EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Specific aspects concerning GMP and GCP inspections in Accelerated Assessment procedures

3rd Industry Stakeholder Platform

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Contents

Good Manufacturing Practice Inspections

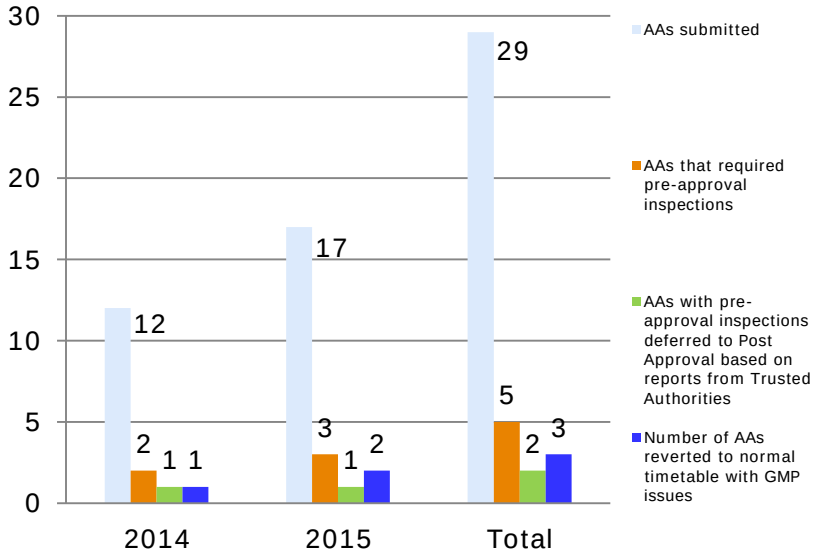
Pre-approval GMP Inspections

- Legal requirement for the manufacturing process of the active substances and finished product to comply with GMP – Art 8 Dir 2001/83/EC
- EMA is responsible acc. to Art. 57 Reg. 726/2004 to verify GMP compliance of manufacturing sites registered for CAPs
- Triggers for inspection - on receipt of the product application EMA identifies any required pre-approval inspections
    - to verify GMP compliance (e.g. if no valid GMP certificate when the site has never been inspected or doesn't cover a specific operations, suspicion of NC)
    - for product or process related issues arising from the assessment
- EMA coordinates the GMP inspections conducted by EEA NCA inspectors
- *The outcome of pre-approval inspections must be submitted to the CHMP in order to complete the assessment of the application*

GMP Inspections in the context of AAs

- Key aspects to consider for pre-approval GMP Inspections in AAs
  - Limited inspection resources - pre-approval inspections conducted in addition to planned routine re-inspections
  - Reduced evaluation time makes it more difficult to plan, conduct and report on GMP inspections within the timetable
  - Need for information regarding manufacturing sites before procedure start, to identify required inspections in advance
  - Manufacturing sites need to be inspection ready starting with submission

AAs with pre-approval GMP Inspections



Early Identification of GMP Pre-approval Inspections

- To better anticipate and accommodate pre-approval GMP inspections into a *reduced evaluation time* it is critical to identify inspections *as early as possible*
  - EMA can start preparing an inspection *before* procedure start to ensure that outcome is available in time
- MAH to provide information on *all* manufacturing sites (active substance and finished product) together with request for an AA (template available)

Manufacturing site details

Name, address, and responsibilities

Information must be: Accurate, Complete and must reflect the content of the dossier to be submitted;

GMP Compliance History

Inspections performed or planned GMP inspections by EEA authorities/Mutual Recognition Agreement Partners/other Authorities

Inspection Readiness

Confirmation that all manufacturing sites will be inspection ready at the time of submission

Points to consider

- Early communication is key
  - Consider supply chain compliance history for the pre-submission meeting
  - If any manufacturing site has never been inspected by an EU/EEA member state or a country with appropriate Mutual Recognition Agreement, contact EMA as early as possible before the submission of a potential request for AA
  - Provide information on all manufacturing sites together with request for an AA using the template
- Ensure that information provided is *accurate, complete* and that it *reflects the dossier* to be submitted
- If a pre-approval GMP inspection cannot be accommodated within the agreed time frame, the procedure timetable may need to be amended as necessary

