

New Frontiers in the Quality of Medicines

Workshop Certification: Inspections

**Moderators:
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EDQM International Conference

13-15 June 2007

Strasbourg, France



Workshop on Certification-inspections

The programme of inspections:
how it works and its impact on the validity
of CEPs

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Brief reminder on the
background of this inspection
programme

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Scope of the Certification Procedure

- Any substance described in the PhEur
 - Active Substances
 - Excipients
 - Herbal drugs/preparations
- TSE-risk products (incl. starting materials, reagents, intermediates,...)
- Excluded:
 - Direct gene products (proteins)
 - Products derived from human tissues
 - Finished/semi-finished products

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The situation today

In application of Directive 2001/83/EC as amended (Article 111) and Directive 2001/82/EC as amended (Article 80)

- Mandate is given to EDQM (by EC) to establish an annual programme for inspection
 - 'For pragmatic way of implementing the EU pharmaceutical legislation'
 - 'While ensuring a coherent and sensible use of Community resources for inspection'

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Mandate to EDQM for an annual programme

- Established in collaboration with national competent authorities and EMEA
- Approved by the EDQM certification SC
- Reports of inspections to be made available to national authorities upon request
- Authorities notified of issues arising
- Annual report to be presented by EDQM to EU Commission

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How the CEP inspection programme works

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Elaboration of the programme

- According to priorities decided by the CEP SC
- In line with EMEA guidance (*“trigger document”*)
 - If requested during/after assessment (2.4)
 - Sterile substances (2.10)
 - CEP held by brokers/traders/distributors; to check their obligations (2.11)
 - TSE-risk substances (*EU/EMEA request*)
 - (Re-)inspection on EDQM/national inspectorate request (2.3, 2.6, 2.7)
 - To join a scheduled national/WHO inspection
 - On justified requests from manufacturers (1.11)

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Inspection progress

- Team of 2 inspectors (of Ph Eur countries)
 - Local inspector invited when site in non-PhEur countries
 - Accompanied by EDQM-CEP representative
- Reference documentation:
 - EU GMP guide for APIs, annex 1 for sterile and any other relevant GMP documents
 - Certification dossier+ up-dates (product related inspection)
 - Any relevant monographs
 - Questionnaire/site master file

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Inspection progress (2)

- Lasts 2-3 days
- Visit of the manufacturing facilities (following the process flow)
- Study of production and QA management documents
- Conclusions orally presented to the company

Follow-up of an inspection

- Report sent to the company (≤ 8 weeks)
- Company requested to answer remarks and deficiencies noticed (within 1 month)
- When positive inspectors' opinion:
 - final summary report
 - EDQM Attestation of Inspection
 - EU GMP certificate can be issued by one of the participating inspectorate

Follow-up of an inspection (2)

- in case of major/critical GMP deficiency(ies)
 - Sufficient level of GMP compliance not demonstrated
- Major deviation(s) compared to the dossier
 - Failure to the declarations and commitments

CEP may be suspended

- Decision on actions and recommendations
 - On existing CEPs/on-going applications
 - Taken by an *ad hoc* board
 - On conclusions of inspectors
- Information of all concerned authorities+EMEA+EU Commission
 - To take any necessary action (regarding MAs, marketed substances,...)
- Information in the published CEP list (website)
- Re-inspection to check implementation of sufficient corrective actions will done
 - Before restoration of CEP

In case of suspension of CEP

- Information of the holder and manufacturer by official letter on :
 - Justification of suspension
 - Conditions for restoration
 - possibility for hearing
 - diffusion of the information to authorities
 - His responsibility to inform all concerned customers

Review to date and perspectives

Some figures

- >120 manufacturing sites inspected
- In 22 countries (incl. China, India, Mexico, Canada)
- 12 cases led to suspension of CEPs
 - A third involving distributors as holder of CEPS
 - Some CEPs restored after satisfactory re-inspection

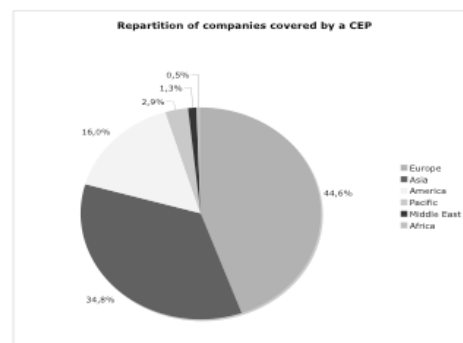
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Some figures (2)

- > 2200 certificates granted
- > 750 substances
- > 800 manufacturers from 57 countries

- 1: India
- 2: China
- 3: USA



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Conclusions

- No major operating problem encountered
- Active collaboration of inspectors
- Coordination of national/EDQM programmes
- Fruitful exchanges with TGA
- Good contacts with 'third party' inspectorates (in China) but to be developed

Perspectives

- To continue the programme
 - Increasing the number of inspections (30 in 2007)
 - Focussing on sites located in Asia
 - Including re-inspections (frequency to be defined)
- Follow-up of defective inspections

Perspectives (2)

- to promote inspections of drug substances and establish an adequate system
 - Reinforce collaboration/exchange with European/international inspectorates and inspection working groups

Thank you!

