# GMP inspection system in the EEA

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# Agenda

- European regulatory structure
- EMA
- EMA and its Euro-partners
- GMP inspections
- The compilation of EU procedures
- Eudra-GMP database
- Mutual Recognition Agreement
- Supervision of non-EU manufacturers
- Supervision of API manufacturers
- Harmonisation in the EEA
- Update from HMA

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# European regulatory structure

| | |
|---|---|
| Directives | **Defines objectives to be achieved. Member States have to define compliance in their own law.** |
| Regulations | **Directly applicable to all Member States.** |
| Guidelines | **Not legally binding.** |

# European regulatory 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.

Part I Medicinal Products

Part II Active substances

Part III Collection of GMP related documents, which clarify regulatory expectations

## Supplementary Guidelines

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

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# European regulatory structure

## Different kind of authorisations

Directives lay down three types of licence

- Marketing authorisation
  - Holder must be established in EU/EEA
  - Authorisations can be centralised or national
    - National authorisations must use mutual recognition of assessment if marketed in >1 Member State
- Manufacturing authorisation
  - Import from outside of EU/EEA is a manufacturing activity subject to the holding of a manufacturing authorisation
  - National authorisations but mutually recognised
- Wholesale distribution authorisation
  - National authorisations but mutually recognised

# European regulatory structure

## Responsibilities of marketing authorisation holder

Includes ensuring that the product is manufactured in accordance with the marketing authorisation (e.g. specifications, methods, authorised manufacturer(s))

# European regulatory structure

Responsibilities of manufacturing authorisation holder:

- Includes:
  - Compliance with GMP, manufacturing authorisation and relevant marketing authorisations
  - Obligation to only use active substances that have been manufactured in accordance with GMP

# EMA

- A “virtual Agency” established through Regulation
- Mobilises existing scientific resources of the EU/EEA to
  - Deliver Opinions on granting/amending of Marketing Authorisations via the centralised procedure
  - Deliver scientific opinions on any matter referred to it
  - Facilitate harmonisation between EU/EEA Member States
  - Provide guidelines to applicants
- The Agency has 6 Scientific Committees (CHMP, CVMP, COMP, PDCO, HMPC, CAT)

# EMA


- Patient Health Protection
  - Compliance and Inspection
    - » Clinical and non clinical compliance
    - » Manufacturing and quality compliance
    - » Parallel distribution and certificates

# EMEA and its Euro-partners

- Over 40 National Competent Authorities
- Network of over 3,500 European experts
- European Commission
  - Proposes legislation
  - Grants centralised marketing authorisations
- European Parliament
- European Directorate for the Quality of Medicines and Healthcare (EDQM)
    - Official Medicines Control Laboratories (OMCL) Network
    - Certification scheme for APIs subject to monographs of the Ph. Eur. (CEP)
    - European Pharmacopoeia (Council of Europe)

# EMEA and GMP

- **<u>EMEA has no inspectors</u>**
- EMEA coordinates inspections connected with centrally authorised products
  - Pre-authorisation and routine re-inspections
  - Manufacturers located within EU/EEA are under national supervision and therefore co-ordination is almost exclusively for inspections in non-EU/EEA countries.
- EMEA coordinates investigations into quality defects involving centrally authorised products
- EMEA is increasingly involved in wider coordination when this is in the interest of the Community

# GMP inspections

- Responsibilities of MS
- Must ensure by repeated inspections that legal requirements are complied with
- Must place information in the EudraGMP database
- Must take account of the Compilation of Community Procedures for Inspections and Exchange of Information

# GMP inspections (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.

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

All inspections are performed on behalf of the Community

The outcome of inspections are mutually recognised

# The Compilation of procedures

**Legal basis**
**Art. 3(1) Directive 2003/94**

- Handling suspected defects and rapid alerts
- Dealing with GMP non-compliance
- Inspection procedures
- Formats for manufacturing authorisation, GMP certificates and inspection reports
- Exchange of information procedures
- Training and Qualifications of GMP Inspectors
- Triggers for API inspections
- Procedures for centralised inspections
- Verification of GMP in 3rd countries
- Risk-based inspection planning
- Quality System for GMP inspectorates

