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)
- Expansion of inspection programme (2005~).
- 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

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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).

ACOFARMA DISTRIBUCION S.A.	c./ Llobregat 20, Pol. Santa Margarita	TERRASSA
AINIA	AVDA. BENJAMÍN FRANKLIN, 5-11, PARQUE TECNOLÓGICO	PATERNA
Air Liquide Ibérica de Gases	PASEO DE LA CASTELLANA 79	MADRID
ALCALÁ FARMA, S.L.	Avenida de Madrid, 82	Alcalá de Henares
ALCALIBER, S.A.	GÉNOVA 27, PLANTA 6	MADRID
ALFARIN QUIMICA, S.A.	CALLE IBIZA 35 - 5º C	MADRID
ALFASIGMA ESPAÑA, S.L.	Avda. Diagonal, 490 - 4º, 2ª	Barcelona
ALGRY QUIMICA, SL	POL. IND. NUEVO PUERTO	PALOS DE LA FRONTERA
ALLIANCE HEALTHCARE ESPAÑA, S.A.	Polígono Industrial Sector 4	Villanueva de Gállego
ALMIRALL, S.A.	Ronda General Mitre, 151	Barcelona
ALTAQUIMICA S.A.	CASPE 86	BARCELONA

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(*)

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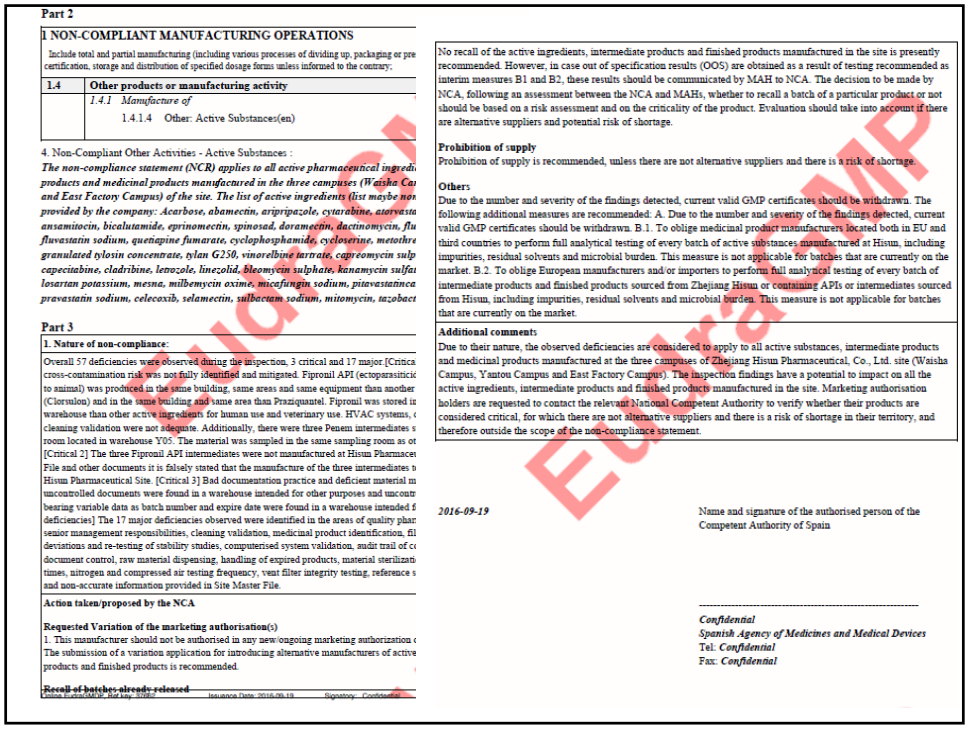
Performance of inspections

- 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? Nor mandatory.
  - New APIs added to the portfolio.
  - Manufacturing lines/routes.



