



Relationship between Receiving Authorities and Monitoring Authorities. The EMEA experience

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Disclaimer

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Agenda

- Introduction to EMEA & Centralised Procedure
- Introduction to work of EMEA Inspections Sector
- GLP Inspections in the Centralised procedure
- Conclusions





Introduction to EMEA & Centralised Procedure



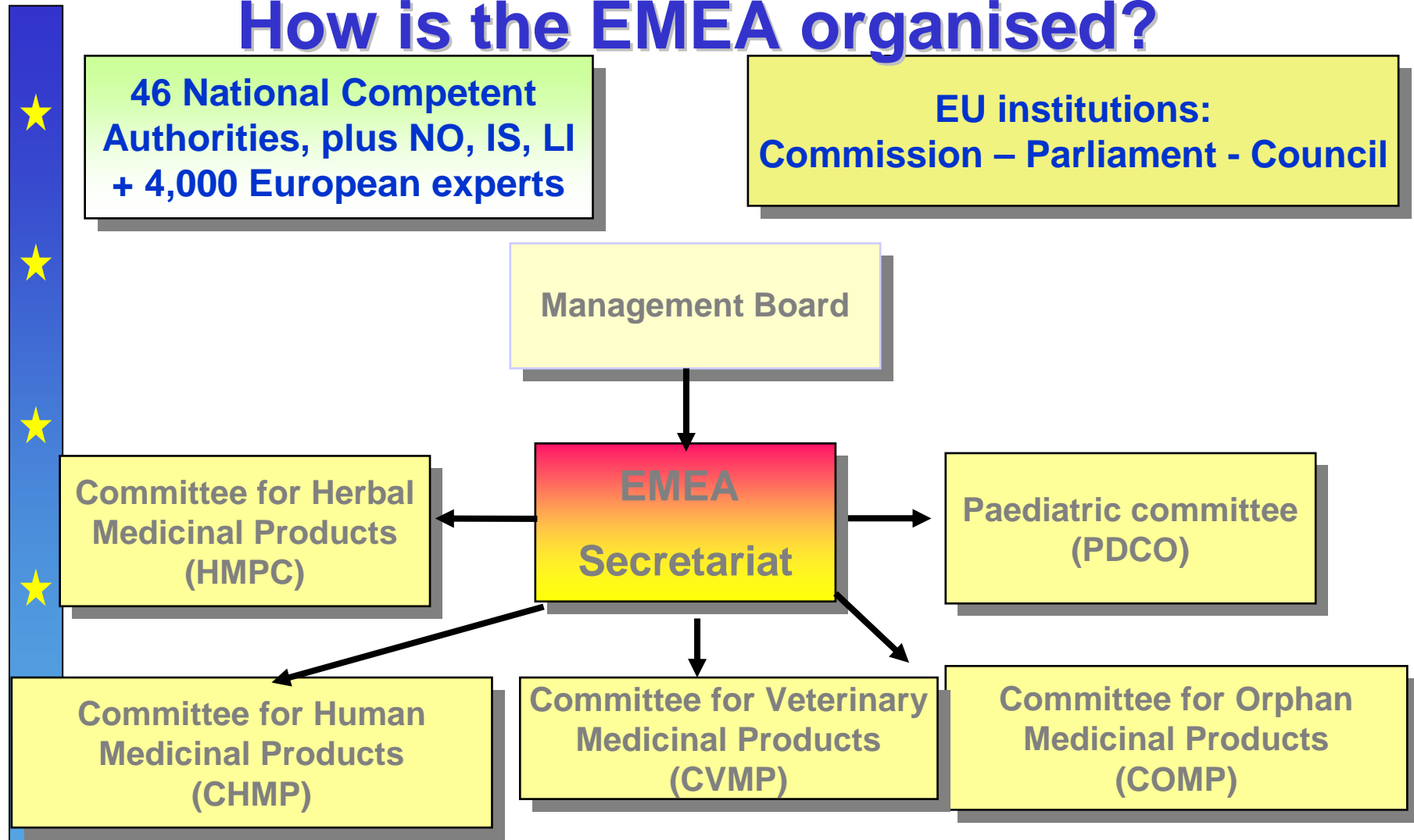
What is the EMEA?

