

Hot Topics in Quality and Regulations

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For PDA Annual Meeting

(Israel Chapter, 15 January, 2017)

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News and updates



16/11/2015

Public consultations on

Notice from the Commission on aspects of the application of Article 3, 5 and 7 of Regulation (EC) N° 141/2000 on orphan medicinal products

Period of consultation from 16 November 2015 to 15 February 2016

27/10/2015

e-
newsletter



10 December 2015

National Contact Points gea

Latest updates

Israel on White list - Implications

02/07/2015

Brazil and Israel have been added to the "list of third countries" having standards of manufacture and supervision of active pharmaceutical ingredients equivalent to those of the EU. The Commission Implementing Decision is [here](#).  (316 KB) 

GMP / GDP Inspectors Working Group



GMP GDP inspectors workplan 2016.pdf

- **Compilation of Union Procedures on Inspections and Exchange of Information**
 - To continue to identify GMP and GDP inspection related topics for development as Union procedures;
 - To develop harmonised approaches to compliance management;
 - Finalisation of the procedure for dealing with serious GDP non-compliance;
 - Dealing with non-compliance in the context of excipients;
 - The group will continue to discuss harmonised approaches to dealing with “atypical actives”.
- **Implementation of GMP guidance on the use of cross-contamination risk management in shared manufacturing facilities for the manufacture of different medicinal products**
 - To establish an EU implementation team.

GMP / GDP Inspectors Working Group

- **Heparin**
 - To develop and implement an appropriate supervision plan for the heparin supply chain in consultation with international partners.
- **GMP Certificates**
 - To harmonise practices in relation to the listing of products or active substances in GMP Certificates.
- **GMP for biological active substances**
 - To harmonise GMP expectations in view of the differing levels of detail between Parts I and II of the GMP Guide.
- **Data Integrity**
 - To develop principles for inspectorates when dealing with findings of non-compliance due to data integrity issues or when dealing with reports of non-compliance due to data integrity issues issued by authorities from third countries.

GMP / GDP Inspectors Working Group

5. GMP and GDP topics

To continue to identify GMP and GDP topics for guideline development or clarification.

- **GMP Guide: Chapter 1**
 - To decide on whether to proceed with a proposal to amend the chapter in order to capture the main principles of the industry inter-association shortages taskforce guidelines aimed at reducing shortages caused by quality/manufacturing problems.
- **GMP Guide: Chapter 4**
 - To consider whether amendments are required in order to assure data integrity in the context of GMP. Early guidance in the form of Q&As will also be considered.
- **GMP Guide : annex 1**
 - To provide a draft text for public consultation;
 - To adopt and publish advance Q&As dealing with the production of Water for Injections by Reverse Osmosis and control of biofilms.
- **GMP Guide: annex 17 (parametric release)**

GMP / GDP Inspectors Working Group

- **GMP Guide: annex 21 (New: Importation of medicinal products)**
 - To provide a draft text for public consultation.
- **GMP Guidance on Data Integrity**
 - To clarify data integrity expectations in relation to GMP including whether short term measures should be developed followed by longer term measures.

Note: In accordance with the cooperation agreement with PIC/S, non-EEA participation in drafting groups will be sought for documents identified as harmonised.

GMP / GDP Inspectors Working Group

Reflection Paper on MAH

- To continue to collaborate with the European Commission and the Committee for Advanced Therapies (CAT) on the proposal for development of GMP guidance for advanced therapy medicinal products.
- **GMP compliance and Marketing Authorisation Holders**
 - To develop a Reflection Paper on the relationship between GMP Compliance and the responsibilities and activities of Marketing Authorisation Holders.
- **EudraGMDP database**
 - To continue to oversee the EudraGMDP database and to act upon the recommendations of the EudraGMDP IT subgroup formed to advise the group;
 - To promote further use of the planning module as a tool for international collaboration;
 - To develop harmonised data entry rules to promote improved data quality and alignment with the Agency's Information Management Strategy;
 - To develop harmonised use of the "Special Requirements" menu in the light of updated GMP guidance on shared manufacturing facilities.

