GLP Inspections in the Centralised Procedure

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Agenda

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

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

OECD Council Decision & GLP Directives

- OECD Council Decisions
  - *1981 Council decision on the mutual assessment of data in the assessment of Chemicals (revised 1997).*
  - *1989 Council decision and Recommendation on Compliance with Good Laboratory Practice*
  - *1997 Council decision on the adherence of non-member countries to the council acts related to the mutual assessment of data in the assessment of Chemicals*
- *EU GLP Directives*
  - *Directive 2004/10 of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and their verification of their application for tests on chemical substances*
  - Directive 2004/09 *of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice*

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.”*

GLP in Guidelines

- Not an exhaustive list !
- GLP Guidelines
  - *OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring*
  - *EU GLP Working Group : Cross-contamination of control samples with test item in animal studies*
- Human Medicines
  - *ICH S3A : Note for Guidance on Toxicokinetics: a guidance for assessing systemic exposure in toxicology studies (CPMP/ICH/384/95)*
  - *ICH S6 : Preclinical safety evaluation of biotechnology derived medicinal products (CPMP/ICH/302/95)*
  - *ICH S7A : Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (CPMP/ICH/539/00)*
- *Veterinary medicines*
  - *EMEA/CVMP/016/00 : Guidelines for the conduct of bioequivalence studies for veterinary medicinal products*

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

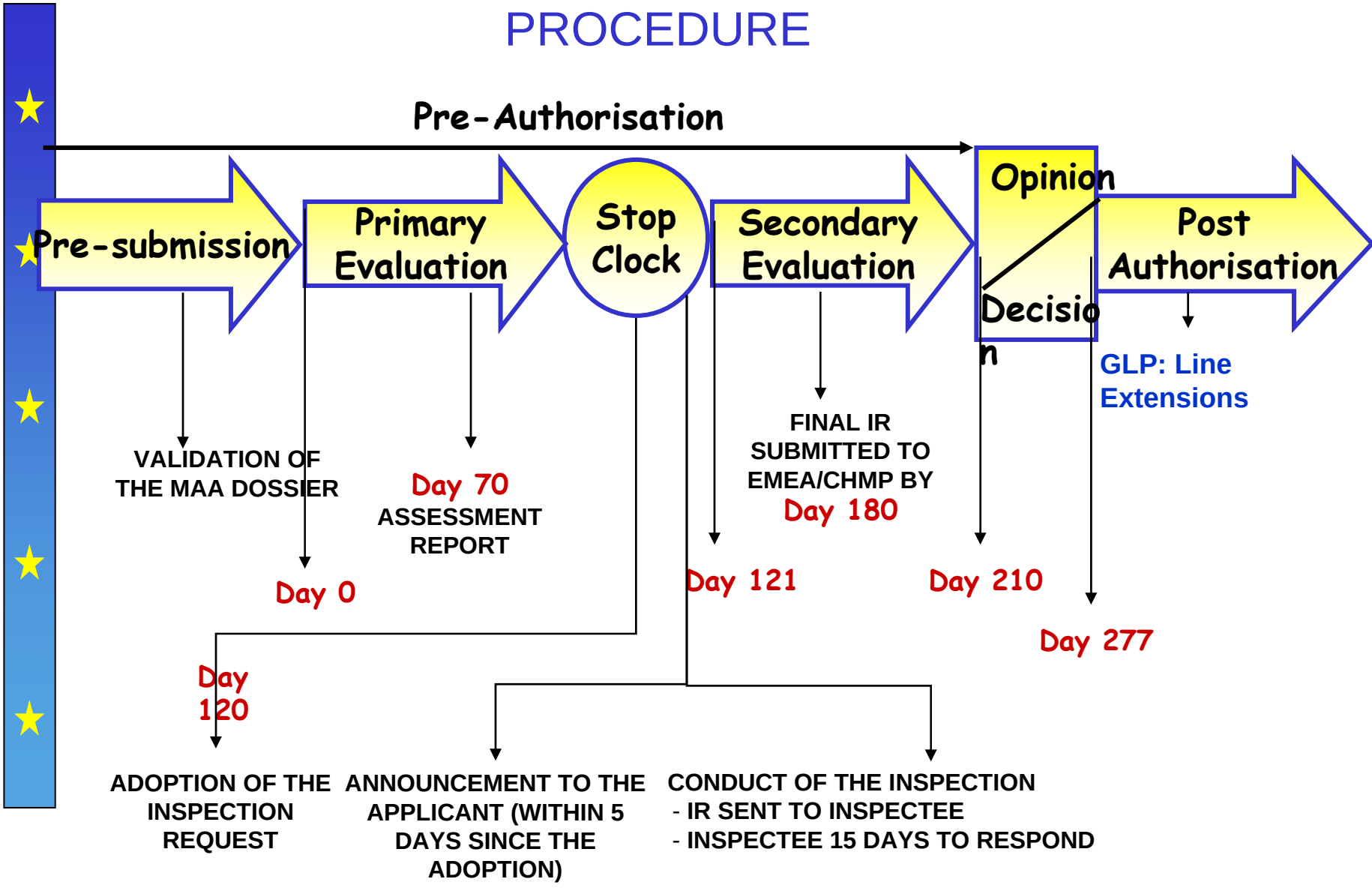
Evaluation of GLP Compliance

- 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.

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.

OVERVIEW OF CENTRALISED EVALUATION PROCEDURE



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. 41 studies audited 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)
  - 10 studies found to be not in compliance

Summary

- Ten studies 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 into the World of GLP

- **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