

API Regulatory Compliance: GMP Inspections and Marketing Authorization

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The Place of the Certification procedure in the global regulatory environment
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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

| Interests in pharmaceutical industry | NO | Current | From 0 to 3 previous years | Over 3 previous years |
|---|----|--------------------------|----------------------------|------------------------------------|
| DIRECT INTERESTS: | | | | |
| 1.1 Employment with a company: pharmaceutical company in an executive role | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> mandatory |
| 1.2 Employment with a company: in a lead role in the development of a medicinal product | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> mandatory |
| 1.3 Employment with a company: other activities | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 2. Consultancy for a company | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 3. Strategic advisory role for a company | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 4. Financial interests | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 5. Ownership of a patent | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| INDIRECT INTERESTS: | | | | |
| 6. Principal investigator | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 7. Investigator | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
| 8. Grant or other funding | x | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> optional |
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N.B. I am not receiving any compensation

Content

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- QP declaration
- Management of GMP Non compliance Statement (NCR)
- Impact on Marketing Authorization Dossier
- European procedures to manage NCR
- Conclusions

EU Legal Framework

- According to the European Legislation the Manufacturing Authorization Holder is responsible to assure that only active substances manufactured according to the GMP and distributed according to the GDP are used to manufacture a medicinal product (Directive 2011/83/EC, as amended; art. 46 f)
- The responsibility is taken on by the QP, through the QP Declaration

Falsified Medicines Directive (2011/62/EU)

Introduces:



- Registration for API manufacturers in Europe
- Inspections by NCA according with frequency defined by a risk-based approach
- Mandatory written confirmation for imported API, to be issued by the NCA of exporting Country (except if the Country is in the «white list»)
- non EU manufacturing site inspections based on risk



The API compliance is assured through an oversight system based on a Regulatory enforcement and an ongoing and continuing supplier qualification monitoring by the Manufacture Authorization Holders

Falsified Medicines Directive

- Modifies the Directive 2001/83/EC by introducing in the article 8(3):
(ha) "A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice".



This is what is called "Qualified Person Declaration"

QP Declaration Template

- QP Declaration becomes “hard law” for human Medicines
- QP Declaration Template and Guidance were published in May 2014
- http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167852.pdf
- http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500167853



QP Declaration Template

QP Declaration Template and Guidance useful to:

- harmonize the format for the declaration
- prevent questions during assessment
- enhance the efficiency of the regulatory process
- provide clear requirements

The template is not mandatory; but if not used the same information is necessary

QP Declaration highlights

- QP declaration is mandatory for any Marketing Authorization to confirm that the API is manufactured in accordance with GMP
- A QP declaration is signed by the QP working for the manufacturing and/or importing site located in EEA
- It is based upon an audit of the active substance manufacturer(s)
- The outcome of the audit confirms that the manufacturing complies with the principles and guidelines of GMP

QP declaration highlights

- It should be based on an on-site audit of the API manufacturer:
 - The audit may be a third party contractor (written agreement)
 - Suitably trained and experienced person(s)
 - The audit cannot be replaced by GMP certificates from a relevant competent authority
- When more than one holder of a Manufacture/importation authorization is involved, it may be acceptable to provide a single declaration signed by one QP, provided that:
 - it is signed on behalf of all the involved QPs
 - the arrangements are covered by a technical agreement

QP Declaration - off site audit

- "Off-site" audit as exceptional case:
 - When an on-site audit is not practical (atypical activities, travel difficulties)
 - An off-site paper-based audit may be justifiable only on a case-by-case basis
 - QP declaration to be supported by:
 - the justification for assessment of GMP compliance without an on-site audit;
 - listing of the documents forming the basis of the off-site audit (i.e., review of documents, quality systems and certification, results of analytical testing, risk analysis, historical experience with the supplier, etc.)

QP Declaration and Marketing Authorizations

Requested for:

- All new MA applications
- All MA renewals
- Relevant variations
 - Addition or replacement of API manufacturer
 - Addition or replacement of finished product manufacturing site
 - Addition or replacement of the Batch Release site



Irrespective of API data submission – CEP, ASMF or 3.2.S.