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# EudraGMP Database

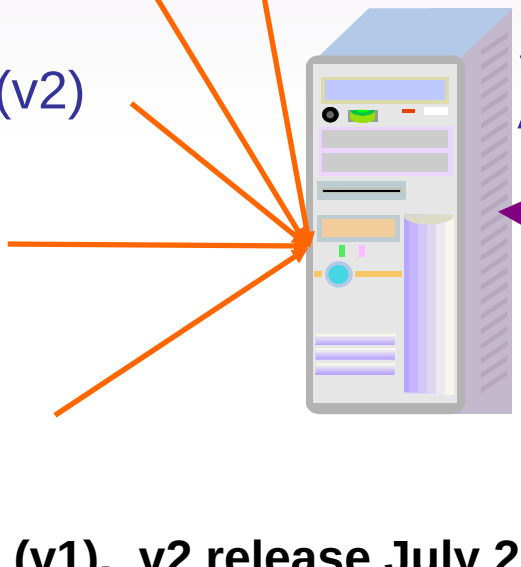
Manufacturing Authorisations (v1)

GMP Certificates (v1)

GMP non-compliance (v2)

Inspection plans
in 3rd countries (v3)

Information on “faulty Manufacture” (v4)



Search capabilities
Alert on event capabilities

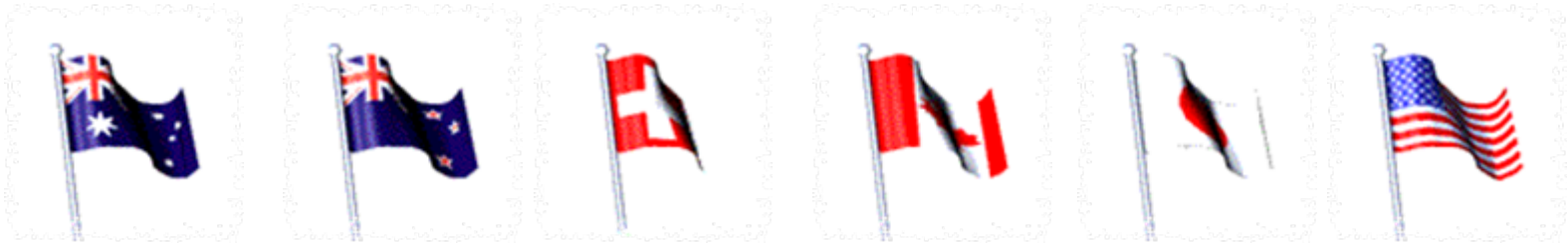
Links to other Community databases e.g. EudraCT

**To be opened by 1st January 2011 to the public**

- **1st release April 2007 (v1). v2 release July 2009.**
- **Limited public access phased in from 2009-2011.**
- **Access by MRA partners and other regulatory agencies in progress**
- **Developed and maintained by EMEA .**

# Mutual Recognition Agreements (MRA)

- Broad trade agreements including the recognition of equivalent GMP standards in the pharmaceuticals sector
  - Avoids duplication of GMP inspections
  - Inspection outcomes accepted based on the exchange of GMP certificates
- The scope varies depending on the individual agreement



