The benefits of the CEP procedure – a national inspector's point of view

EDQM: 50 years of leadership in the quality of medicines, paving the way for the future

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Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator	X				
Individual's Institution/Organisation receives a grant or other funding	X				

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N.B. I am not receiving any compensation

Content of the presentation

- GMP inspections within the Certification of suitability to the monographs of the European Pharmacopoeia
- Benefits for EU/EEA NCA and International Partners
- Benefits for GMP inspectors

Certification Procedure

- Adopted the 1st July 1993 by the Public Health Committee of the Council of Europe and revised in 1996, 1998, 1999, 2007
- The current version is the Resolution AP-CSP (07) 1
- Initially focused only on the assessment of the dossier, later enlarged to the *on site* inspection, selected according to specific criteria

Inspections within the CEP procedure

- An inspection pilot phase was launched in 1999 with the aim to verify the GMP compliance of manufacturing sites producing/trading substances covered by CEP (active substances or excipients)
- Initially it involved only manufacturers located in Europe then the program was enlarged to extra-EU countries
- Consolidated phase: the European Commission gave a mandate to the EDQM to establish an annual program for inspections

Inspections within the CEP procedure

- Starting November 2005 new obligations for manufacturing authorizations holders to use only active substances manufactured according to the GMP came into force (directive 2001/83/EC and 2001/82/EC as amended)
- The same year a new EMA guidance on "*When it is appropriate for Competent Authorities to conduct inspections at premises of manufacturers of active substances used as starting materials*" was issued

EDQM Inspection program: a step by step development

Milestones:

- An annual program regularly developed, initially based on the requests from assessors and then on the basis of new triggers, as defined by the EMA procedure
- Initially inspection team composed of one or more GMP inspectors from NCAs working with CEP personnel (assessors)
- Recruitment of GMP inspectors in secondment from NCA

EDQM Inspection program: a step by step development

- Establishment of an EDQM inspection Unit, with GMP inspectors recruited from NCAs thorough a selection process managed by the Council of Europe (temporary or permanent agents = EDQM inspectors)
- Inspection team composed of an EDQM inspector and a NCA inspector, whose NCA is responsible for issuing responsibility to issue the GMP certificate
- Regular participation to the EMA GMDP-IWG discussion

Evolution of the legal framework for APIs manufacture and importation in Europe

- Before directive 2011/62/EU each NCA might have had different approaches for API manufacturers oversight, according to the national legislation:

- Mandatory registration/authorization
- No legal requirements for registration/authorization
- Inspections carried out in EU or extra-EU countries for specific category of APIs (i.e. biological origin/sterile APIs)

Evolution of the legal framework for API manufacture and importation in Europe

- Inspections carried out in Europe or extra-EU countries if requested by the manufacturer to grant a GMP certificate
- Inspections carried out if deemed necessary during the assessment (NCA inspections, EMA inspections)

Same market, different regulatory approaches

Directive 2011/62/EU:common legal basis

- The directive 2011/62/EU introduces the mandatory registration for manufacturers, importers and distributors of active substances, located in the European Union territory (art.52*a*)
- EU Member States have to take appropriate measures to ensure that manufacture, import and distribution on their territory of active substances, including that are intended for export, comply with GMP and GDP (art. 111, 1*b*)

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Directive 2011/62/EU:common legal basis

•NCAs shall have a system of supervision including inspection at an appropriate frequency, based on risk, at premises of manufacturers, importers or distributors of active substances, located in their territories and effective follow-up thereof

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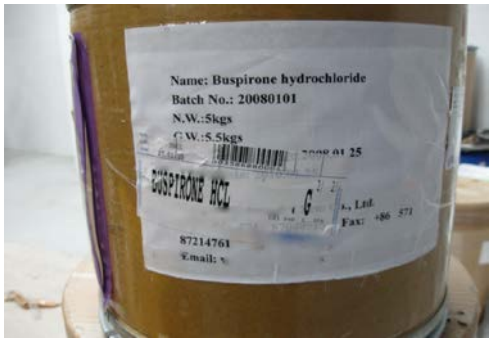
Directive 2011/62/EU:common legal basis