Good Clinical Practice Inspections

Pre-approval GCP Inspections

Verifying GCP compliance of clinical trials supporting MAAs

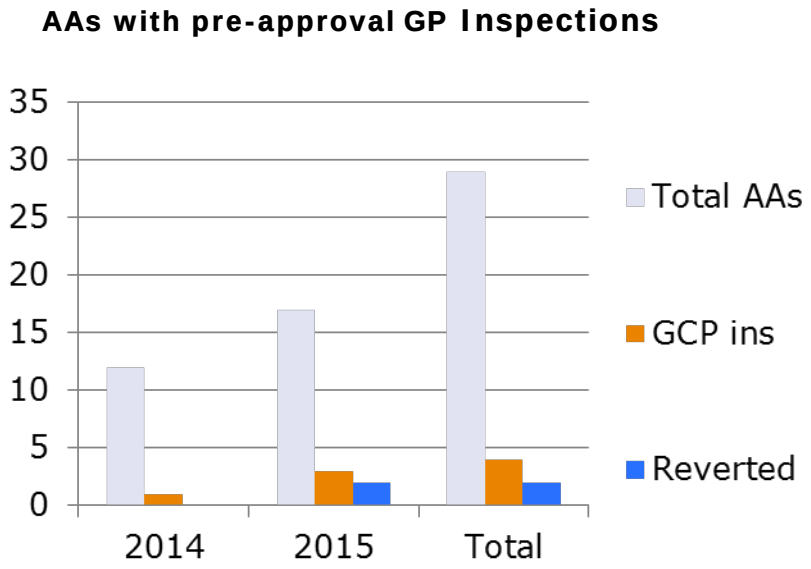
- Clinical trials included in any marketing authorisation application (MAA) in the EU and in any subsequent application to the initial one are required to be conducted in accordance with Good Clinical Practices (GCP). [Dir 2001/83/EC and Dir 2001/20/EC]
- The Agency has a legal obligation for the coordination of good clinical practice inspections [Regulation (EC) 726/2004]
- EMA reviews all new applications/line extensions/type II variations for evidence of GCP compliance and assesses, in collaboration with EPL, Rapporteurs/assessors and inspectors the need for GCP inspection(s).

Reference: Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for **"routine"** and/or **"for cause"** inspections, their investigation and scope of such inspections

GCP Inspections in the context of AAs

Key aspects to consider for pre-approval GCP Inspections in AAs

- Reduced evaluation time makes it more difficult to plan, conduct and report on GCP inspections.
- Limited inspection resources.
- Need for information before procedure start so that the need for GCP inspection is identified as early as possible.
- Need for applicant/sponsor and sites to be inspection ready.



For the period 2014 – 2015, out of the 29 applications under AA, GCP inspections were requested for 4 applications. Out of the 4 applications inspected, two reverted to standard TT but only one due to GCP inspection issues.

Early Identification of GCP Pre-approval Inspections

Information required

- List of all the pivotal clinical studies (protocol number and title)
- For each pivotal study:
  - the study synopsis (or a mature draft with information at least on the design and conduct of the study);
  - a short discussion on the GCP compliance status (listing any GCP non-compliance identified, any breach of GCP, providing information on any site excluded including the reasons, etc.);
  - List of investigator sites (name, address, country), in a tabular form, showing the number of patients enrolled by each site, and the total number of sites.
  - Study administrative structure (clear identification of the sponsor and of the parties who have performed the monitoring, data management, statistics, laboratory assessments, randomization, other applicable activities and the location of the trial master file)
- List of GCP inspections conducted/planned by any regulatory authority. Alternatively, a confirmation that no inspections had been requested nor taken place and that no inspections are planned. (template available)

Key messages

- Early communication with EMA:
  - Highlight any GCP deviations/non-compliances and discuss those in the pre-submission meeting to ensure that if there is a need for GCP inspection, this is identified as early as possible.
  - Provide the information required for the application review, as early as possible.
  - Ensure that information provided is accurate, complete and that it reflects the dossier to be submitted.

- The procedure timetable may need to be amended, as necessary:
  - If a pre-approval GCP inspection is requested and cannot be accommodated within the agreed time frame.
  - When major objections have been identified that cannot be handled in an accelerated timetable assessment.

GxP inspections and Accelerated Assessment procedures

Steps for success

- **request of pre-submission meeting before submission** to better prepare for evaluation under accelerated assessment.
- **submission of request for accelerated assessment as early as possible,** at least 2-3 months before the actual submission.
- **Provision of information concerning GMP and GCP aspects with the request for AA** so that routine GCP and pre-approval GMP **inspections can better be anticipated** and **integrated** into the accelerated assessment procedure.

Early provision of GxP information does not mean that an inspection will be requested but it ensures that if a need for an inspection is identified, this is requested as early as possible in the evaluation procedure to ***avoid delays and facilitate the AA timetable****.*

Thank you for your attention

Further information

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