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SCIENCE MEDICINES HEALTH

International cooperation for inspections of API manufacturers

The place of the Certification Procedure in the global regulatory environment
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An agency of the European Union

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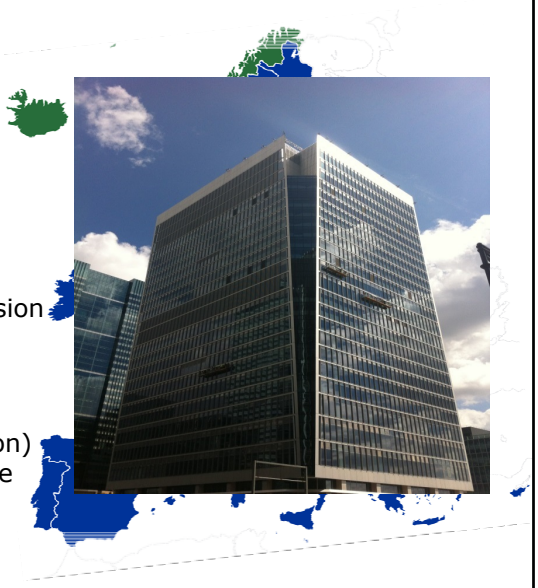
Contents

EMA – EU Network

- 28 EU member states + 3 EEA members states
- ~50 National Regulatory Authorities, 4500 Experts
  ~500 million citizens
- **EMA**
  - Decentralised agency of the EU
  - founded in 1995
  - Located in London, ~890 staff

  responsible for **coordinating** the evaluation, supervision and pharmacovigilance of medicinal products**:**

  - Facilitate development and access to medicines
  - Evaluate applications for marketing authorisation (over 1000 medicines recommended for authorisation)
  - Monitor the safety of medicines across their life cycle
  - Provide information on human and veterinary medicines to healthcare professionals and patients



EMA role in the area of GMP and inspections

- Co-ordination of verification of GMP compliance
- Facilitating cooperation between Member States for inspections of manufacturers in third countries
- Sampling and Testing planning for Centrally Authorised Products (CAPs)
- Coordination of the actions at EU level in case of Quality Defects
- Developing and maintaining the EudraGMDP database
- GMP/GDP Inspectors Working Group
- Developing EU-wide procedures on GMP inspections and related activities
- Ensuring common interpretation of EU GMP requirements and related technical issues

2. Current EU regulatory requirements

EU Regulatory Requirements – Need for Inspection

EU legislation does not require repeated inspections of active substance manufacturers.

In summary, inspections of active substance manufacturers take place:

- API sites located in the EEA: inspections at appropriate frequency based on risk
- At the request of a MS, EMA or the EC whenever there are grounds for suspecting non-compliance (often based on information from trusted authorities)
- At the request of the EMA or the EC on behalf of EDQM to verify data submitted in order to obtain a Certificate of suitability of the monograph of the European Pharmacopoeia
- In the context of a MA application or variation (product- or process-related)
- At the request of the manufacturer itself.

Prime **responsibility for ensuring active substance manufacturers comply with GMP** lies with the **manufacturing authorisation holder (MIAH) that uses the active substance** and this is verified through repeated inspections at the premises of the MIAH.

EU Regulatory Requirements – MAA Submission

Directive 2001/83/EC Art. 8 : In order **to obtain an authorization to place a medicinal product on the market**….

- The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I;
- Annex I (6) : The **manufacturing process shall comply with** the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (**GMP**) for medicinal products for human use and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.

MA applicants are required by virtue of Art. 8(3)ha to submit a written confirmation that the manufacturing authorisation holder has fulfilled their obligations, explicitly through audit. This is commonly achieved through the so-called "**QP declaration**".

CEPs are deemed to replace the relevant data of the corresponding sections described in Module 3.

EU Regulatory Requirements – Importation into EU

Globalisation has had a significant impact on supply of medicinal products. The EU has attempted through legislative change to strengthen the supply chain for medicinal products (→ **Falsified Medicines Directive)**

APIs for medicines for human use **can only be imported** into the EU if:

- Written confirmation on GMP for API; or
- Exporting country is "listed" by the European Commission („white list")
  currently listed: USA, CH, AU, JP, BR, IL
  under assessment: KR, NZ, SG
- Exceptionally - EU GMP certificate

Requirements for **API manufacturers**:

- Registration of EU API manufacturers and importers - EudraGMDP;
- Audit by manufacturers of medicinal products;
- Inspections by NCAs;
- Legally binding GMP for APIs (based on ICH Q7) – Regulation 1252/2014

EU Regulatory Requirements – GMP non-compliance

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Consequences in case active substance manufacturing site is found not to comply with EU GMP for active substances:

- Publicly available statement of non-compliance with GMP (published on EudraGMDP)
- Impact on CEP
- Normally results in measures taken by the relevant EU authorities to prevent the uses across EU of the active substance(s) produced by the site in question.
  Supersedes the corresponding written confirmation (if it exists) issued by the third country.
- Suspension, revoking or variation of marketing authorisation (in accordance with Article 118 of directive 2001/83)
- Prohibition of supply of medicinal product / recall (in accordance with article 117 of Directive 2001/83)
- Suspension of manufacturing / import authorisation