- If there are grounds to suspect non compliance NCAs may carry out inspections at premises of manufacturers or distributors of active substances located in third countries or manufacturers or importers of excipients (in their territory)



APIs market globalization

Quality of APIs

↓

Common quality standards

↓

Regulatory convergence on inspections

↓

Inspection resources

(From presentation of L.Pani, AIFA Director General, 19th May, 6th expert circle on APIs, Rome)

EDQM inspection program: its contribution to the API oversight system

1) Development of a risk based inspection program
2) Inspections of sites under common interest for the European market
3) Involvement of inspectors working for different NCAs: promotion of harmonized approaches for inspection of API manufacturers

4) Development of a standardized post inspection procedure
5) Sharing/optimization of inspection resources within EU/EEA NCAs

1) Development of a risk based inspection program

- Requests from assessors of EU/EEA authorities
- API related criteria
- Company related criteria
- History of inspection by authorities (worldwide)
- Re-inspections

Benefit for NCAs/inspectors: be sure that the sites under higher risk are inspected; have suggestions on criteria to be adopted «in house»

2) Inspections of sites under common interest for the European market

- The sites selected as candidates for the inspection are listed in programme circulated as a draft to the EU/EEA NCAs through the GMDP-IWG
- The NCAs can check if among the listed sites there are some under their own interest
- For sites under common interest inspections are organized as first option with the interested NCA

Benefit for NCAs: to be informed in advance about planned EDQM inspection

3) Harmonization of inspection's approaches

Inspectors coming from NCAs have the opportunity:

- to share work, harmonize inspection approaches and methodology and participate to inspections under interest of many NCAs/International partners
- To enhance their experience in the specific field of GMP inspections for APIs

Benefit for NCA inspectors: improve skills and be key player in activities intended to protect the public health on the whole European market