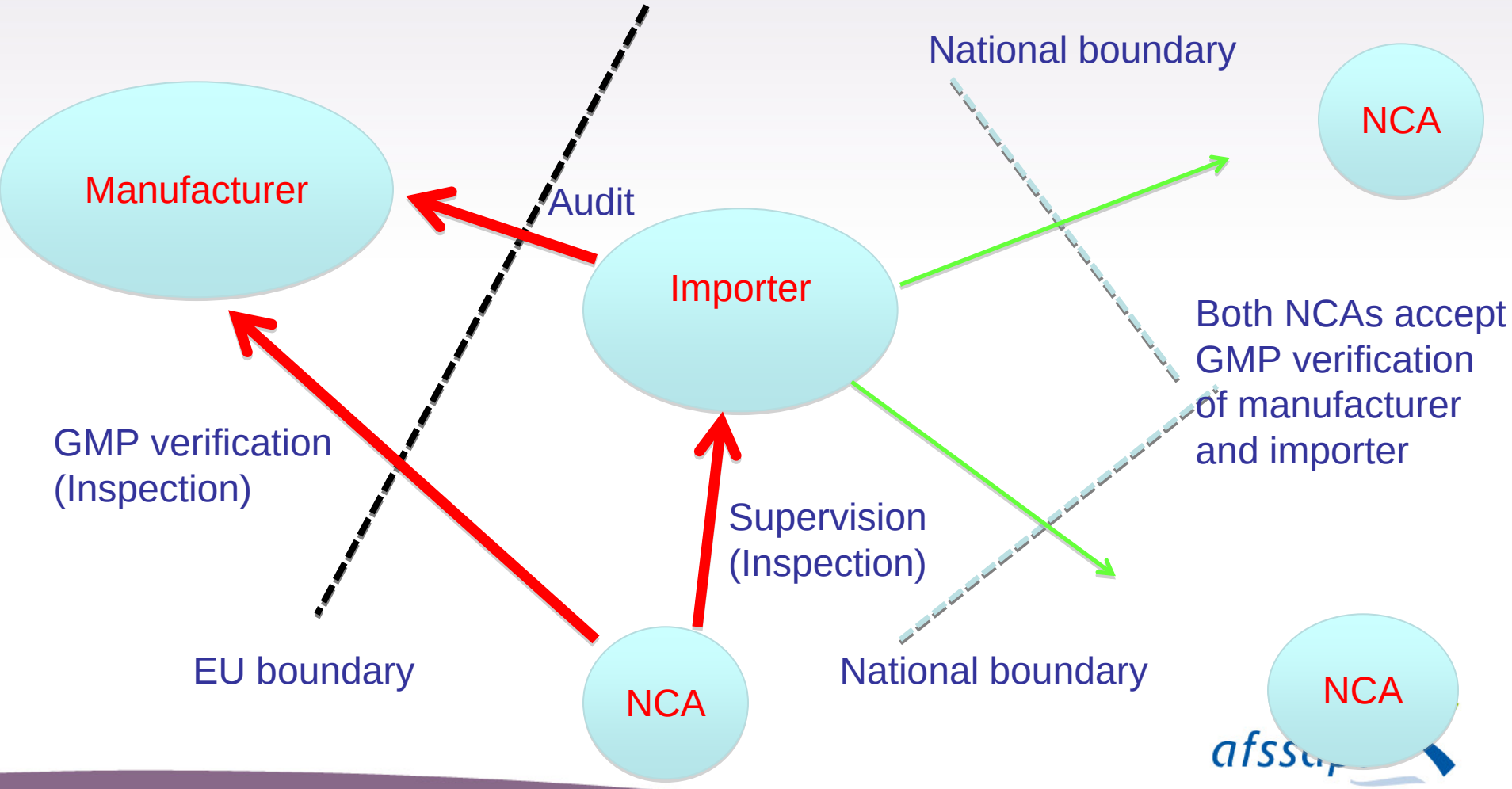
USA agreement is partially operational

An enhanced agreement (ACAA) is being negotiated with Israel. This is based on the adoption of identical standards

