "Tue 16 Sep 2014 17:27:11 BST".

The main content area is titled "Search GMP Compliance" and contains the following fields:

- Certificate Number:** [Text input field]
- Inspecting Authority Country:** [Dropdown menu, selected: ITALY]
- Inspecting Authority:** [Dropdown menu, selected: IT_AIFA]
- Site Details:**
 - DUNS Number:** [Text input field]
 - Name:** [Text input field]
 - City:** [Text input field]
 - Country:** [Dropdown menu, selected: ITALY]
 - Postcode:** [Text input field]
 - EudraGMDP Key:** [Text input field]
 - NCA Reference Key:** [Text input field]
 - MIA Number:** [Text input field]
- Legal Basis Of Certificate:** [Text input field]
- Type of Inspection:** [Text input field]
- Enable Scope Search:** [Checkbox]
- Enable Inspection:** [Checkbox]

The browser's taskbar at the bottom shows various application icons and the system clock indicating 18:33 on 16/09/2014.



EU GMP: EudraLex Volume 4

EudraLex Volume 4 has three parts and 19 annexes:

- Introduction
- Part I - Basic Requirements for Medicinal Products (9 chapters)
- Part II - Basic Requirements for Active Substances used as Starting Materials (19 chapters)
- Part III - GMP related documents (in order to clarify some regulatory expectations and to have some harmonized format)
- Annexes (19 annexes)
- Glossary



EU GMP Part I: Finished Dosage Form

Chapter 1-Pharmaceutical Quality System

Chapter 2-Personnel

Chapter 3-Premises and Equipment

Chapter 4-Documentation

Chapter 5-Production

Chapter 6-Quality Control

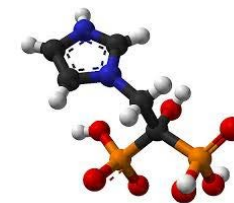
Chapter 7-Contract Manufacture and Analysis

Chapter 8-Complaints and Product Recall

Chapter 9-Self Inspection



EU GMP Part II: Active Substances



1. Introduction
2. Quality Management
3. Personnel
4. Buildings and Facilities
5. Process Equipment
6. Documentation and Records
7. Materials Management
8. Production and In-process Controls
9. Packaging and Identification
labelling of APIs and Intermediates
10. Storage and Distribution
11. Laboratory Controls
12. Validation
13. Change Control
14. Rejection and Reuse of Materials
15. Complaints and Recalls
16. Contract Manufacturers (including
Laboratoires)
17. Agents, Brokers, Traders, Distributors,
Repackers and Relabellers
18. Specific Guidance for APIs Manufactured
by Cell Culture/Fermentation
19. APIs for Use in Clinical Trials
20. Glossary



EU GMP Part III: related GMP documents

- Site Master File
- Q9 Quality Risk Management
- Q10 Note for Guidance on Pharmaceutical Quality System
- MRA Batch Certificate
- Template for the “written confirmation” for active substances exported to the European Union for Medicinal Products for human use

EU GMP: Annexes

1. Sterile medicinal products
2. Biological products
3. Radiopharmaceuticals
4. Veterinary products
5. Immunological vet. products
6. Medicinal gases
7. Herbal medicinal products
8. Sampling of materials
9. Liquids, creams and ointments
10. Pressurised metered dose aerosol preparations
11. Computerised systems
12. Use of ionising radiation
13. Investigational Medicinal Products
14. Products derived from Human Blood or Human Plasma
15. Qualification and validation
16. Certification by QP and batch release
17. Parametric release
- 18....(former part II).
19. Reference and retention samples



Periodic revision of EU GMP

GMPs (both chapters and annexes) are reviewed periodically based on technological improvements, scientific knowledge and cultural awareness.



PIC/S

- The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP
- PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."



PIC/S

- This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations
- There are currently 46 Participating Authorities in PIC/S
- Pharmaceutical inspections Co-operation Scheme (PIC/S) website:
<http://www.picscheme.org/>

AIFA: Inspections and Certification Dept.