4) Post inspection process

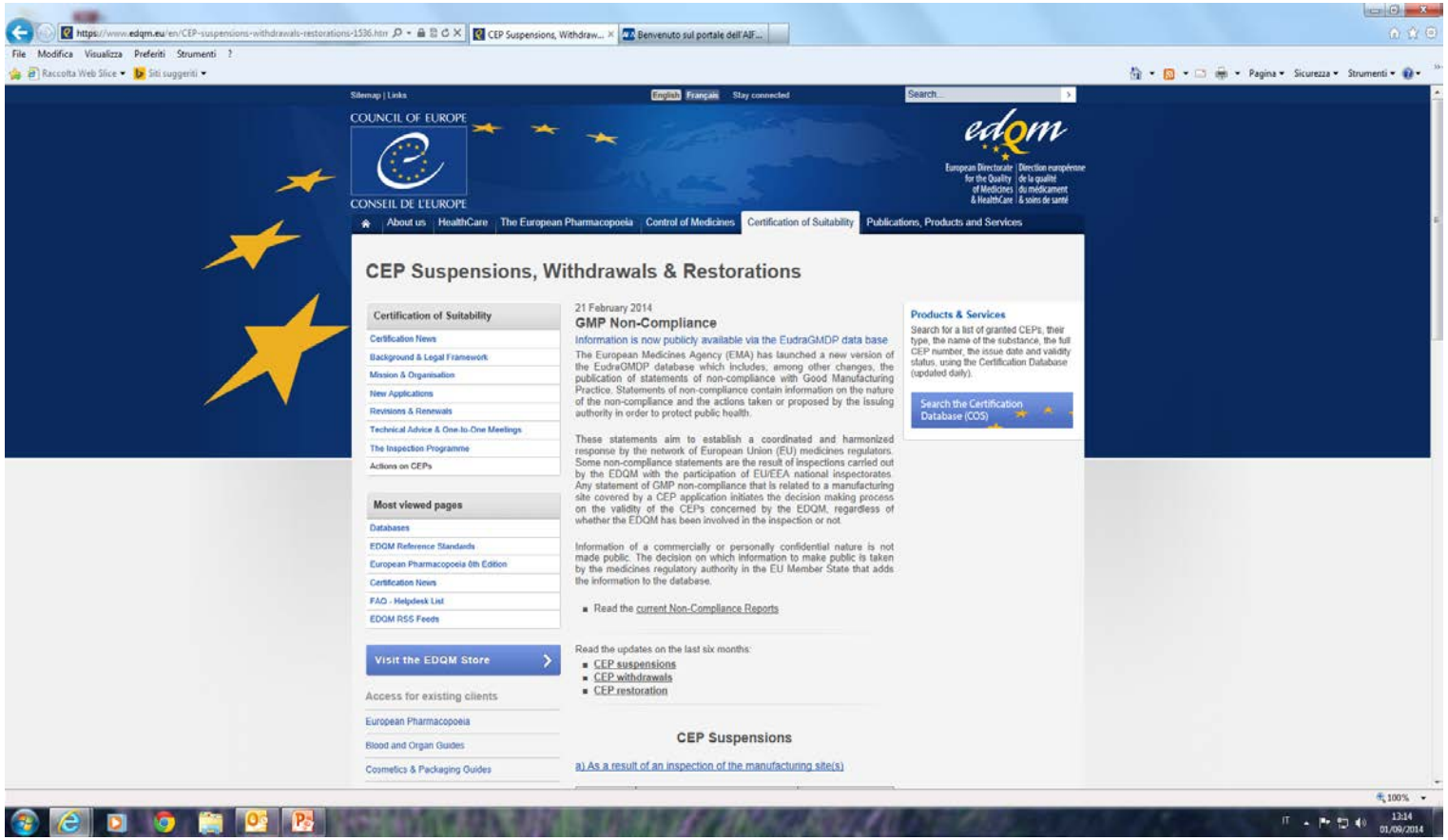
- Standardized post inspection process with the aim to assess the outcome of the inspection and discuss cases of possible non compliance (Internal Decision Board)
- Whether the site is deemed non compliant by the inspectors, the case is discussed within the Ad hoc Committee who makes the final decision to suspend/withdrawn the CEP
- The participating NCA has the responsibility to issue the statement of GMP non compliance or the GMP certificate

4) Post inspection process

- Procedure for suspension or withdrawal of CEP for inspections related reasons (PA/PH/CEP (08) 17, R4)
- The procedure works in parallel with the EMA procedure on issuance of the statement of GMP non compliance
- Transparency: publication on the EDQM website of reasons for suspension or withdrawal of the CEP

Benefits: the decision making process is shared with experts

4) Post inspection process



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5) Resources saving

- Participating to the EDQM inspection program means that for a site which may be under the interest of several NCAs only one inspector is involved (in team with the EDQM inspector)
- When the inspection is carried out under the EDQM program, the participating NCA saves one or more inspector
- Example 2014: AIFA participation to 5 extra-EU inspections, 4 of them are under the interest of AIFA:

Benefits: 3 inspectors instead of 6-8!!
(team always composed of 2 insp.)

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Inspection process

- 1st phase: preparatory meeting

- Exchange of information between NCA and EDQM inspectors
- Evaluation of the dossier and study of the assessment report (Report A), SMF review, preliminary information requested and previous reports
- Background information (Report C -trigger for the inspection-, Eur. Ph. Monograph and Standard in use, current version of the CEP with specific requirements (i.e residual solvents, retest date, etc.)

Inspection process

- 2nd phase: on site inspection

- Compliance with EU GMP Part II (general assessment of the overall system: quality assurance, material management, process equipment, cleaning, batch records and distribution, QC lab.)
- Assessment of the compliance amongst the dossier and the real life (manufacturing process, critical parameters, impurity controls, specifications of raw materials, intermediate and solvents, recovery of materials, stability data, etc.)