The floor is yours for discussion

Workshop 14 June 2007
Certification: Inspections

VIEWPOINT AND EXPERIENCES OF AN INSPECTOR

Dr. Tobias Godtschan, Inspector
Swissmedic, Swiss Agency for Therapeutic Products

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EXPERIENCES

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The opportunity

- You have now the unique opportunity to receive insight in the diary of an inspector
- Join him during his journey to India and take part in his experiences throughout a CEP inspection campaign

DISCLAIMER

Any resemblance to living or inspected persons or companies are purely coincidental

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The diary of a CEP inspector



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Some months before

- A request from EDQM to participate in this year's inspection programme arrives
- After convincing the boss, that it makes sense to participate and after checking the availabilities, you can give a positive feedback to EDQM



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Some weeks before

- The inspection programme becomes more and more concrete
- There will certainly be some changes up to the final programme, but it's concrete enough to finally queue up at the Embassy for the visa application



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The weekend before

- You enjoy the last weekend with your family before you leave on Thursday to Strasbourg
- You normally start to pack your luggage, because you won't have too much time throughout the remaining days (there will be such a lot of things to do and to organise at the office)



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The last day at the office

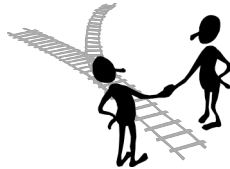
- You arrive at the office with the big suitcase and everyone says: Oh, you're travelling to India, you lucky one. Have fun in the sun! (If they knew that there will be more organic vapours throughout the day than sun...)
- And there are just a few dozen "short last questions before you leave", before you can run and catch the train/plane in the last minute



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Thursday evening, Strasbourg

- The inspectors, who will travel together to India and will there split up into teams, meet and have dinner together
- It's very nice to meet some colleagues from the last campaigns again and to meet new colleagues from all over Europe



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Friday, preparatory meeting

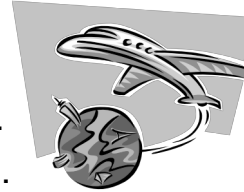
- All inspectors meet at the EDQM facilities in order to review the documentation and the assessment report for the substance, whose manufacture will be inspected
- Each inspector reviews carefully the dossier for the inspection, for which she/he has the lead, and can brief the colleague inspector/s of her/his team



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Saturday morning 5 a.m.

- A taxi brings the inspectors to the airport
- Flight to Paris CDG
- Long distance flight to India
- Arrival on Sunday morning 1 a.m.
- Transfer to hotel, arrival 2:30 a.m.
- This was a long journey and it will be a short night



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Sunday morning, 7 a.m.

- Another taxi to another airport
- This time it is an Indian taxi which brings you to the local airport for the flight to your first inspection destination
- Well, at least near to the airport next to the destination, because there is another 2 hour car journey to the hotel
- Arrival in the afternoon, short break, then meeting for preparing the first inspection



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First inspection week, Monday

- The first inspection day
- Pick up at 8 a.m. from the hotel by the company
- One hour drive to the factory
- Start of the inspection at 9 a.m.
- Introduction of the people
- Company presents their facility, their QA system and the manufacturing process
- In the afternoon: Start of plant tour (warehouse, water system)



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In the evening



- Inspection is finished at around 6 p.m.
- You are back at the hotel around 7 a.m.
- After a short break for changing into some comfortable clothes, the dinner is taken at the restaurant of the hotel
- Afterwards, the inspectors review the day and make the planning for the next day
- At around 11 p.m. the night is still young and your laptop is eager to receive some input for the inspection report...