2015 - 2016 The DI Guidances – a race to the finish? Harmoni(z)sation?



Jan 2015

MHRA Data integrity.pdf



Sept 2015

WHO Good Data Management Practice.pdf



Apr 2016

FDA Data Integrity marked up.pdf



Jul 2016

MHRA GxP data integrity draft 2016.pdf



10 Aug 2016

PI_041_1_Draft_2_Guidance_on_Data_Integrity.pdf



11 Aug 2016

EMA Data Integrity 110816.pdf

FDA Guidance Agenda 2017



Guidance Agenda 2017_2017.01.11.pdf

CATEGORY — Pharmaceutical Quality/CMC

- CMC Postapproval Manufacturing Changes for Specified Biological Products to be Documented in Annual Reports
- Container Closure Systems for Packaging Human Drugs and Biologics; Revised Draft
- Drug Master Files; Revised Draft
- Drug Products, Including Biological Products, That Contain Nanomaterials
- GDUFA II Priority ANDA Pre-Submission Communications
- Harmonizing Compendial Standards with Drug Application CMC Approval Requirements Using the USP Pending Monograph Process
- In-vitro Methods for Evaluation of Abuse Deterrent Properties of Opioid Products
- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing, and Controls Documentation; Revised Draft
- Type V Drug Master File (DMF) for Combination Products with CDER Jurisdiction Utilizing a Device Part with Electronics or Software
- Use of the FDA Inactive Ingredient Software (IID)
- Visual Inspection of Injectable Drug Products

FDA Guidance Agenda 2017



Guidance Agenda 2017_2017.01.11.pdf

CATEGORY — Pharmaceutical Quality/Manufacturing Standards (CGMP)

- Current Good Manufacturing Practice for Medical Gases; Revised Draft
- Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products; Revised Draft
- Field Alert Report Submission
- Repackaging of Certain Drug Products by Pharmacies and Outsourcing Facilities

FDA Metrics draft original

- **Lot Acceptance Rate** = $1 - x$ (x = the number of specification-related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe).
- **Product Quality Complaint Rate** = the number of product quality complaints received for the product divided by the total number of lots of the product released in the same timeframe.
- **Invalidated Out-of-Specification (OOS) Rate** = the number of OOS¹⁹ test results for the finished product invalidated by the establishment divided by the total number of OOS test results divided by the total number of tests performed by the establishment in the same timeframe.
- **Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate** = the number of APRs or PQRs completed within 30 days of annual due date at the establishment divided by the number of products produced at the establishment.

FDA metrics new draft

Nov 2016



Quality Metrics draft rev 1.pdf

- **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance. LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe.
- **Product Quality Complaint Rate (PQCR)** as an indicator of patient or customer feedback. PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
- **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation of a laboratory. IOOSR = the number of OOS test results for lot release²⁷ and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe.^{28,29}

FDA metrics new draft

Stick or Carrot?

B. Quality Metric Reporters List

FDA intends to publish a list of the names of establishments that voluntarily report all or a subset of quality data as described in this guidance (i.e., product reporting establishments and site reporting establishments). We believe that there is a benefit to publicly sharing the names of establishments that voluntarily choose to submit these quality data to FDA because, through their participation, these establishments demonstrate a willingness to proactively engage with the Agency in pursuit of the goals described in this guidance. Participation in this voluntary reporting phase of the program also demonstrates a commitment to increasing transparency between industry and FDA and a contribution to improving quality monitoring throughout the industry.

FDA does not intend to publicly disclose information submitted to the Agency as part of the voluntary phase of the quality metrics program that is exempt from disclosure under the Freedom of Information Act as confidential commercial information, e.g., information that would reveal nonpublic commercial relationships and production volumes.