- One of the 15 independent European Community agencies
- Composed of a secretariat (EMEA staff), management board, scientific committees, working parties and expert groups (members nominated by EU/EEA Member States)
- Mobilises existing scientific and inspection resources of the EU/EEA for
 - evaluation of centralised medicinal products
 - preparing of guidelines on safety/quality/efficacy
 - coordination of verification of compliance with principles of GMP, GCP, GLP





How is the EMEA organised?





Where Does EMEA fit in?

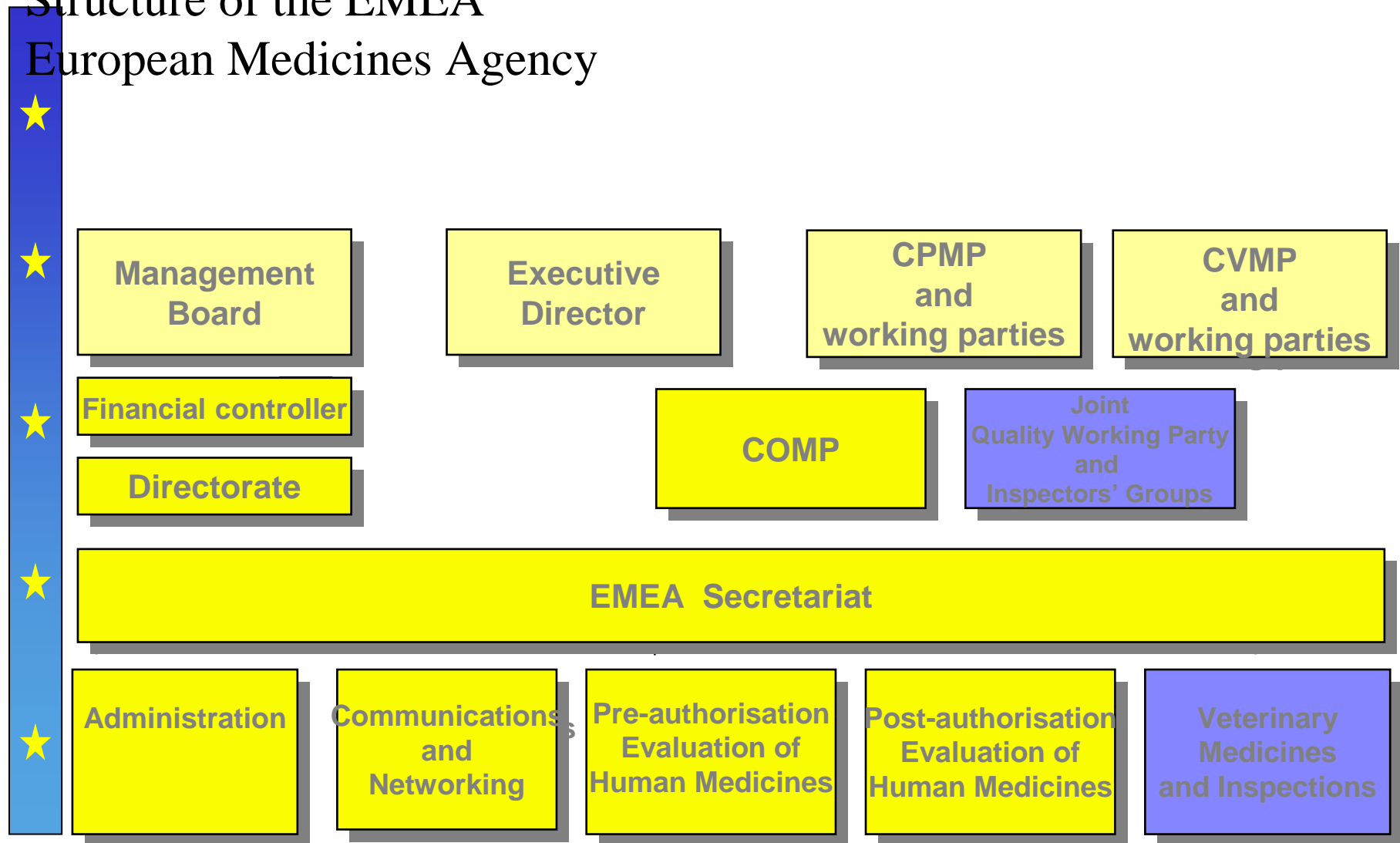
“Europartnership”