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First inspection week, Tuesday

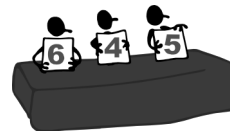
- Continuation of plant tour
(production workshop, following the flow of the manufacturing process and including production equipment, documentation and instructions, sanitation, cleaning and maintenance, batch records, calibration, contamination control, in process controls)
- Review of related documents (partly during the tour, partly in the later afternoon)



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First inspection week, Wednesday

- Visit of QC laboratory
(procedures, sampling, impurity profile, reference samples, analytical method validation, stability testing)
- Review of further documents
- Preparation of closure meeting (inspectors only)
- Closure meeting (including presentation of the findings)



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The second inspection

- Thanks to the organisation talent of EDQM, you are lucky and can stay at the same hotel, because the second company is located in the same area as the first one
- You only have 2.5 days for this inspection, because you have to take a flight for the third inspection at Saturday afternoon
- You arrive at your next destination late in the evening



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Sunday

- You enjoy to sleep a little bit longer
- You are alone, because your colleague inspector returned to Europe and the next colleague will arrive in the afternoon
- After breakfast, you allow yourself a short walk through the town, before you return and continue to write your inspection report
- Your new colleague arrives in the afternoon and you prepare the next inspection together



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Second inspection week

- The third inspection lasts 4 days, because you have to cover 2 sites of the company
- On Thursday afternoon, you close the inspection, take the early evening flight to Mumbai and wait there until 2:30 a.m. for your long distance flight back to Europe



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The journey home



- Your flight is late and you are allowed to board only at 4:30 a.m.
- You miss your connecting flight at Paris
- Due to bad weather, 50 flights are cancelled and you have the pleasure to stay until 6 p.m. at Paris CDG airport
- Late in the evening you arrive at home (without your suitcase, which didn't make it...)
- 4 days later your suitcase arrives – it was its last journey, because it was irreversibly damaged

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Back at the office



- On Monday, you regret that you have been away from the office for more than two weeks
- You draft the report and send it to your colleague inspector for review
- After finalising the report, you send it to EDQM who forwards it to the company and requests a corrective action plan for the deficiencies, which were noted

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The follow up

- 2 months after the inspection, you receive from EDQM a nicely smelling package, which turns out to be the company's corrective action plan
- You investing a considerable amount of time for reviewing and cross check the response with your colleague inspector
- If you are lucky, you can right away accept the response and write the final summary report (otherwise - 1 or 2 other rounds...)

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Finally, you ask yourself:



... do I do these inspections
and take all that burden on me ?

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VIEWPOINT

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There are several
good reasons !



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Need for inspections

- The pharmaceutical industry is a globalised industry
- APIs are more and more produced in non-European countries like China, India etc.
- For APIs used for medicinal products in Europe, a GMP compliant manufacture is a must
- Not all quality related aspects can be assessed on paper only, especially GMP compliance needs to be checked at inspections

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An international approach makes sense

- Medicines agencies can pool resources and inspect more manufacturers with the same resources
- Internationally coordinated GMP inspections according to a common standard (i.e. ICH Q7A) avoid the multiplication of inspections of the same manufacturer by several countries
- At the same time, a contribution is made for the harmonised performance of inspections

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Inspectors' benefits

- Inspectors get the opportunity to broaden their horizon
 - by exchanging experiences on an international basis
 - by discovering that GMPs are universally applicable, even if organisational approaches in their practical realization may differ slightly, due to differing cultural backgrounds

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SUMMARY

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CEP inspections are...

... no vacation,



but hard work



and...

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CEP inspections are also...

... beneficial for ... and

- agencies
- industry
- inspectors

... a contribution to the increase of
the quality of medicinal products
worldwide



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**Thank you very much
for your attention!**



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EDQM certification scheme and Inspections Partnership with EMEA

Emer Cooke
EMEA Inspections sector
June 2007

Disclaimer

The views presented in this presentation are those of the author and should not be understood or quoted as being made on behalf of the EMEA and/or its scientific committees.

Contents

- ✓ New framework for Inspections of active substance (API) manufacturers
- ✓ Triggers for inspections
- ✓ Community database for GMP inspection information
- ✓ Dealing with non-compliance, withdrawal of CEPS

What are the new requirements for GMP for starting materials?

- New obligation (November 2005) for manufacturing authorisation holders
 - ◆ Only to use active substances that have been manufactured in accordance with GMP
- Detailed guidelines on the principles of GMP as regards active substances need to be complied with
- Additional provision for GMP inspections
 - ◆ May inspect in 3rd countries
 - ◆ May inspect active substance manufacturers (under conditions laid down)



New approach based on self-regulation and risk management principles

- Self-regulation by finished product manufacturer through audits of their suppliers
- Declaration by the Qualified Person of the Finished Product Manufacturer of compliance of active substance manufacturers
- Inspections principally when outstanding risks are perceived

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The conditions for inspection of active substance manufacturers

- Where there are grounds for suspicion of non-compliance
 - ◆ At request of member state, EMEA or Commission
- To verify data submitted in application for a CEP
 - ◆ At request of EDQM
- At the request of a manufacturer itself

