EUROPEAN MEDICINES AGENCY
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Supervision of manufacturers: What is expected of National Competent Authorities?

Fergus Sweeney, PhD,
European Medicines Agency
Head, Compliance and Inspections

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EU Network of Competent Authorities for supervision of GMP and GDP compliance

Carefully established roles and responsibilities

Mutual recognition of inspections

Sharing of information, database, urgent communication procedures

Processes for urgent action to manage potential threats to public health arising from Quality defects or GMP non-compliance

Links to assessors and licensing authorities at national and EU level

EU and international partners

Cooperation in the supervision of manufacture and import

Member States, in cooperation with the Agency, ensure that the legal requirements governing medicinal products are complied with,

- By inspection (may be unannounced),
- where appropriate, by testing samples, with OMCLs.

Cooperation through sharing information with the Agency on planned inspections and those that have been conducted.

Member States and the Agency cooperate in the coordination of inspections in third countries.

GMP Inspections

Responsibilities of Member States

Appoint suitability qualified and trained inspectors

Ensure by repeated inspections that legal requirements are complied with

Inspectors must be empowered to:

- Inspect manufacturing, wholesale distribution or commercial establishments or laboratories
- Take samples
- Examine documents
- Prepare reports after each inspection
- Communicate reports to the manufacturer
- Place information in the EudraGMDP database

Key concepts

Supervisory authority

The competent authority that grants the manufacturing authorisation. For third country imports, the competent authority that grants the manufacturing authorisation to the importer.

Carries out supervision, inspection and controls on sites in their Member States or third countries on behalf of the EU.

Free movement between Member States - no duplication of controls between Member States

GMP inspections

- Type of inspections:

- **General GMP**:
  - where GMP compliance is unconfirmed or routine surveillance (can be targeted to product or process).
- **Product related:**
  - To assess compliance with the marketing authorisation
- Both types can be performed pre- or post-authorisation
- May be within or outside EU, all sites within EU, sites outside of EU to support Marketing Authorisation process within EU
- **Other:**
  - E.g. Follow-up of earlier inspection, complaint, sampling, quality defect or recall

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Procedures Related to GMP Inspections

Conduct of Inspections of Pharmaceutical Manufacturers or Importers

Table of contents:

EU GMP Structure

Principles and Guidelines

Laid down in Directives 91/412/EEC and 2003/94/EC. Compliance mandatory.

Detailed Guidelines

EC GMP Guide Basic Requirements. Interpretation of Principles and Guidelines.

Medicinal

Part II Active substances

Supplementary Guidelines

Annexes to EU GMP Guide. Provide detail on specific areas and modify detailed guidelines.

Harmonisation in the EU/EEA

Harmonising factors

Collective implementation of Directives into nationa legislation

- National Manufacturing Authorisations
- Concept of Supervisory Authority
- Mutual recognition of inspection outcomes. All inspections "performed on behalf of the Community"

Collective adoption of identical guidelines

Harmonised practices

- Compilation of Community Procedures
- Joint audit programme
- Regular meetings of the GMP/GDP Inspectors Working Group

GMP/GDP Inspectors Working Group

Chaired by EMA

Meets 4 x year

- Develops GMDP related guidelines
- Agrees on GMDP related procedures
- Facilitates Exchange of information
- Harmonisation of GMDP Inspections in the EEA
- Implementation of Mutual Recognition Agreements (MRAs) with third countries
- Liaison activities : QWP, BWP, GCP inspectors, Interested parties, PIC/S, WHO, international partners

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16 July 2012
EMA/INS/GMP/321252/2012 Rev 15
Compliance and Inspection

Compilation of Community Procedures on Inspections and Exchange of Information

The Compilation of Procedures

- Quality System framework for GMP inspectorates
- Handling suspected defects and rapid alerts
- Inspection procedures
- Formats for manufacturing authorisation, GMP certificates and inspection reports
- Exchange of information procedures
- Procedures for centralised inspections
- Verification of GMP in 3rd countries

Joint Audit Programme

Established in 2002 under the authority of the Heads of Medicines Agencies

Programme of audits of member states' GMP Inspectorates by auditors from two other member states

Audit tools are harmonised with those used in MRA evaluations and PIC/S assessments

- The results of these audits are mutually recognised within PIC/S and EEA to avoid duplication

Assesses the Implementation of Community legislation and the Compilation of procedures

EudraGMDP

Mon 6 May 2013 13:23:41 BST

Welcome to EudraGMDP

Directives 2004/27/EC on human medicinal products and 2004/28/EC on veterinary medicinal products introduce the legal framework for the Community database.