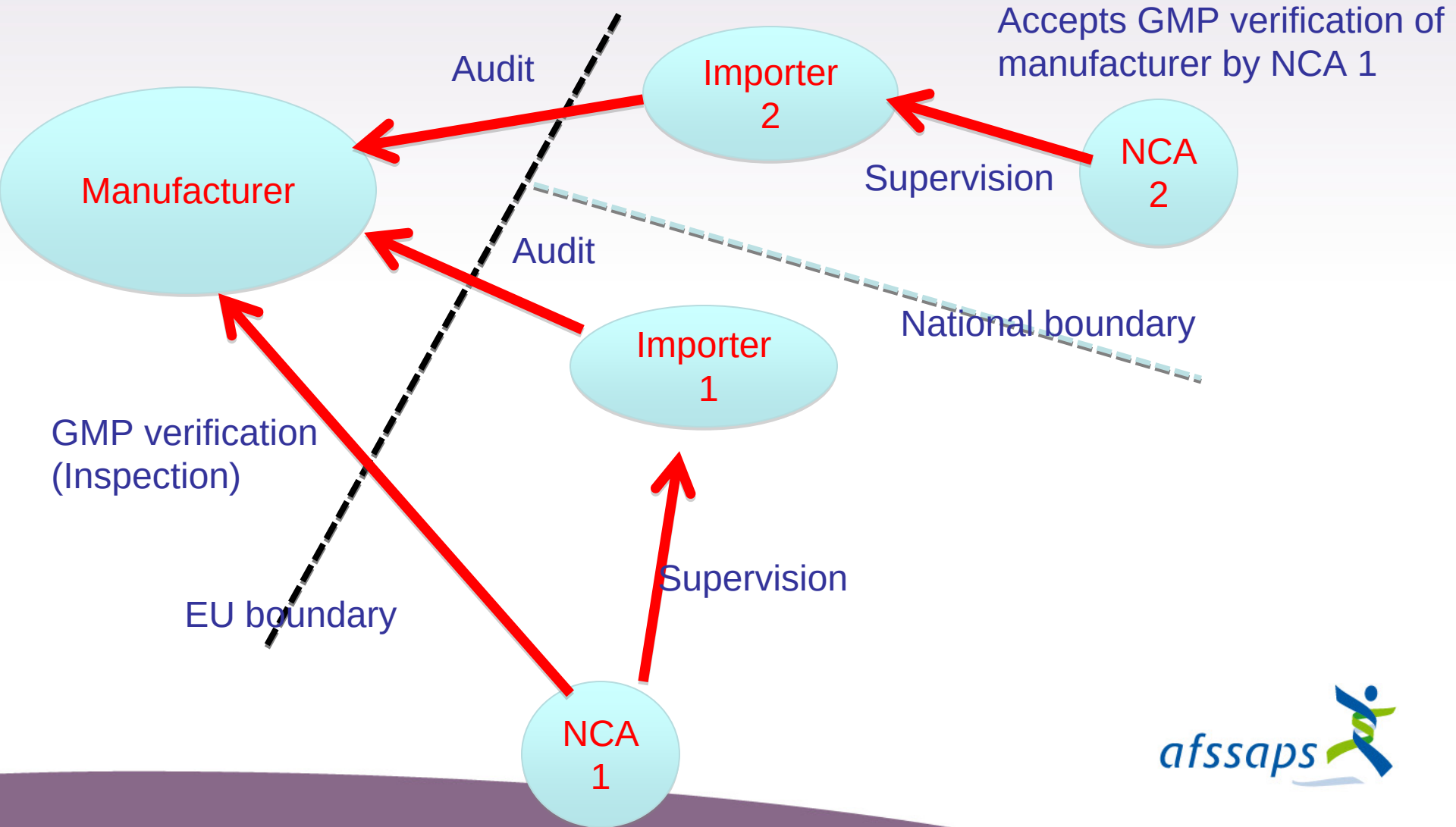
# 3rd country manufacturers

- Importer is responsible for ensuring equivalent standards of GMP are followed at manufacturer e.g.
  - Supplier qualification
  - Contractual arrangements
  - Audit
- Supervisory Authority is responsible for verification of equivalent standards of GMP
  - Supervision of importer
  - Inspection of manufacturer
    - May be delegated to another (usually Supervisory) Authority
  - GMP certificate from MRA partner
- There may be >1 Supervisory Authority