QP Declaration and Marketing Authorizations

- New MA applications, type IB and type II variations: QP declarations properly assessed
- The vast majority of QP declarations are presented for Type IA notifications which are not systematically assessed. For example: the change to a new active substance manufacturers supported by a CEP can be submitted as "Do and tell" notification
- The Type IA notifications are mainly linked to changes in EU batch release responsibilities and changes in drug substance manufacturers and as a consequence the QP declarations are likely to be based upon the outcomes of new audits

QP declaration and variations on quality changes

- B.I .a.1 Change in API manufacturer:

The manufacturer is part of the same pharmaceutical group as the currently approved manufacturer \implies QP Declaration

- B.II.b.2 Change to batch release arrangements and quality control testing of the finished product:

Already approved API manufacturer \implies QP declaration

- B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:

*Already approved API manufacturer /
New Manufacturer (Replacement or addition)* \implies QP declaration

Common deficiencies of QP declaration

- Audits are performed with a low frequency without any justification
- Audits not performed "on site" without any justification
- Intermediate sites not covered

If the initially proposed starting material definition is requested to be changed by the assessor, the GMP compliance must be verified/declared for upper steps of the synthesis: a new QP declaration needed



None of the deficiency identified is related to the GMP Compliance, which can only be trusted by the NCA!

Something went wrong...



Inspection performed by an EU National Competent Authority



Negative outcome (no matter if the QP declaration was available, a written confirmation from the exporting Country was available, a previous GMP Certificate was granted)



Statement of GMP non compliance (draft circulation, discussion among the EU network, final NCR issuance through EudraGMDP database)



Coordinated actions to: possible removal of the API manufacturer from the MA, find and qualify a new supplier, submit variation, suspend/withdraw the CEP (if granted), evaluate the need to recall the medicinal products, suspend the MA...

GMP issues



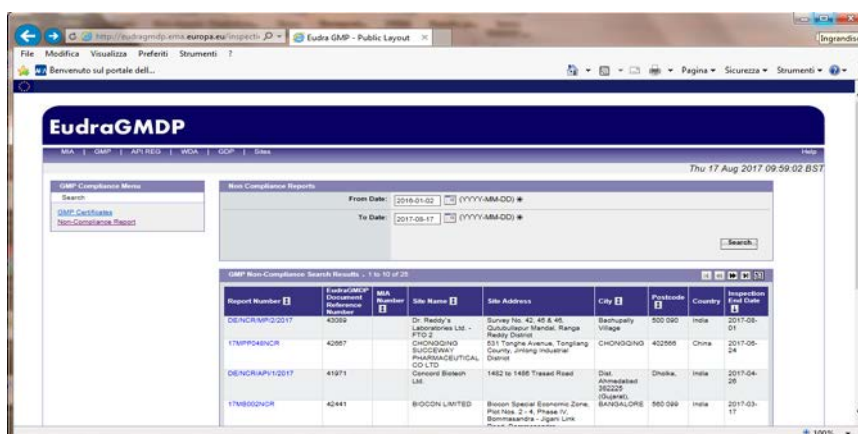
Several cases in which MIA auditors (QP or third party) and inspectors reach very different conclusions concerning GMP compliance of a manufacturing site

Why this difference?

- Inspectors might have more training and experience?
- Inspectors might have full access to facilities/documents?
- Authorities' and industry's assessment can be based on different interpretation of the guidance?
- QP/third party evaluation is less "independent" ?

Whatever the reasons the effect can be a disaster with significant impact on Mas. *As example: Zhejiang Hisun case impacted on n. 41 medicinal products (20 MAHs) on the Italian market*

EudraGMDP Public Layout (NCR)

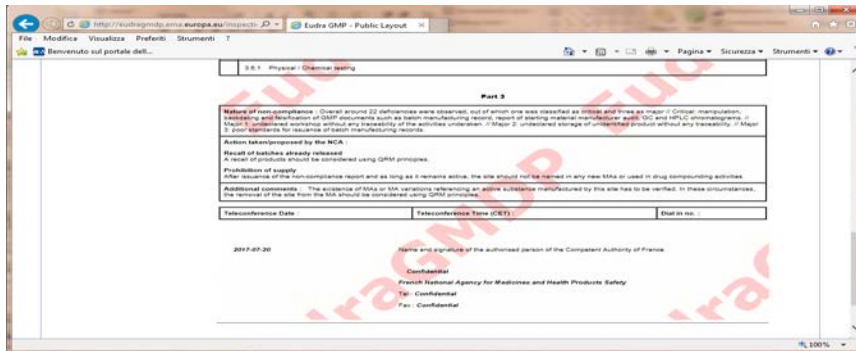


Search filters: From Date: 2019-01-02 (YYYY-MM-DD), To Date: 2017-08-17 (YYYY-MM-DD)

