Understanding Updated EDQM Certification Procedure and First Hand Experience With Regards to On-site API Inspections in China

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Overview

- The EU GMP for APIs
- International API inspection programme
- What's new ?
- Main deficiencies
- Statistics: activity review, compliance trends
- EDQM communication in China and future outlook

Responsibility of the marketing authorisation holder (MAH) of the medicine

- APIs must be produced according to EU GMP (Directives 2001/83/EC and 2001/82/EC)
- It is the responsibility of the manufacturer to ensure EU GMP compliance of the active substance manufacturer
- Declaration of the Qualified Person (QP) of the manufacturer in the marketing application (and subsequent variation)

Role of the National Competent Authority in EU

- The Competent Authority may inspect an API manufacturer in order to ensure that the manufacturing authorisation holder of a medicinal product has fulfilled its obligations under Article 46 (f) and/or Article 50 (f) of the below mentioned Directives (Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC)

- NB: in contrast to medicines, inspections are not carried out systematically

Responsibility of the manufacturer

- In the CEP procedure the API manufacturer has to declare:

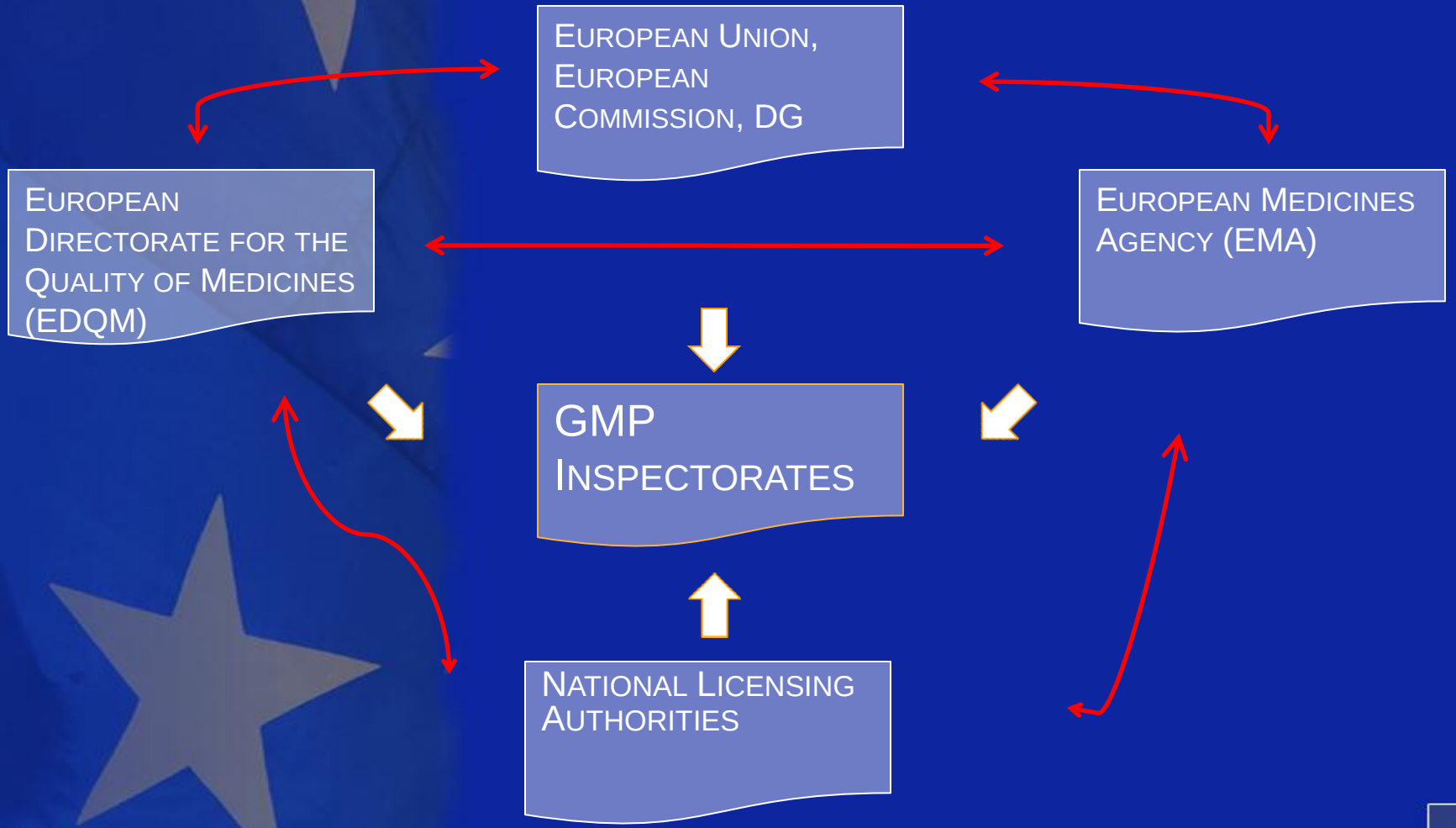
  - Compliance to Good Manufacturing Practices (GMP)