The concept of a European Inspections database is included in the above specified legislation to provide EEA National Competent Authorities and the European Medicines Agency (EMA) with an overview of the status of pharmaceutical manufacturers. The legislation provides for an electronic tool containing complete information on all pharmaceutical manufacturers. This includes information on Manufacturing and Importation Authorisations (MIA) and Good Manufacturing Practice (GMP) Certificates for authorised sites in the EEA and information on GMP certificates for manufacturers in third countries.

Compliance with Good Manufacturing Practice:

A certificate of Good Manufacturing Practice (GMP) is issued to a manufacturer by the national competent authority that carriers out an inspection if the outcome of the inspection confirms that the manufacturer complies with the principles of Good Manufacturing Practice, as provided by European Union legislation. If the outcome of the inspection is that the manufacturer does not comply a statement of non-compliance may be entered into EudraGMDP. Certificates and statements of non-compliance may be issued to manufacturers of medicinal products and manufacturers of active substances located inside and outside of the European Union.

Manufacturing and Importation Authorisation:

Manufacture of medicinal products in the EU or importation from a third country is subject to the holding of a Manufacturing and Importation Authorisation. The National Competent Authority of the Member State in which the manufacturer or importer operates issues these authorisations.

Compliance with Good Distribution Practice:

A certificate of Good Distribution Practice (GDP) is issued to a wholesale distributor by the national competent authority that carriers out an inspection if the outcome of the inspection confirms that the wholesale distributor complies with Good Distribution Practice, as provided by European Union legislation. If the outcome of the inspection is that the wholesale Distributor does not comply a statement of non-compliance may be entered into EudraGMDP. GDP certificates and statements of non-compliance may be issued to wholesale distributors of medicinal products and distributors of active substances.

Wholesale Distribution Authorisation:

The wholesale distribution of medicinal products is subject to the holding of a Wholesale Distribution Authorisation. The National Competent Authority of the Member State in which the wholesale distributor operates these authorisations.

Registration of Active Substance manufacturers, Importers and Distributors:

Manufacturers, importers and distributors of active substances are required to register their activities with the National Competent Authority of the Member State in which they operate.