| Report Number | EudraGMDP Document Reference | MIA Identifier | Site Name | Site Address | City | Postcode | Country | Inspection End Date |
|---------------|------------------------------|----------------|--|---|-----------------------------------|----------|---------|---------------------|
| DENCR/MP/2017 | 4359 | | Dr. Reddy's Laboratories Ltd. FTD 2 | Suburbur Mandi, Rang Reddy District | Bachupally Village | 502 030 | India | 2017-08-01 |
| 17NPP48NCR | 4267 | | CHONGQING SUZHENWAY PHARMACEUTICAL CO.,LTD | 531 Tangle Avenue, Tongxiang County, Jiangsu Industrial District | CHONGQING | 402006 | China | 2017-09-24 |
| DENCR/MP/2017 | 41971 | | Genentech Biotech Ltd. | 1482 to 1486 Tread Road | Dhaka. | | India | 2017-04-28 |
| 17N802NCR | 42441 | | BIOCON LIMITED | Biocon Special Economic Zone, Plot Nos. 2-4, Phase IV, Bommasandra - Jagan Link Road, Bangalore | Dial Abmalasat (Dhaka), BANGLAORE | 560 048 | India | 2017-03-17 |

NCR: some figures

2016-2017 (July): 14 GMP non compliance Statement for API Manufacturers. The last one issued the 20 July 2017



Compilation of Community procedures on Inspections and Exchange of Information



EMA/572454/2014 Rev 17
Compliance and Inspection

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- *Procedure for dealing with serious GMP non-compliance requiring coordinated measures to protect public or animal health:*
 - Coordinated actions at Union level
 - Actions commensurate to the risk
 - The lead Inspectorate: responsibility to issue a Supervisory Risk assessment and assure the entry of the final non-compliance statement into EudraGMDP database

Compilation of Community procedures on Inspections and Exchange of Information

- EDQM is informed if not directly involved in the inspection (and the possible impact on CEP released is evaluated)
- Each NCA has to evaluate and decide the impact of the statement of non-compliance on national marketing authorizations (or applications)
- Discussion at CMDh/CMDv for decentralised/mutual recognition MA in accordance to the specific guidance (RMS can propose actions after consultation with CMS)
- Discussion at EMA level (via the CHMP and/or CVMP) for centralised products

Compilation of Community procedures on Inspections and Exchange of Information

- The evaluation of the impact of the statement of non-compliance on marketing authorisations (applications) should take into account the appropriate legal framework for granting the marketing authorization as well as the potential impact of the findings on any data submitted to the competent authority
- The appropriate competent authorities should decide whether a marketing authorisation should be suspended, revoked or varied and/or whether a marketing authorisation application should be refused as a result of the non-compliance with GMP

Compilation of Community procedures on Inspections and Exchange of Information

- Any decision to suspend a marketing authorization has to be strongly motivated and the principle of proportionality taken into account
- EDQM has the responsibility for evaluating and deciding on the impact of the non compliance Statement (if CEP involved)
- Lead Inspectorate should evaluate on the quality and safety of batches on the market or awaiting the release
- Different actions may be necessary in different MS due to the criticality of the medicinal products and potential shortage

Supervisory Risk Assessment: example 1

... Due to the number and the severity of the findings, the NCA recommends:

- Action on MAs: removal of the site from the MA should be considered using QRM principles
- Recall of batches already released: recall of products should be considered using QRM principles
- Prohibition of supply
- After issuance of the non-compliance report and as long as it remains active, the site should not be named in any new MAs or used in drug compounding activities

Supervisory Risk Assessment: example 2

- *Interim urgent measures:* Prohibition of supply is recommended, unless there are not alternative suppliers and there is a risk of shortage
- *Final actions:* If there are alternative suppliers and there is no risk of shortage, recall of medicinal product should be evaluated. A complete retest of all imported batches of active substance is needed. This supplier should not be approved in any new/ongoing applications.
- *Other considerations:* The observed deficiencies are considered to apply to all other active substances/intermediates manufactured at the same site and reported in attachment ...

Recommendation to suspend all the CEPs was officially endorsed by the Ad Hoc Committee on ...

