GMP Inspections of API manufacturers:

Experience of a National Competent Authority with inspection of APIs

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Introduction:

- Spanish Agency for Medicines and Medical Devices.
  - Competent regulatory authority in EU.
  - 19 inspectors (GMP for finished products and APIs).
  - Regional inspectorates.
- 221 firms registered as importers, distributors or manufacturers (total or partial) of APIs:
  - 86 manufacturers, 101 sites.
  - 67 importers
  - 57 distributors of APIs.
- On average 10 inspections abroad/year:
  - Av. 2 joint inspections with EDQM.
Legal and regulatory framework (Spain)

- Pre-existing regulation (78~): registration and annual update, legal power to inspect, routine inspections non-mandatory.
  - Lack of detailed guidelines (ICH Q7- Part II in 2000s)
- Falsified medicines directive: changes in national regulations.
  - Mandatory registry and changes in registry format.
  - Mandatory routine inspections, incl. unannounced
  - Risk based frequency.
- Public registry (RUESA), available online and feeding EudraGMDP:
  https://labofar.aemps.es/labofar/registro/ruesa/consulta.do

Registry

- Key to enable effective supervision.
- Manufacturers, importers, distributors. National level only.
- Initial notification (60 days in advance) (inspection may follow)
- Regular updates
- Notify changes which may affect product quality (inspection may follow).
The place of the Certification Procedure in the global regulatory environment, Prague, 19-20 September 2017

Information in the registry

**Administrative information.**

**Activities: M, I, D**

**Manufacturing:**
For each active substance:  
Use (H,V)  
Manufacturing steps.  
Manufacturing volume (*).  
CEPs, ASMF, as applicable (*).  
Inspection by other authorities (*).  
Customers in Spain, EU and third countries (*).

**Distribution / Importation:**
For each active substance:  
Use (H,V)  
Manufacturer (*).  
Amount imported/distributed (*).  
CEPs, ASMF, as applicable (*).  
Customers in Spain, EU and third countries (*).

Some of the fields may be considered as confidential and shown in the restricted access part only (*).

Performance of inspections

- Evaluation if an inspection is needed upon registration or update of registry (non-routine inspections).
- Annual inspection plan for periodic inspections.  
  - Focused on national manufacturers.
- SOP for performing inspections:  
  - Inspection preparation. Request for SMF and additional information.  
  - Announced/unannounced.  
  - Inspection records.  
  - Inspection report (initial, final).
- Post-inspection activities.  
  - NCS- GMP certificates.  
  - Follow up inspections / Restricted GMP certificates (scope /validity).
Regulatory action – post inspection activities.

- Immediate action if critical deficiencies are found.
- GMP certificate / Non-compliance report.
  - EU formats available in compilation.
  - Recommended actions.
  - GMP certificate with restrictions (scope)
- Uploaded in EudraGMDP.
  - Key to cooperation among EU NCAs and MRA partners.
- Renewal and update of GMP certificates:
  - Include all APIs? Not mandatory.
  - New APIs added to the portfolio.
  - Manufacturing lines/routes.
International inspections.

- Linked to national authorizations.
  - Resource-demanding.
  - Periodic inspections not mandatory.
    → Difficulty in risk-based approach, information gathering and analysis is costly, time consuming.
- At the request of EMA.
- Collaboration with EDQM.
  - EDQM Inspection plan, risk based.
  - Limited scope to CEP applications.

More frequent deficiencies in GMP Non-compliance statements in API manufacturers

- Risk of contamination / cross contamination or mix ups.
- Data integrity issues: creation and falsification of GMP documents, analytical data integrity, QA records.
- Housekeeping and maintenance.
- Undeclared/shadow factories or workshops.
- Problems in sterility assurance.
- Lack of proper investigation of deviations/OOS results.
- Poor validation (cleaning, analytical...).
- Failures in environmental monitoring.
- Poor implementation of QMS.
- Lack of documentation (rework, packaging...) and/or traceability (biological starting materials).

NC-reports published in EudraGMDP; last 2 y
Some challenges

- Advanced intermediates:
  - control over supply chain, transfer of information, regulatory filing.
- Importers and distributors of APIs: obligations and responsibilities.
  - GMP compliance of manufacturers/suppliers in third countries.
  - CoAs and transfer of information.
- Records of supply chain; documents.
  - Importation documentation.
- Changes which may affect quality:
  - Notification to competent authorities.
  - Decision for inspection – Resources.
- Handling of APIs as mere “chemical substances” (bypassing requirements, REACH).

Thank you!!
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