FDA metrics new draft

B. Quality Metric Reporters List

This list may be useful to establishments within the pharmaceutical manufacturing industry when selecting contract manufacturers and component suppliers as one element of robust outsourcer or supplier selection (e.g., past inspection and regulatory authority history, audits of the facility and associated systems, and analytical testing). This list may also be useful for healthcare purchasing organizations, healthcare providers, patients, and consumers in sourcing drugs when used in conjunction with other information (e.g., inspection history). The list will provide information about *whether* an establishment voluntarily submitted quality metrics data to the Agency, and if so how much data was submitted. It should be noted that inclusion on the list is not an indication of FDA's *evaluation* of the submitted data.

FDA Optional Metrics Related to Quality Culture and Process Capability/Performance original draft – disappeared?

FDA acknowledges the importance of quality culture to the overall state of quality of the product, process, and commitment to quality. We also recognize that many companies measure quality culture and encourage this practice. FDA is proposing the following metrics for comment:

- **Senior Management Engagement:** A corporate commitment to quality has been identified in multiple public forums as a strong indicator of a robust PQS. FDA recognizes the difficulties in measuring senior management engagement and support of quality, including manufacturing and facility improvements. Proposed Optional Metric 1 is intended to identify whether senior management with the resources and authority to implement changes are engaged in the assessment of product quality, as well as whether there is shared knowledge of this assessment with the quality and manufacturing organizations. Comments are requested on Proposed Optional Metric 1 and alternative approaches.

Proposed Optional Metric 1:

Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither?²⁰

FDA Quality Agreements

Final November 2016

- *Commercial manufacturing* does not include research and development activities, manufacturing of material for investigational new drug studies (e.g., clinical trials, expanded access), or manufacturing of material for veterinary investigational drugs. Although this guidance does not explicitly apply to the manufacture of investigational, developmental, or clinical trial materials, FDA believes that quality agreements can be extremely valuable in delineating the activities of all parties involved in contract research and development arrangements. Many of the principles described in this guidance could be applied in pre-commercial stages of the pharmaceutical life cycle.
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FDA Quality Agreements

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IV. DOCUMENTING CGMP ACTIVITIES IN QUALITY AGREEMENTS

If an owner employs a contract facility for all or part of the manufacturing (including processing, packing, holding, or testing) of a drug or drug product, the owner's quality unit is responsible for approving or rejecting the contract facility's product or service.¹⁸ The contract facility is also required to comply with statutory CGMP and applicable CGMP regulations, including requirements for its quality unit.¹⁹ CGMP regulations require that quality unit activities and procedures be in writing, and that these procedures be followed.²⁰

Implementing a written quality agreement can facilitate compliance with CGMP and, in particular, with 21 CFR 211.22(d), which states that quality unit activities and procedures should be in writing. FDA recommends that owners and contract facilities establish a written quality agreement to describe their respective CGMP-related roles, responsibilities, and activities in drug

FDA Quality Agreements

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A quality agreement describes the owner's and the contract facility's roles and manufacturing activities under CGMP. A well-written quality agreement will use clear language. It will define key manufacturing roles and responsibilities. It will establish expectations for communication, providing key contacts for both parties. It will specify which products and/or services the owner expects from the contract facility and who has final approval for various activities. Most quality agreements contain the following sections:

- Purpose/Scope — to cover the nature of the contract manufacturing services to be provided
- Definitions — to ensure that the owner and contract facility agree on precise meaning of terms in the quality agreement
- Resolution of disagreements — to explain how the parties will resolve disagreements about product quality issues or other problems
- Manufacturing activities — to document quality unit and other activities associated with manufacturing processes as well as control of changes to manufacturing processes
- Life cycle of, and revisions to, the quality agreement

The owner may consider including the contract facility's established processes and procedures as part of the quality agreement (for example, by incorporating certain standard operating

FDA Quality Agreements

Final November 2016

procedures by reference). Doing so could reduce the risk of misinterpretation or error during manufacturing. The quality agreement should explain how the contractor will report manufacturing deviations to the owner, as well as how deviations will be investigated, documented, and resolved in compliance with CGMP. Quality agreements should state that manufacturing services provided by contract facilities (including laboratories) will comply with CGMP.

From a CGMP perspective, manufacturing activities are the most important element in a quality agreement. The most critical pieces are quality and change control, as described in the following sections.

THANK YOU FOR LISTENING!