CMDh Guidance

CMDh Best Practice Guidance on collaboration between Member States in relation to serious GMP Non Compliance (Doc Ref.: CMDh/316/2014, Rev.1 March 2017)

- Interaction with Lead Inspectorate Authority



- Possible scenarios:

- The affected supplier is the only site approved in the MA
- The affected supplier is one of more sites approved in the MA

CMDh Guidance



A) Already approved medicinal products:

- Possible different situation in the affected MS. This will have to be evaluated on a case by case basis
 - Maintain the MA
 - Request a variation to the MA
 - Suspend the MA (e.g until the existing manufacturer is replaced by a new one, through a variation/or to maintain the suspension until the GMP issue solved)
 - Revoke the MA
- In parallel with the regulatory actions above, possible recall of the product from the market – and at what level – should be discussed

CMDh Guidance

B) Ongoing procedures:

- The RMS may justify to put the procedure on hold (in clock stop) until the issue is evaluated. If not possible (i.e. no alternative manufacturer is available, the GMP non-compliance issue is not resolvable during the procedure), the application has to be refused.

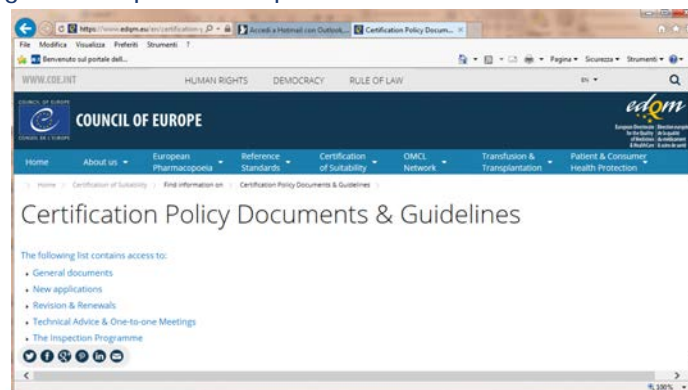
Final decision to any market action or suspension/revocation of a MA in a MS is a matter for the NCA, depending on the criticality of a medicinal products (therapeutic alternatives available or same products from different manufacturing sites)

If the manufacturing site granted a CEP?

- On each CEP is stated that "*manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted. Failure to comply with these provisions will render this certificate void*"
- As a consequence, after a GMP non compliance, the EDQM may suspend or withdraw the CEP or the CEP may be revised to remove the site(s)
- Appropriate action regarding the usage of the existing stocks and the MA affected should be taken by competent authorities.

If the manufacturing site granted a CEP?

- A further regulatory process is initiated at EDQM, Certification Division, according to the implemented procedure



AIFA Departments Concerned

- Inspection and Certification Department:
 - GMP API Inspections and Authorization (if AIFA is the Lead inspectorate): issue the SA risk assessment and the NCR
 - Quality of Products on the market and Counterfeiting (always involved)
- Marketing Authorization Department:
 - Dept. Office: deal with the NCR and CEP status, GMP deviations affecting the MA received by the Inspections and Certification Dept.
 - Marketing Authorization Office (check the MA and applications affected)
 - Post Approval Procedure Office (deal with variations)

Summarizing: impact of GMP issues on MA process/procedures

- A NCR creates a numbers of regulatory actions for Authorities:
 - Lead Inspectorate: issuance of the NCR and Risk Assessment
 - All EEA NCA: to verify the MA/MA applications and variations on going
 - All EEA NCA: to verify the criticality of the medicinal product for market supply
 - Discussion at NCA/CMDh level or EMA level

Summarizing: impact of GMP issues on MA process/procedures

- All EEA NCA concerned take appropriate measures (i.e. suspend the MA if appropriate, recall the product if appropriate)
- EDQM: suspend/withdrawn the CEP following the internal procedure (ad Hoc Committee discussion)
- Reinspection needed to verify the GMP compliance of the site



Additional Administrative burden!!!



Summarizing: impact of GMP issues on MA process/procedures

For the MIA/MA holders: regulatory burden/commercial challenge:

- Find a new API supplier (if the only one)
- Manage the production plan
- Submit variation(s)
- Manage the shortage
- New QP declaration/audit
- Loss of money (loss of product, loss of market, requalify a new supplier, fees for variations, etc.)

Conclusions

- Regulatory Governance is in place to assure that the NCR are managed in an effective manner, adopting a risk based approach, maintaining a balance among clinical need and quality/safety need
- Nevertheless a GMP non compliance statement for an API manufacturer may indicate that MIA holder and MA holder have failed to fulfil their legal/ethical obligations
- Need to discuss at EU level, how to check/improve the performance of the QP audits (which normally can only be assessed during the inspection of the MIA holder site)



The challenge for Regulators/Companies

Always keep a balance!



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Thank you for your attention!