Part 2

1 NON-COMPLIANT MANUFACTURING OPERATIONS

Include total and partial manufacturing (including various processes of dividing up, packaging or pre certification, storage and distribution of specified dosage forms unless informed to the contrary;

1.4	Other products or manufacturing activity
	1.4.1 Manufacture of
	1.4.1.4 Other: Active Substances(en)

4. Non-Compliant Other Activities - Active Substances :

The non-compliance statement (NCR) applies to all active pharmaceutical ingredi products and medicinal products manufactured in the three campuses (Waisha Ca and East Factory Campus) of the site. The list of active ingredients (list maybe no provided by the company: Acarbose, abamectin, aripiprazole, cytarabine, atorvasta ansamitocin, bicalutamide, eprinomectin, spinosad, doramectin, dactinomycin, flu fluvastatin sodium, quetiapine fumarate, cyclophosphamide, cycloserine, metothre granulated tylosin concentrate, tylan G250, vinorelbine tartrate, capreomycin sulp capecitabine, cladribine, letrozole, linezolid, bleomycin sulphate, kanamycin sulfa losartan potassium, mesna, milbemycin oxime, micafungin sodium, pitavastatinca pravastatin sodium, celecoxib, selamectin, sulbactam sodium, mitomycin, tazobact

Part 3

1. Nature of non-compliance:

Overall 57 deficiencies were observed during the inspection, 3 critical and 17 major.[Critica cross-contamination risk was not fully identified and mitigated. Fipronil API (ectoparasiticic to animal) was produced in the same building, same areas and same equipment than another (Clorsulon) and in the same building and same area than Praziquantel. Fipronil was stored in warehouse than other active ingredients for human use and veterinary use. HVAC systems, cleaning validation were not adequate. Additionally, there were three Penem intermediates s room located in warehouse Y05. The material was sampled in the same sampling room as ot [Critical 2] The three Fipronil API intermediates were not manufactured at Hisun Pharmacei File and other documents it is falsely stated that the manufacture of the three intermediates w Hisun Pharmaceutical Site. [Critical 3] Bad documentation practice and deficient material m uncontrolled documents were found in a warehouse intended for other purposes and uncontr bearing variable data as batch number and expire date were found in a warehouse intended f deficiencies] The 17 major deficiencies observed were identified in the areas of quality phar senior management responsibilities, cleaning validation, medicinal product identification, fil deviations and re-testing of stability studies, computerised system validation, audit trail of cc document control, raw material dispensing, handling of expired products, material sterilizati times, nitrogen and compressed air testing frequency, vent filter integrity testing, reference s and non-accurate information provided in Site Master File.

Action taken/proposed by the NCA

Requested Variation of the marketing authorisation(s)

1. This manufacturer should not be authorised in any new/ongoing marketing authorization The submission of a variation application for introducing alternative manufacturers of active products and finished products is recommended.

Recall of batches already released

No recall of the active ingredients, intermediate products and finished products manufactured in the site is presently recommended. However, in case out of specification results (OOS) are obtained as a result of testing recommended as interim measures B1 and B2, these results should be communicated by MAH to NCA. The decision to be made by NCA, following an assessment between the NCA and MAHs, whether to recall a batch of a particular product or not should be based on a risk assessment and on the criticality of the product. Evaluation should take into account if there are alternative suppliers and potential risk of shortage.

Prohibition of supply

Prohibition of supply is recommended, unless there are not alternative suppliers and there is a risk of shortage.

Others

Due to the number and severity of the findings detected, current valid GMP certificates should be withdrawn. The following additional measures are recommended: A. Due to the number and severity of the findings detected, current valid GMP certificates should be withdrawn. B.1. To oblige medicinal product manufacturers located both in EU and third countries to perform full analytical testing of every batch of active substances manufactured at Hisun, including impurities, residual solvents and microbial burden. This measure is not applicable for batches that are currently on the market. B.2. To oblige European manufacturers and/or importers to perform full analytical testing of every batch of intermediate products and finished products sourced from Zhejiang Hisun or containing APIs or intermediates sourced from Hisun, including impurities, residual solvents and microbial burden. This measure is not applicable for batches that are currently on the market.

Additional comments

Due to their nature, the observed deficiencies are considered to apply to all active substances, intermediate products and medicinal products manufactured at the three campuses of Zhejiang Hisun Pharmaceutical, Co., Ltd. site (Waisha Campus, Yantou Campus and East Factory Campus). The inspection findings have a potential to impact on all the active ingredients, intermediate products and finished products manufactured in the site. Marketing authorisation holders are requested to contact the relevant National Competent Authority to verify whether their products are considered critical, for which there are not alternative suppliers and there is a risk of shortage in their territory, and therefore outside the scope of the non-compliance statement.

2016-09-19

Name and signature of the authorised person of the Competent Authority of Spain

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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.

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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/supppliers 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).

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Thank you!!

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Chairmanship of the Czech Republic
Council of Europe
May – November 2017

Présidence de la République tchèque
Conseil de l'Europe
Mai – Novembre 2017

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