EudraGMDP Database

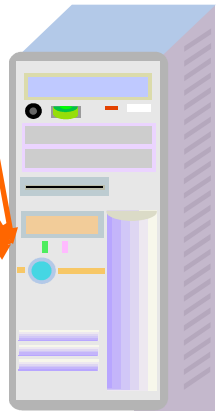
Manufacturing Authorisations (v1) 2007

GMP Certificates (v1) 2007

GMP non-compliance (v2) 2009

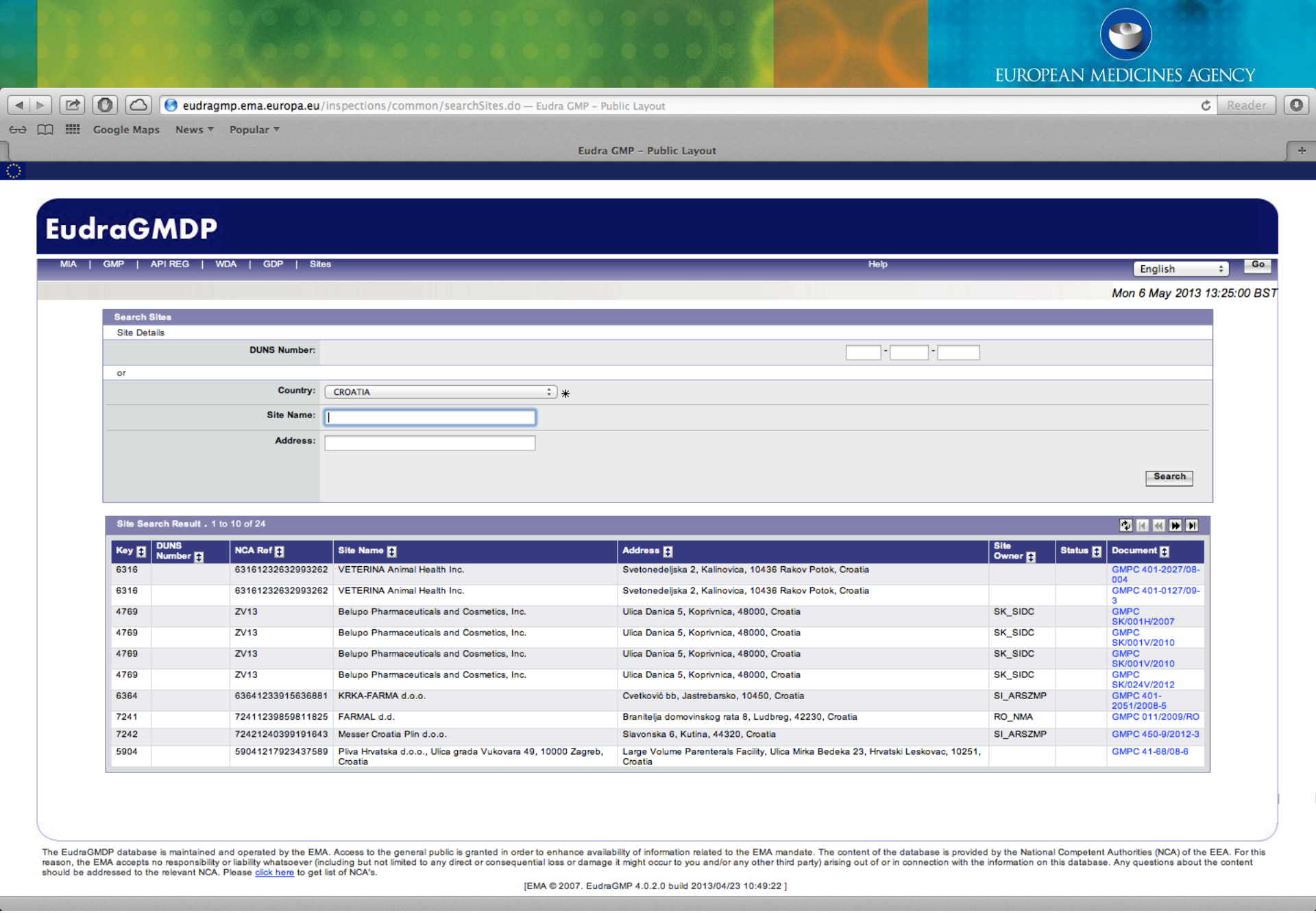
Inspection plans in 3rd countries (v3) 2012