- Evaluation of Centralised Marketing Authorisation Applications/variations - through CPMP/CVMP
- Evaluation of referrals/arbitrations (mutual recognition or national – through CPMP/CVMP)
- Coordination of GMP/GLP/GCP – through supervisory authorities in Member States
- Sampling and testing of centrally authorised products – through OMCLs and supervisory authorities
- Working parties, expert groups – consist of experts nominated by Member States – 3000 experts
- Partnership with European Pharmacopoeia






Structure of the EMEA European Medicines Agency



National Competent Authorities

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- Responsible for issuing and supervising national marketing authorisations (pharmacovigilance, inspections, sampling and testing)
 - Authorisation of clinical trials on their territory
 - Authorisation and supervision of manufacture and importation on their territory
 - Supervision of GLP Test facilities
 - Nominating members to EMEA Scientific Committees, working parties and other groups



Marketing Authorisation Systems

- Same dossier requirements
 - Same requirements for Quality, Safety and Efficacy
- 4 Different authorisation possibilities:
- National
 - Mutual recognition
 - Decentralised procedure
 - Centralised procedure



Centralised Procedure (CP) - Mandatory Scope (1)

Medicinal products developed by means of one of the following biotechnological processes:

- Recombinant DNA technology
- Controlled expression of gene coding for biologically active proteins
- Hybridoma and monoclonal antibody methods



CP - Mandatory Scope (2)

As of Nov. 2005, in addition mandatory for

- new active substances for the indications
 - diabetes
 - cancer
 - acquired immune deficiency syndrome (HIV)
 - neurodegenerative disorder (Alzheimer, ...)
- not licensed before coming into force of regulation
EC 726/2004
- orphan medicinal products

CP - Mandatory Scope (3)

**Biosimilar Medicinal Products
(‘Biogenerics’)**


... if biotechnological medicinal products




Mandatory for the Centralised Procedure



CP - Optional Scope (1)

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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically.
- Products containing a **new active substance not** authorised before coming into force of the Regulation EC 726/2004
 - Products constituting a significant therapeutic, scientific or technical innovation
Will be evaluated on a case by case basis (consultation of two sponsors out of CHMP and, when needed, the relevant working parties)

CP - Optional Scope (2)

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- A vertical blue bar with five yellow stars arranged vertically, positioned to the left of the main text.
- Generic of a centrally –authorised product
 - Products which are in the interest of patients at community level:
 - Generic of a National/MRP product
 - Pandemic medicinal products

Centralised Procedure

- Submission of dossier to EMEA
- CXMP appoints rapporteur and co-rapporteur
- Rapporteur and co-rapporteur perform assessment and prepare draft assessment report
- All other CXMP members provide comments
- Adoption of CXMP opinions, final assessment report, summary of product characteristics



Decision by European Commission



FDA

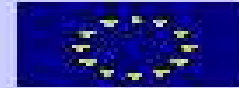


Council of Europe



International Conference on Harmonization

ICH



EEA Countries



EMEA - European and International Partners

Mutual Recognition Agreements



Candidate Countries



European Institutions



World Health Organization





Introduction to EMEA Inspections Sector



Main Activities of the EMEA Inspections Sector

- Good Manufacturing Practice (GMP)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Pharmacovigilance compliance verification
- PMF/VAMF inspections
- Mutual Recognition Agreements (MRA)
- Joint CHMP/CVMP Quality Working Party (QWP)





Main Activities of the EMEA Inspections Sector (2)