These and other conditions are further elaborated in a guideline for Competent Authorities included in the Compilation of procedures (“Inspection Triggers”)

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Possible Triggers (1)

- Routine inspections of APIs manufacturers not foreseen by new legislation
- Underlying principles - Risk based
- Unsatisfactory evidence of audit by manufacturer of medicinal product
- Competent authority not satisfied with measures taken by medicinal product manufacturer
- Concerns about distribution chain
- Previous unsatisfactory inspection history

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Possible Triggers (2)

- Concerns raised through CEP scheme
- When disagreement on the conclusions of an inspection
- Non compliance with specifications
- Suspicions relating to authenticity of data

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Other issues in relation to GMP for active substances

- Biologicals
 - ◆ The quality of biological medicinal products are highly dependent on the manufacturing process and are usually characterised by it. GMP has therefore always been applied to the biological substance.
- Sterile active substances
 - ◆ The sterilisation step in the production of a sterile active substance, where the active substance is to be incorporated aseptically in the manufacture of the medicinal product, is a manufacturing step of the medicinal product and has always been subject to GMP.

Therefore subject to routine inspections

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Important points

- The primary means by which compliance with GMP for active substances will be verified is through inspections of manufacturing authorisation holders
- The distribution chain between manufacturing source and the user of an active substance is often complex and not always transparent
 - ◆ This is an important focus for inspections

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EudraGMP Database

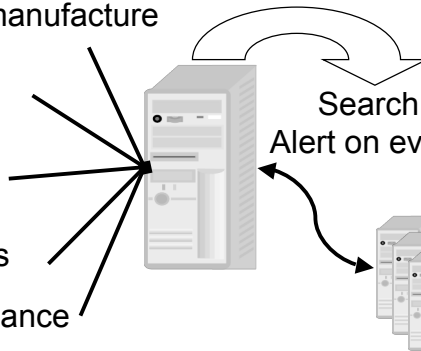
Information on faulty manufacture

Manufacturing Authorisations

Inspection plans in 3rd countries

GMP Certificates

GMP non-compliance



Links to other Community databases

- Facilitates exchange of information between member states
- Limited public access and access by MRA partners foreseen
- First release launched April 07

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Content of EudraGMP: Manufacturing Authorisations and GMP certificates

Manufacturing authorisations – not a new concept but now standard harmonised published European Format and database implications

- Member States shall forward to the Agency a copy of the **manufacturing authorisation**. The Agency shall enter that information on the Community database.

GMP certificate – new concept and database implications

- Standard harmonised published European Format
- Compatible with format agreed with MRA partners
- GMP certificate issued to the manufacturer (may be Finished product or active substance or investigational medicinal products)
- Certificate issued within 90 days of inspection
- Member States shall enter the certificate of GMP which they issue in a Community database managed by the Agency on behalf of the Community.
- Non- compliance with the principles and guidelines of GMP..., the information shall be entered in the Community database.

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EudraGMP- Business Case

- No single pan European source of information on European manufacturers or on inspections performed by European Competent authorities
- Procedure for exchange of information exists, but not used effectively due to administrative burden and delays
- Resulting planning difficulties and duplication of inspections (particularly for 3rd country inspections)
- Situation exacerbated with new GMP requirements for active substances (used in multiple countries and multiple applications)
- Non-compliant information difficult to find and follow-up difficult to co-ordinate

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Community database for GMP. Benefits

- To introduce a harmonised approach to the receipt and recording of Manufacturing Authorisations and GMP certificates
- To facilitate the exchange of information.
- To assist EMEA, EDQM and MSs in planning inspection schedules.
- To facilitate best use of resources and, therefore, avoidance of duplication of inspections.
- To provide a tool to alert MSs in cases of either suspected non-GMP compliance or revocation of the Manufacturing Authorisation.
- To facilitate international cooperation (GMP certificates required to be provided by the various MRAs)

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EudraGMP – Current status

- 1st release end April 2007
- This release only includes GMP certificates and Manufacturing authorisations from some Member States
- CEP inspections- member state conducting inspection to enter data into database
- Next release (July 2007) will allow entry by other Member States using XML
- All competent authorities will include GMP certificate for all inspections conducted (EU, Non-EU, FP, API)
- No access to public foreseen until initial loading completed
- Public access will be to Manufacturing authorisations and GMP certificates for medicinal product sites only
- Discussions with MRA partners, EDQM, WHO and FDA ongoing

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Other areas of cooperation: Dealing with serious GMP non-compliance including withdrawal of CEPs