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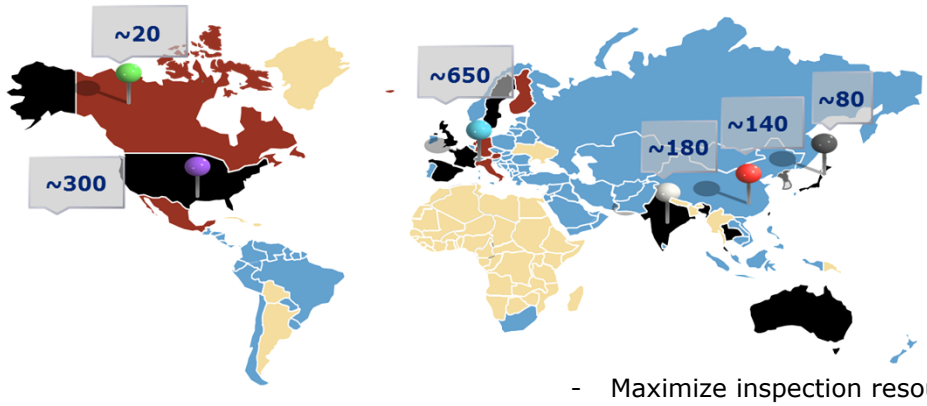
3. Why do we need to cooperate and how do we do it?

Example: API manufacturers registered for CAPs



EudraGMDP

API registration:

~ 1800 sites in IN

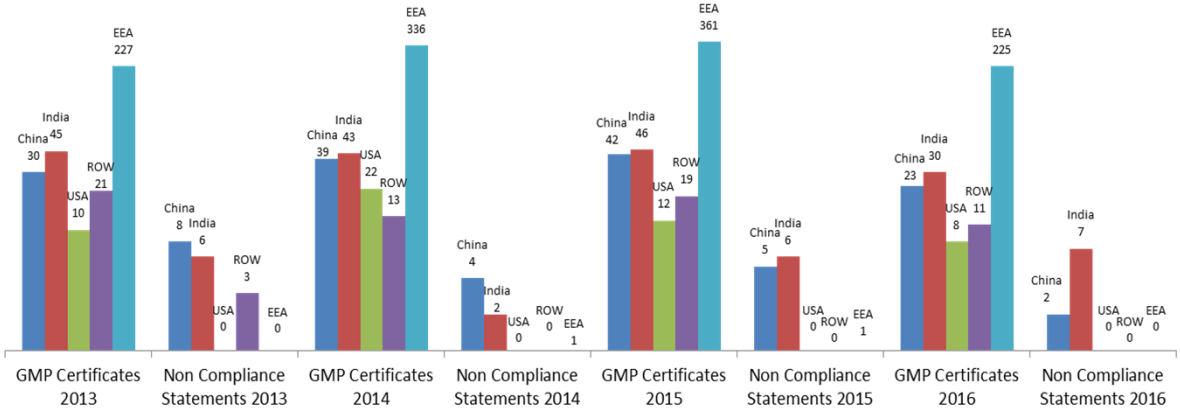
~ 1050 sites in CN

International collaboration - Aims

- Maximize inspection resources
- Broaden inspection coverage
- Minimize duplicates
- Focus on sites of highest risk

Inspections of API manufacturers

2013-2016 GMP Certificates & Non Compliance Statements Issued by EU Authorities for API Manufacturing Sites



International collaboration on GMP inspections (1)

- EudraGMDP Inspection planning module
- **Mutual Recognition Agreements**
  - legal framework to allow authorities to accept conclusions of GMP inspections performed by other party
  - agreements recognise the equivalence of systems regarding oversight wrt GMP
  - remove the need to re-test batches upon importation
  - MRA partners attend IWG meetings

(ACCA)

- **EDQM**
  - sampling and testing programme for CAPs
  - collaboration on coordination of API inspections
- **WHO**
  - optimisation of the use of inspection resources
  - capacity building
  - promoting the adoption of EU regulatory approaches

International collaboration on GMP inspections (2)

- **PIC/S** (Pharmaceutical Inspection Co-operation Scheme)
  formal agreement between EMA and PIC/S to collaborate to maintain common GMP guideline at international level
  - aim to better use inspection resources, avoid duplication of activities
  - aim to maintain mutual confidence and promote quality assurance of inspections
- **ICMRA** (International Coalition of Medicines Regulatory Authorities)
  - forum to support international cooperation among medicines regulatory authorities
  - has a work stream that is trying to develop a procedure for mutual recognition of GMP inspections
- **ICH**
  to support the EU constituency in developing guidelines with particular emphasis on GMP inspection and pharmaceutical quality systems approach (Q9, Q10, Q11)
- **Collaboration with US FDA**
  exchange of liaison officers, exchange of information on GMP including un-redacted inspection reports
- Support for capacity building – inspector training

International API inspection Pilot Programme

An **informal initiative** for International Collaboration on GMP inspections of API Manufactures (in operation since 2012)

Objectives

- Programme to rationalise international GMP inspections of active substances manufacturers worldwide
- Increasing global coverage of inspections through minimising duplications

Activities:

- Increasing number of joint inspections (collaboration on GMP inspections of third country API manufacturing sites of common interest)
- Exchange of inspection outcome
- Collaboration on exchange of information on API training

Members: USA FDA & EMA (joint leads), Italy, France, Denmark, Ireland, UK, Australia, WHO, EDQM, Canada and Japan.

4. Outlook, Conclusions

EMA long term vision

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Global supervision of the supply chain

- Creating synergies through communication, collaboration and cooperation with international partners;
  e.g Using non-compliance information received from 3rd country authorities
- Supporting a global approach to authorisation and supervision of medicines
  - Initial focus on inspection cooperation and best use of inspection resources
  - Standards based on ICH and WHO requirements
  - Using existing partnerships (bilateral/multilateral) and tools (guidelines, mechanisms for information sharing, unique facility identifiers/inspection schedules).
- Broaden inspection coverage and maximize the impact of limited inspection resources by focusing on sites of highest risk

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