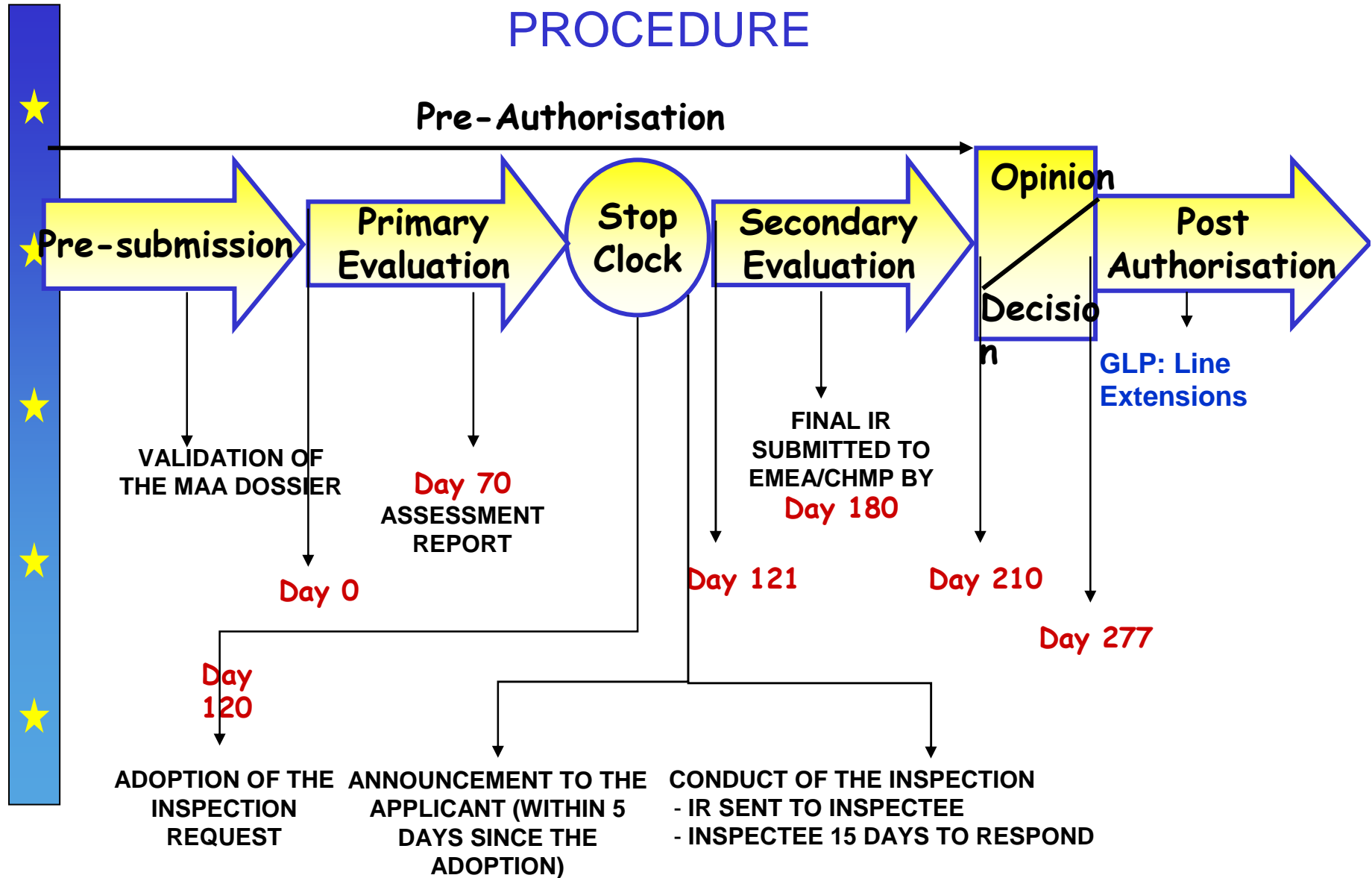
- EMEA Certification of Medicinal Products
- Sampling and Testing (S&T)
- Product Defects i.e. Quality problems
- GMP aspects of applications/validations
- Chair of GxP meetings
- Co-ordination of EudraCT and EudraGMP projects



GLP Inspections in the Centralised procedure



OVERVIEW OF CENTRALISED EVALUATION PROCEDURE





Product Specific Directives for Medicines

- Legal Basis – Marketing Authorisation Applications
 - Human:
 - 2003/63 Annex 1 Non-Clinical Introduction And General Principles
 - *(pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances and 88/320/EEC on the inspection and verification of good laboratory practice (GLP)*
 - Veterinary
 - 2001/82 Annex 1 Part 3, Safety and Residues Testing
 - *“Member states shall ensure that the tests are carried out in conformity with the provisions relating to good laboratory practice...”*