- New guidance under development, agreed by GMP inspectors and QWP with input from EDQM, now being discussed with other relevant groups
- Deals with serious non-compliance where administrative action is recommended
- Potential impact throughout the Community
 - ◆ Action on manufacturing authorisations impacts marketing authorisations sourcing from the affected manufacturer
 - ◆ In some cases direct action on marketing authorisations is appropriate
 - Particularly if a third country manufacturer is involved
- Lack of existing co-ordination, although national responses may be different based on risk benefit principles and availability of alternatives

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Principles behind the Community procedure for dealing with serious GMP non-compliance

- The authority performing the inspection has first-hand knowledge and is in the best position to recommend action
 - ◆ This is normally the Supervisory Authority
- The Supervisory Authority takes action on manufacturing authorisations
- NCAs take action on purely national marketing authorisations
- The reference member state initiates action on MRP/DCP marketing authorisations
- EMEA coordinates action on central marketing authorisations
- The Supervisory Authority deals with batches on the market following the relevant Community procedure if needed

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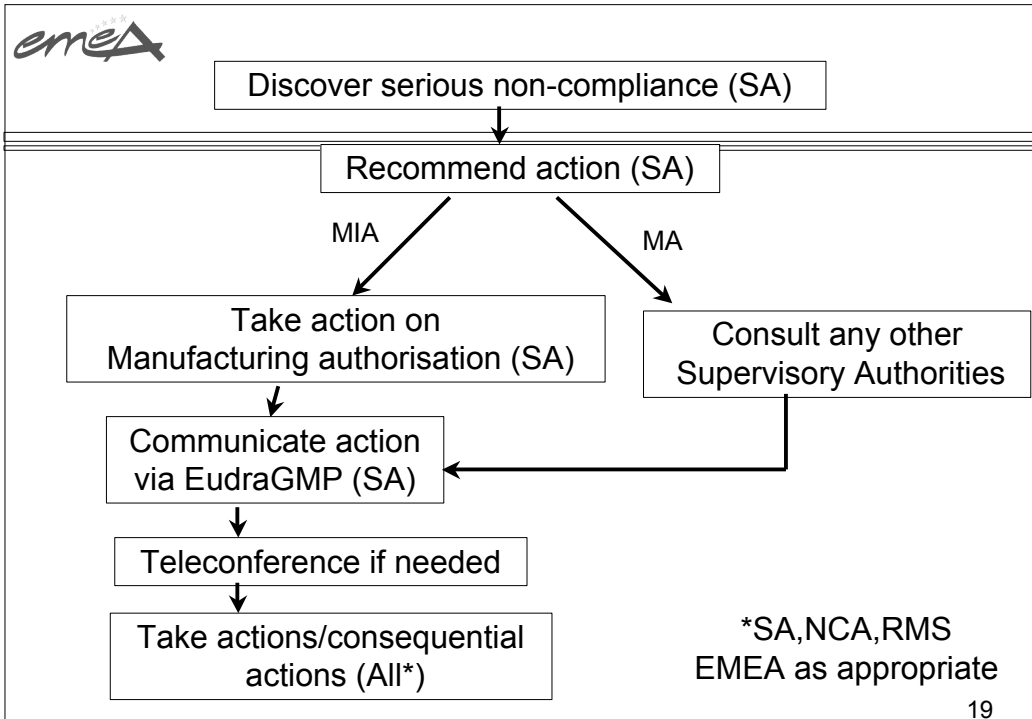


Voiding or withdrawal of CEPs

- If voiding of a CEP is recommended as a result of a GMP inspection then the main procedure for dealing with serious GMP non-compliance applies
- EDQM publishes this info and informs authorities
- However, companies using CEPs concerned expected to take action
- These companies should take immediate action to inform authorities and vary authorisations as necessary
- Risk of them being in non-compliance if they fail to do this

- EDQM may void CEPs for other reasons
 - ◆ Similar coordinated action to that in connection with serious GMP non-compliance is required

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Conclusion- 1

- One year on – large range of initiatives completed or well underway
- Priority to make existing legislation work
- Balance between increased enforcement and better risk management
- Importance of international cooperation
 - ◆ Discussions with MRA partners, FDA, WHO, EDQM ongoing

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Conclusion- 2

- New paradigm for manufacture of active substances
- New responsibilities – finished product manufacturers/ active substance manufacturers (including traders/brokers etc.)/competent authorities/inspectors
- New climate of transparency and information sharing
- Risk based approach assures best use of resources
- Aim is to better assure supply chain/overall quality of medicinal products for European patients by ensuring that everyone assumes these new responsibilities

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Thank you for your attention

Any questions?

EMEA:

<http://www.emea.europa.eu/Inspections/index.html>

DG Entr:

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

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