  - Willingness to be inspected

Conditions for an inspection

- When requested by a member State, EMA (European medicines agency), European Commission or EDQM (if there are grounds for suspicion of non-compliance, need to verify data submitted)
- When requested by the manufacturer itself

European Authorities



GMP / GDP Inspectors Working Group

- Takes place at EMA, London
- Gathers EEA member states representatives
- Provides input and recommendations on all matters relating to
  - Good Manufacturing Practice (GMP)
  - Good Distribution Practice (GDP)

GMP / GDP Inspectors Working Group: main activities relating to GMP

- Discussions of EU Legislation
- EudraGMP database
- GMP for Medicinal Products (Part I, Annexures)
- GMP for Active Substances (Part II, Annexures)
- GDP
- Product defects & inspections under centralised procedure
- Management of MRA in the field of GMP
- ICH Q8, Q9 and Q10 implementation
- Management of the Community Procedures

Role of EMA: Compilation of Procedures

- EMA is responsible for maintaining and publishing on behalf of EC Commission
- Collection of GMP inspection-related procedures and forms (Quality System for GMP Inspectorates) agreed by all member states
- To facilitate:
  - Collaboration
  - Harmonisation
  - Exchange of Information

Role of EMA: Compilation of procedures EMA/INS/459921/2010

- Quality systems framework for GMP inspectorates
- Procedures related to rapid alerts
- Procedure related to GMP inspections
- Procedures related to GDP inspections
- Forms used by regulators
- Procedures related to centralised procedures

(one single reference for all documents since March 2011)

Sharing of information- API program

- International API Inspection Program initiated by EMA in 2007 after approaching Authorities:
  France, Germany, Italy, UK, EDQM, Australia, USFDA, Ireland
- All agreed to participate in a pilot phase = total duration 2 years (end 2010)
- Aim :
  - To make best use of Inspectorate's resources
  - To increase the inspectional coverage

Sharing of information- API program

- Confidentiality agreements signed
- Pilot program is built up with bilateral and general teleconferences
- Running the program is based on
  - Sharing inspection reports
  - Performing joint inspections (with scope extension if necessary)

Sharing of information- API program

- The participants to the program provided alltogether a list of 1110 sites (as published in 2011 at the end of the pilot phase)
- As several sites were shared sites, there were a total of 646 sites listed from which:
  - 408 sites were of interest to only one of the participants
  - 238 were of interest to 2 or 3 of the participants
- USFDA has taken an import alert decision based on an EDQM inspection with negative outcome
- Next steps :
  - To continue the program (no longer pilot) with teleconferences, information exchange
  - To improve process monitoring
  - To enlarge the number of participants

EDQM Inspection programme

- Optional part of the Certification Procedure (Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC, Compilation of Community Procedures)
- Performed before or after the CEP is granted
- Aim: to verify the compliance with
  - ✓submitted dossier
  - ✓EU GMP Part II
  - ✓EU GMP Annexes (e.g. Annex 1 / sterile substances)

EDQM Inspection Program

- In application of Directives 2001/82/EC and 2001/83/EC as amended, the European Commission gave a mandate to the EDQM to establish an annual program for inspections
- Inspections are performed inside and outside Europe and involve manufacturing sites and brokers/distributors holding CEP(s)

EDQM Inspection Program

- The draft program is circulated to the Member States for comments and presented to the GMP/GDP Inspectors Working Group at EMA for discussion.
- The program is finally adopted by the CEP Steering Commitee.
- The final program is circulated to all EEA Member States Competent Authorities

Selection of the sites

- Done in accordance with the EU guidance published by EMA (EMA/INS/GMP/459921/2010 Compilation of community procedures on inspections and exchange of information)
- According to a risk-based approach:
  - main criteria: request from the assessors
  - sterile substances
  - inspection by equivalent authority
  - several triggers involved
  - regulatory environment of the manufacturing site