Wholesale distributors, API manufacturers (v4) 2013 live



Search capabilities
Alert on event capabilities

- 1st release April 2007
- Limited public access phased in from 2009-2011 extended 2013.
- Access by MRA partners and other regulatory agencies in progress.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Reader
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MIA | GMP | API REG | WDA | GDP | Sites
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Key
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Site Name
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6316 63161232632993262 VETERINA Animal Health Inc. Svetonedeljska 2, Kalinovica, 10436 Rakov Potok, Croatia GMPC 401-2027/08-004
6316 63161232632993262 VETERINA Animal Health Inc. Svetonedeljska 2, Kalinovica, 10436 Rakov Potok, Croatia GMPC 401-0127/09-3
4769 ZV13 Belupo Pharmaceuticals and Cosmetics, Inc. Ulica Danica 5, Koprivnica, 48000, Croatia SK_SIDC GMPC SK/001H/2007
4769 ZV13 Belupo Pharmaceuticals and Cosmetics, Inc. Ulica Danica 5, Koprivnica, 48000, Croatia SK_SIDC GMPC SK/001V/2010
4769 ZV13 Belupo Pharmaceuticals and Cosmetics, Inc. Ulica Danica 5, Koprivnica, 48000, Croatia GMPC SK/001V/2010
4769 ZV13 Belupo Pharmaceuticals and Cosmetics, Inc. Ulica Danica 5, Koprivnica, 48000, Croatia SK_SIDC GMPC SK/024V/2012
6364 63641233915636881 KRKA-FARMA d.o.o. Cvetković bb, Jastrebarsko, 10450, Croatia SI_ARSZMP GMPC 401-2051/2008-5
7241 72411239859811825 FARMAL d.d. Branitelja domovinskog rata 8, Ludbreg, 42230, Croatia RO_NMA GMPC 011/2009/RO
7242 72421240399191643 Messer Croatia Plin d.o.o. Slavonska 6, Kutina, 44320, Croatia SI_ARSZMP GMPC 450-9/2012-3
5904 59041217923437589 Pliva Hrvatska d.o.o., Ulica grada Vukovara 49, 10000 Zagreb, Croatia Large Volume Parenterals Facility, Ulica Mirka Bedeka 23, Hrvatski Leskovac, 10251, Croatia GMPC 41-68/08-6
The EudraGMDP database is maintained and operated by the EMA. 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. For this reason, the EMA accepts no responsibility or liability whatsoever (including but not limited to any direct or consequential loss or damage it might occur to you and/or any other third party) arising out of or in connection with the information on this database. Any questions about the content should be addressed to the relevant NCA. Please click here to get list of NCA's.
[EMA © 2007. EudraGMP 4.0.2.0 build 2013/04/23 10:49:22]

What's New in EudraGMP?

- GMP Certificates according with the new agreed format
  - API Manufacturing Operations;
  - Part 2 according with the new format;
- MIA according with the new agreed format
  - Annex I and II according with the new agreed format;
  - New concept of suspension and partial suspension based on sites management;
- GDP Certificates and Non-Compliance Reports for Wholesale Distributors and API Distributors; Searches, Drafts, etc;
- Wholesale Distribution Authorizations, including the suspension and partial suspension concept based on site management; Searches, Drafts, etc;

What's New?

- Registration of Active Substance manufacturers, Importers and Distributors (API Registration); Searches for third country manufacturers and Registrant Sites;
- New XML Files
  - New format for GMP and MIA (backward compatibility);
  - GDP files
  - WDA files
  - API Registration files
- New user interface, leaner, faster and optimized to 1280 x 1024 (current standard resolution);

Rapid alerts, quality defects, GMP non-compliance, and related product supply shortages

Compilation of Community Procedures

Procedures Related to Rapid Alerts

Handling of Reports of Suspected Quality Defects in Medicinal Products

Procedure for Handling Rapid Alerts Arising From Quality Defects

Rapid Alert Notification of a Quality Defect / Recall

Follow-up and Non-urgent Information for Quality Defects

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Procedures Related to Rapid Alerts