# Supervision of non-EU manufacturers



# Supervision of non-EU manufacturers



# Supervision of API manufacturers

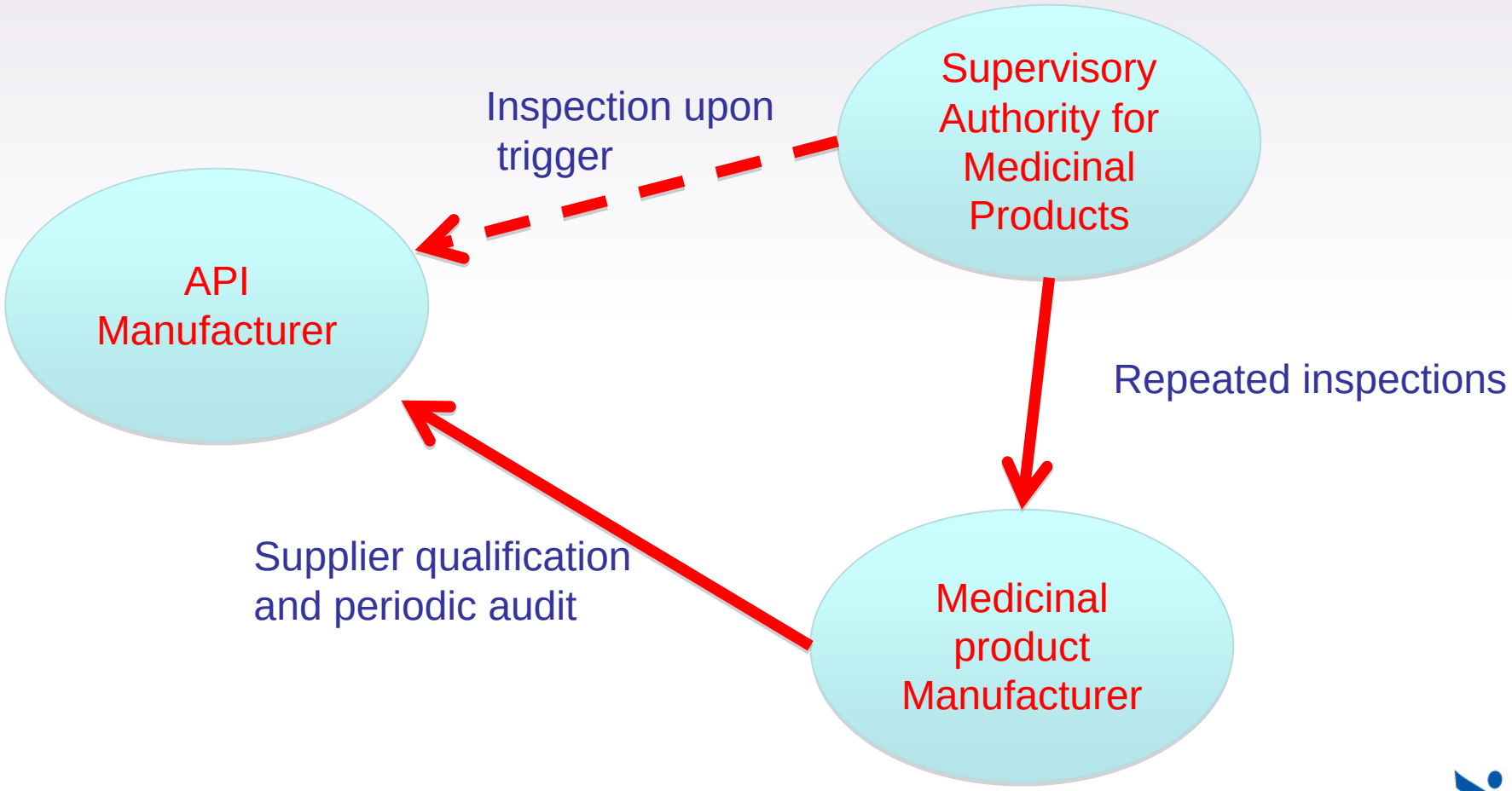
- Prime responsibility rests with user (manufacturing authorisation holder)
  - A declaration is required in all marketing authorisation applications
- Community legislation provides for inspection by National Competent Authorities
  - Upon request
  - When non-compliance is suspected
- A risk-based approach is defined in the compilation of Community procedures
  - Routine inspections for biological substances and for sterilisation/sterile finishing of API

# Supervision of API manufacturers

- Today, no concept of Supervisory Authority, but:
  - Inspections on behalf of Community
  - Inspection outcomes recognised by all Member States

- Work in progress at the GMDP IWG level for assigning responsibilities in case of non compliance to GMP

# Supervision of API manufacturers



# Harmonisation in the EU/EEA

- Collective implementation of Directives into national legislation
  - National manufacturing authorisations with harmonised format
  - Harmonised GMP certificate format
  - Concept of Supervisory Authority
  - Mutual recognition of inspection outcomes
  - All inspections “performed on behalf of the Community”
- Collective adoption of identical guidelines (EU GMP guide)
- Harmonised practices
  - Compilation of Community Procedures
  - Joint audit programme
  - Regular meetings of the GMP/GDP Inspectors Working Group

# Harmonisation in the EU/EEA

Regular meetings of the GMP/GDP Inspectors Working Group

Chaired by EMEA

Meets 4 times per year

Members appointed from each National Competent Authority

Representative of European Commission

Observers from Accession Countries (including Serbia), MRA partners and EDQM

- Develops GMP related guidelines
- Agrees on GMP related procedures
- Facilitates Exchange of information
- Works towards harmonisation of GMP Inspections in the EEA

# Harmonisation in the EU/EEA

## Joint Audit Program (JAP)

- 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 (notion of pre-MRA visits on behalf of the EC) and PIC/S assessments
- Monitored by the Compliance group (issued from GMDP IWG)
- The results of these audits are mutually recognised within PIC/S and EEA to avoid duplication
- Work in progress for mutual recognition with MRA partners

# HMA updates

- Product testing working group
- Training

# Further information

## European Commission

http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

## EMEA

http://www.emea.europa.eu/Inspections/GMPhome.html

# Thank to the EMA for helping me to develop this presentation

# Хвала вам на аттентон

## Thank you for your attention