Requests from Assessors

Sterile Grade

- Inspection is routinely performed for any sterile substance
- Preferably prior granting the CEP
- Draw attention to a specific point; e.g. tray lyophilisation

Suspicion regarding the dossier

- Inconsistencies in the data
- Suspicion of fake data

Potential weak points: process-related or specification-related

- Starting material close to the final step is not prepared by the manufacturer itself + lack of information
- Complex or badly explained process steps
- Subcontracting some steps of manufacturing process

Potential weak points:

site-related

- Suspicion of low awareness and knowledge of the GMP principles
- Suspicion of risk of cross-contamination

How the System Works

- Inspection performed by team composed of an EDQM inspector and an inspector coming from an EU/EEA or MRA National Competent Authority
- Scope of an EDQM inspection:
  - Compliance to the submitted dossier
  - Compliance to the EU GMP Part II
  - Compliance to EU GMP annexes when relevant
  - Compliance to the European Pharmacopeaia
- Actions are taken <u>immediately</u> after the inspection in case of major or critical deficiencies (public health issue)

Role of inspectors, observers, interpreters

- Inspectors: 1 EDQM inspector and 1 inspector (EU/EEA or MRA NCA)
- Observers: Inspectors from local authorities
- Interpreters:
  - When the working language cannot be English
  - In China: mainly appointed by EDQM
  - Translate the words of inspectors and inspectees

Participation of Inspectorates

EEA:
Austria
Czech Republic
Denmark
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Netherland
Norway
Romania
UK
Sweden
Spain

MRA partners:
Switzerland
Australia

Other partners:
WHO

Inspection Outcome

- According to the inspection results the Company is quoted as compliant, borderline or non compliant.
- Borderline status is only a provisional status: after assessment of the corrective action plan, the outcome is upgraded or downgraded to compliant or non-compliant.
- Companies found compliant may be re-inspected/re-evaluated within 2-5 years depending on the numbers and classification of deficiencies found.

Inspection follow-up

- The company must reply to the deficiencies found within one month from the receipt of the inspection report
- The replies should be fully documented and reflect actual measures in place
- Discrepancies with the certification dossier are specifically addressed and managed by the revision process at DCEP

Positive Outcome

- In case of positive conclusion of the inspection,and if any expected changes for CEP revision have been submitted, an inspection attestation is delivered, stating the compliance with the CEP and with the GMP

- A GMP Certificate should be issued by the participating Inspectorate (EMA/INS/GMP/459921/2010 Rev 13 Compilation of Community Procedures)

Negative Outcome

- In case of critical/major GMP deficiencies or in case of major deviation compared to the dossier (failure in the declarations and commitments)
  - CEP(s) suspended or withdrawn
  - on-going CEP application(s) rejected
- Suspension/Application rejection is
  - Advised by the inspectors
  - Discussed within the Certification Division
  - Endorsed by an Ad Hoc Committee
- PhEur Member States, EMA, EU Commission and local Inspectorate are informed

Negative Outcome

- Information published on the EDQM website (CEP database and Certification webpages)
- Holder and manufacturer are informed and a possibility of hearing is given
- Statement of GMP non-compliance should be issued by the EEA Inspectorate

Actions taken by the EDQM

The EDQM announces the suspension of the following CEPs :

- As a result of an inspection of the manufacturing sites:

Date	Substance name	CEP Number

- As failure to commitments of willingness to be inspected (refusal of inspection, reconstruction/restoration of sites to achieve GMP level, temporary closure of a site…) and/or to operate according to EU GMP:

Suspension of the CEPs

- CEPs are suspended for a period of 2 years
- Company is requested to apply within this timeframe for a re-inspection
- Based on a valid justification, the company may ask for an extension of this period
- Lifting the suspension can only be done after an inspection with positive outcome

Suspension vs withdrawal: what's the difference ?