Inspection process

- 3rd phase: post-inspection process

- Inspection report according a specifically designed format (initially based on EMA template)
- Discussion within the Internal Decision Board
- For non compliance cases: discussion within the Ad hoc Committee ⇨ CEP suspension/withdrawn

  Statement of GMP non compliance (NCA)
- For compliant cases: Follow-up process, evaluation of CAPA plan, issuance of the final report, issuance of the GMP certificate and EDQM Attestation

EDQM contribution to the International network

- Network activities of EU/EEA inspectorates
- Primary role in the International API Inspection program (launched in 2007 by EMA, involves EMA, EDQM, some EU member States, USFDA, TGA, WHO)
- Several joint inspections with FDA, TGA, WHO, EU NCAs
- US-FDA can take into account negative EDQM inspection results to issue warning letters or take actions on the market (i.e. import alerts)

EDQM contribution to the International network

- Falsification cases/falsification trends found out during EDQM inspections (trainings of PIC/S inspectors on how to detect falsification, i.e. Singapore and Rome APIs expert circles)
- >250 sites inspected/1000 listed in CEPs, located in more than 50 countries
- 2013 EDQM program showed that 38% of the inspected sites were non GMP compliant, confirming the adequacy of the risk assessment tools in place

Cases of falsification

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Title:	**Cases of falsification of data in the context of the CEP procedure**
Reference Document:	**PA/PH/CEP (12) 11 EN**

In the framework of the EDQM inspection programme for companies who have requested or are holders of a Certificate of Suitability to the European Pharmacopoeia monographs (CEP), inspectors have come across several cases where data had been falsified, in some cases extensively and even systematically. The falsifications consisted of deliberately altering or creating data; be it in the CEP application, in batch records or any other records in order to hide a gap in information between the records and the true state of affairs.

In case of critical/major deficiencies in GMP or in CEP dossiers, the Certification Ad Hoc Committee usually decides to temporarily suspend CEP(s). However, in such particularly serious cases, the Ad Hoc Committee has decided to immediately withdraw the CEP(s) concerned. To date, four companies have been the subject of such decisions.

EU Inspectorate's benefits: examples

- AIFA inspection of a site located in China in 2011: GMP certificate granted for 3 APIs;
- The same site was granted some CEPs and was inspected by the EDQM in 2007
- 2013 US-FDA inspected the same site (for different APIs) and issued a Warning Letter in July 2014
- Considering the relevance of the deviations found, EDQM accepted AIFA proposal to carry out a joint inspection and readapted the program consequently: the site will be inspected in September

Conclusion: benefits for inspectors

- Closer relation with a European organization and working procedures and standards implemented
- To have deeper insight about the Certification Procedure
- To understand the criteria identified for the risk evaluation
- To face new cultures, challenging the inspection methodology
- Exchange with colleagues having different professional history and cultural background (experience, education)

Conclusion: benefits for inspectors

- To learn more about the Eur.Ph. Monographs (and its revision process, Report B)
- To familiarize with the Ph.Eur. Reference standards manufacturing process
- To move from a “national/regional” system and approach to an “international” one

Conclusion: benefits for inspectors

- To have a better understanding of the evaluation done by the assessors (Report A), which can be strictly related to the focus of the inspection (i.e. issues identified during the assessment can represent the critical area during the inspection)
- To learn the approach for process related inspections, where, instead of a general GMP assessment, the main task is to assess the quality of the API in the full process (Process related inspection: assessment/inspection are closely related)

Personal experience

- Working with the EDQM at the very beginning of the consolidated phase offered me:

- the opportunity to learn about the “global APIs world supply chain” and have an international experience
- the opportunity to contribute to implement a system in its first phase
- the opportunity to meet many other colleagues coming from several NCAs/different background and build mutual trust

Final remarks

- To support the EDQM inspection program means:

- For participating inspectors: increase knowledge and understanding of the global API market and have an active role in a challenging regulatory area
- For participating inspectorate: opportunity to contribute to a program where there is mutual interest among EU/EEA NCAs and International Partners
- For EU/EEA citizens (and not only..): a higher and common level of public health protection

Final remarks

Cooperation

is always beneficial for

all involved parties!!

Thank you for your attention!

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