Procedure for Handling Rapid Alerts Arising from Quality Defects

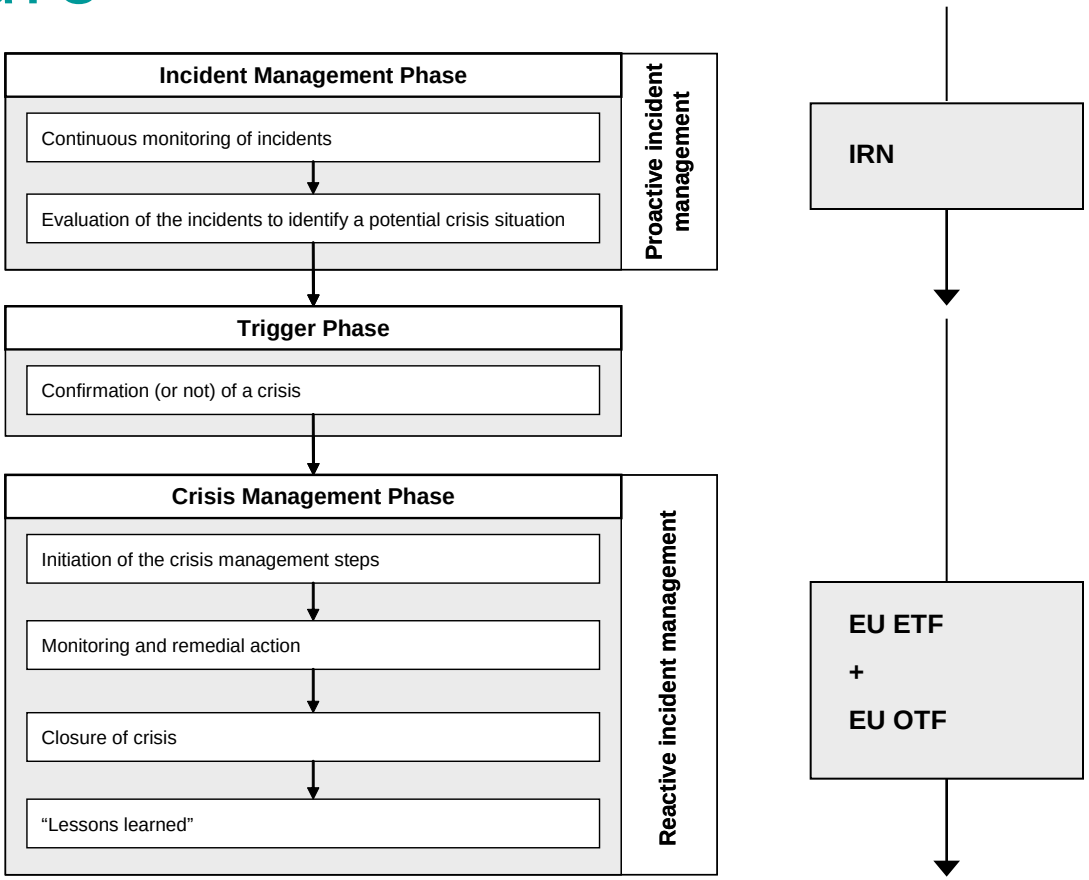
Table of contents:

- EU Regulatory Network Incident Management Plan For Medicines For Human Use;
  - Emerging pharmacovigilance issues as well as combination of quality and safety concerns (e.g. viral contamination with biological products)
  - Irrespective of the authorisation procedure
  - Incidents caused by product quality problems should be dealt with in accordance with the existing procedure on the handling of quality defects

Crisis Management Procedures

- Emerging issue due to (potential) major public health impact needs to be escalated in order to facilitate co-ordination at EU level;
  - Supply shortages caused by manufacturing/GMP non-compliance problems;
  - Incidents which involve a combination of quality and safety concerns;

Outline of the Incident Management Procedure



Incident management and medicinal product shortages caused by manufacturing/GMP compliance problems

- Discussion within the Regulatory Network on lessons learned and possible remedies
- Resulted in Reflection Paper published in November 2012 – short term and medium term actions
- At same time also Implementation Plan 2012-2015 published

Product shortages caused by manufacturing/GMP compliance problems ../..

- Shortages - important public health issue
- Increasing trend & often very complex
- Initiatives have been/are being taken by Regulators
- Need for continuing international collaboration and co-operation
- Next important milestone: workshop with pharmaceutical industry Q3 2013

International Activities

- Ensuring globalisation of GMP standards
- Information sharing, subject to agreements
- Best inspection coverage internationally, avoid duplication
- Surveillance and dealing with non-compliances

- MRAs – Switzerland, Canada, Japan, Australia, New Zealand
- ACAA - Israel
- Joint inspection initiatives with FDA, EDQM, TGA, Health Canada, WHO, increasing number of EU MS …. API manufacturers , finished products
- PIC/s
- ICH

Working together

Making effective use of inspection resources

Harmonised, standard and inspection procedures

Clear, standardised information, readily available

Rapid, responsive, constantly available to manage defects

Protecting the supply chain and quality of medicines

Protecting patients

Thank you