- **Suspension**: A temporary cancellation
  - ➢ CEP can be restored
- **Withdrawal**: A definitive cancellation
  - ➢ When no corrective actions are deemed possible (e.g. extensive cases of falsification of data, repeated non-compliance)
  - ➢ A new dossier should be applied for

What's new ? SMF

- The « EDQM questionnaire » is now replaced by a Site Master File (SMF) based on the PIC/S template
- EU has also a similar SMF
- Rationale: having a document potentially recognised by numerous inspectorates in the world

What's new ? GPS/DUNS

- GPS coordinates and DUNS number requested for any CEP application (as well as prior to an inspection)
- EDQM specific requirements:
  - GPS is mandatory, DUNS is optional
  - System: WGS 84 (World Geodetic System 1984)
  - Unit: degree minutes seconds

  DDD,DDDDD or DDD MM,MMM or DDD MM SS
  - Recorded at the entrance of the site

– Also requested in the EU and PIC/S SMF

New requirement for GPS/DUNS: how the forms look like

GPS (WGS 84) coordinates of the site*:

Latitude (S or N) and Longitude (E or W) expressed in Degrees Minutes Seconds to 1 decimal place
(Alternatively it can be expressed in Degrees to at least 5 decimal places or Degrees Minutes to at least 3 decimal places)

☐ main entrance:

☐ if not main entrance, specify place:

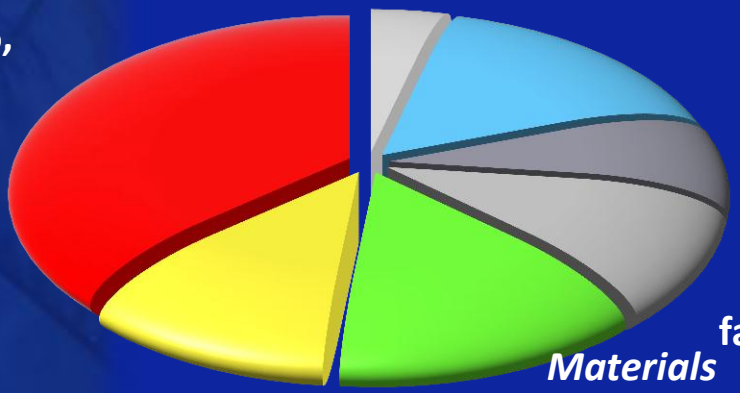
DUNS number	

- To be recorded with a GPS device or by using appropriate softwares (eg Google Earth or other equivalent application)

GPS/DUNS: why ?

- Experience with CEP applications showed that the addresses may be incomplete or inconstant:
  - Addresses with a street or road name without a number
  - Street/road name or number has changed for urban or administrative reason
  - Reorganization by the local authorities
- Need to better identify the location of the manufacturing sites

2011 main GMP deficiencies



Quality related matters: Quality management, Personnel, Documentation, Validation, Change control, Complaints and recalls, Contract manufacturers