Verification of compliance with GLP

- Legal Basis for Inspection during Assessment of MAA.
 - Regulation 726/2004 Article 57 (i)
 - *“co-ordination of the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations.”*





EMEA SOP



- Procedure for co-ordinating GLP inspections of the
 - Pre-clinical studies
- Human and Veterinary applications.
- Pre-authorisation GLP inspections.
- Developed in collaboration with *ad hoc* GLP Inspectors Group



EMEA SOP

- Inspection requests triggered by assessors, prepared by EMEA and adopted by CxMP
- EEA Test Facility: GLP monitoring authority of MS where lab located & experts if nominated
- For 3rd country Lab: GLP monitoring authority of (Co)- Rapporteur MS to provide inspection resources;
- Possibility for study audits and exceptionally facility audits

Evaluation of GLP Compliance

- The assessor is responsible for evaluating
 - the statements on GLP compliance provided in the application
 - the scientific content of each study.
- The assessor includes in the assessment report a standard statement that GLP audits are not considered necessary for the evaluation of the application or, if an audit is considered necessary, asks the inspections sector to prepare an inspection request for Day 90 or 120.

eme Adoption of Inspection request

- The IS circulates to the CxMP during the plenary meeting the GLP Inspection Request recommended by the Rapporteur and Co-Rapporteur.
- The CxMP adopts, rejects or postpones the recommended request.




Summary

- 1995 - 2003 : 2 GLP Inspection Requests by CPMP
- 2004 - 2007: 6 GLP Inspection Requests by CHMP – study audits
- 2008 – 4 GLP Inspection Requests by CHMP – study audits
- 9 Marketing Authorisation Applications for medicines for human use
 - 9 Test facilities, 2 in EU, 4 in Canada, 3 in Non-OECD
 - c. 31 studies audited (&10 outstanding)
 - Inspection duration of 3 – 6 days
 - 29 studies so far found to be GLP compliant
 - 2 studies found to be not compliant with GLP (in full or partially)



Summary

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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically.
- One study found to be not in compliance with GLP
 - One study only partial non-compliance
 - Minor deviations from GLP were observed in remainder of study audits
 - Integrity of study data was not jeopardised
 - 27 studies were recommended to be used for the respective safety evaluation.



Inspection Findings



- Test facilities should pay particular attention to the difference between amendments and deviations, how and when each should be documented and how and when their impact on the study is evaluated by the Study Director.
- Study directors should ensure that GLP principles are adhered to when amendments and deviations to study reports are needed.



Inspection Findings



- The use and supervision of sub-contractors in accordance with the GLP principles concerning multi-site studies.
- The role of Quality Assurance, and how the QA audits of studies are documented so that the types of inspections performed and the critical phases inspected are recorded.



Inspection Findings



- Lack of information regarding the determination of the homogeneity, concentration and stability of the test item prior to the commencement of the study.



Findings of non-compliance with GLP



- Findings of non-compliance with GLP should be used by the assessor as one piece of information to decide whether or not a study can be used in the application and in turn if the exclusion of a study affects the final opinion for the application



Post-Authorisation

- A post authorisation inspection may be requested by a rapporteur/co-rapporteur to clarify any GLP issues that may arise after the authorisation has been granted.





EMEA Feedback

- **GLP Inspections in Canada advised**

- It has come to our attention that Health Canada has not established a GLP compliance monitoring programme for Canadian laboratories that are engaged in the pre-clinical testing of medicinal products. Due to the uncertain GLP compliance status of pre-clinical studies originating from Canada, the EMEA Inspections Sector has advised the CHMP and CVMP that pivotal studies for centralised products should be inspected to assess their compliance with the Principles of GLP.

- **OECD Guideline on Cross-contamination**



Conclusions

- SOP has provided a comprehensive framework for CHMP to request GLP audits.
- SOP has provided a comprehensive set of standard documents for reference when preparing inspection, communicating outcome of inspection and preparing inspection report.
- Administrative aspects of inspections are easily dealt with.
 - All inspectorates approached have assigned resources to the inspections.
 - Inspections have been performed within the timeframe indicated in the inspection request and contract.
 - Performing and reporting the inspection by inspectorates has been done in accordance with procedure