- Manufacturing Authorization Office
 - Issuance of manufacturing authorizations/registrations for Italian manufacturing sites
 - Issuance of GMP certificates for national manufacturing sites
- GMP Inspection Office
 - National and international inspections of finished dosage manufacturing sites
 - Issuance of GMP certificates for inspected extra-EU sites
 - International working groups on finished dosage form production
 - EMA and PIC/S inspections



AIFA: Inspections and Certification Dept.

- API Inspection Unit
 - National and international inspections of active substance manufacturing sites
 - Issuance of GMP certificates for inspected extra-EU sites
 - International working groups on active substances production
 - EMA, EDQM, PIC/S and WHO inspections

AIFA: Inspections and Certification Dept.

Inspections are carried out on behalf of the Community and the results shall be recognised by all the other Member States.



Italian Manufacturing sites

There are about 570 manufacturing sites operating in Italy: all of them need to be licensed by AIFA, regardless if they manufacture for the domestic market or for export only.

- About 260 sites: finished dosage form
- About 125 sites: active substances
- About 185 sites: medicinal gases



With current resources, AIFA performs about 800 inspections (national and international) per year

About 70% of finished dosage form production and 85% of active substances production is for export.

Frequency of National Inspections

All sites on the Italian territory are regularly inspected (finished dosage forms every 2 years, active substances – so far - every 3 years)

Following implementation of the “Falsified Medicines Directive”, a risk based approach is now in place for determining frequency of APIs inspections, which can now be performed every 2-4 years on average, depending on the risk rate for each site.



Training to become a GMP Inspector

Requirements concerning experience, training and qualifications of GMP inspectors are outlined in the EMA "Guideline on Training and Qualifications of GMP Inspectors" included in the Compilation of Community Procedures on Inspections and Exchange of Information.

Objectivity, professional integrity, competence in technical matters and inspection skills should be the main features of inspectors.

The guideline provides information on minimal requirements. Member States may decide to add supplementary national requirements.



Training to become a GMP Inspector

AIFA GMP Inspectorate includes (both for finished dosage form and active substances inspections):

- Senior Inspectors
- Junior Inspectors
- Observers

Inspectors have a University Degree in Pharmacy, Chemistry, Pharmaceutical Technology or Biology.

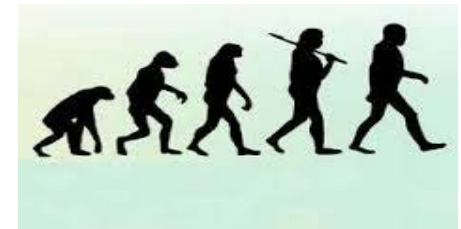


Training to become a GMP Inspector

Observers can become junior inspectors after performing at least 10 inspections (NLT 30 days), with a positive feedback at least for the last 8 inspections.

Junior inspectors can become Senior inspectors after performing at least 20 inspections as Junior inspectors (NLT 60 days), with a positive feedback. They also need to perform at least 8 inspections in a year in order to maintain their qualification.

Senior inspectors need to perform 8 inspections in a year (if they are full-time inspectors) or 4 inspections in a year (if they are part-time inspectors) in order to maintain their qualification.



Training to become a GMP Inspector

As per the EMA procedure, all the Inspectors and Observers must receive at least 10 days per year of theoretical training.

The inspectorate quality system is periodically assessed via internal audits.



Types of inspections performed

- Periodical general GMP inspections
- Follow-up inspections (to monitor, if deemed necessary, the corrective actions required during a previous inspection)
- Inspections to approve new facilities or new manufacturing lines in already approved facilities
- Inspections following complaints/recalls
- Inspections aimed at verifying counterfeit-related issues
- Extra-EU inspections (also requested by EMA or performed within EDQM, WHO, PIC/S inspection programmes)





THANKS!

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