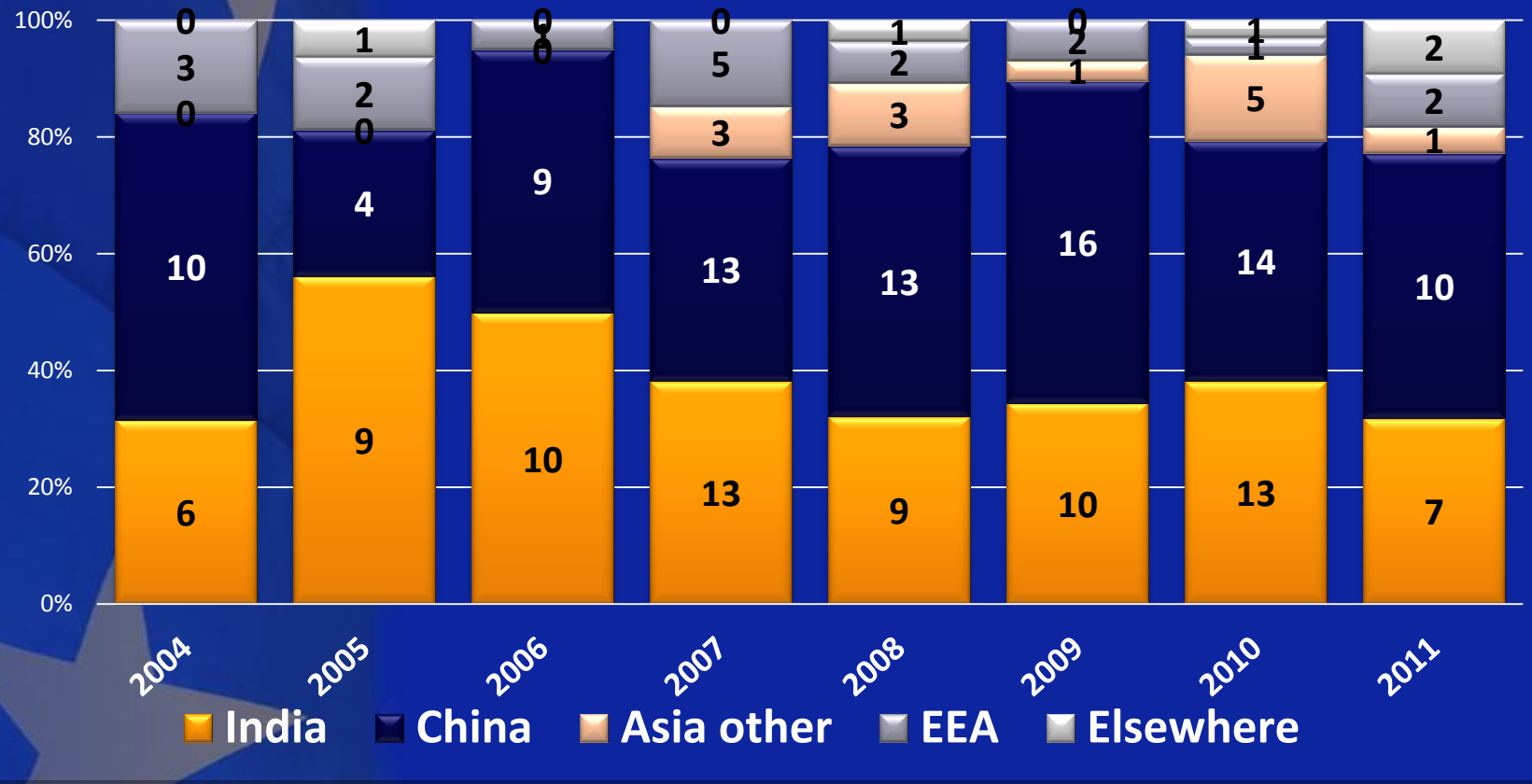
Main GMP deficiencies

- Quality related matters
  - Quality review: not a quality tool for companies
  - Change control / Deviation management: not a deep-rooted practice, deviations are underreported
  - Validation of processes: CPP not based on scientific rationale, micronisation not addressed
  - Cleaning validation poor
  - Qualification of equipment: lack of appropriate user requirement specification, weakness of water systems

Main GMP deficiencies

- Process equipment / Buildings and facilities
  - Design – Cleanliness- Maintenance
- Laboratory controls
  - Qualification of equipment
  - Chemical reference standards
- Materials management
  - Traceability
  - Key starting material vendor approval
  - Storage

Statistics 2004-2011: Locations



Inspection figures in 2011

- 22 sites covered by EDQM inspections
- 25 sites covered by exchange of information (inspections by EEA inspectorates)
  - 3 sites refused to be inspected (suspension of CEPs)
- CEPs suspended: 16
- CEPs withdrawn : 8

General Compliance Trends

- Non compliant inspected sites:
  - 2007: 18%
  - 2008: 21%
  - 2009: 34%
  - 2010: 18%
  - 2011: 32%

This is seen as the result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them

EDQM communication in China and future outlook

- CPHIs
- Conferences and tutorials (SFDA / WHO, CCCMHPIE)
- One-to-One
- Outlook: continue inspections and take into consideration regulatory implementation of the falsified medicines directive (FMD)

Perspectives

- Further develop the risk-based approach when elaborating the programme
- Reinforce collaboration and sharing of information with EU and International Inspectorates

Aim: optimise inspection resources

  - Program for exchange of information on API (EMA): increasing number of contributors expected
  - Inspector working group GMP/GDP (EMA)
  - Committee of officials of PIC Scheme (PIC/S)
  - Confidentiality agreement with PIC/S, TGA Australia, USFDA, WHO, Ukraine, Russian Federation…
  - Development of a Distant Assessment

- Close collaboration between assessors and inspectors

Conclusions from the companies' side

- Drug manufacturers must improve their ability to select GMP compliant suppliers and audit/monitor them properly
- Drug manufacturers and their suppliers must be aware that any changes in the manufacturing process (including change in suppliers of starting materials) may impact the impurity profile.
- API suppliers should endorse their responsibilities and be supportive to customers (and vice versa)

Conclusions from the inspectorates' side

- Inspection remains a powerful tool to detect non-compliances and take necessary actions
- Optimising inspection ressources is of paramount importance
- More stringent requirements apply for inspecting/ auditing GMP compliance of API manufacturing sites as of 2013 with coming into force of "FMD" 2011/62/EU

Thank you for your attention

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