efpia
European Federation of Pharmaceutical Industries and Associations

Position Paper

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A Concept for Harmonized Reporting of Inspections[1]

Executive Summary

As the FDA and EMA evaluate the potential of an EU-US Mutual Recognition Agreement (MRA) on GMP inspections - an exercise and goal that PhRMA and EFPIA strongly support - a complementary exercise would be to consider how the EU and U.S. could harmonize the reporting of GMP inspections. Although harmonized reporting is not a requirement for moving forward with an MRA, greater uniformity in the reporting of inspection findings would benefit that effort. This includes the manner in which the findings are described in the inspection report, the factors applied to assign a risk classification to the findings, the processes through which the specific language for those findings is drafted (e.g. with dialogue and input from personnel at the inspected facility), and the overall format of the inspection report. To this end, this paper outlines potential approaches for:

- **Standardizing inspection reports -** to allow the comparison of results across various inspections and provide a rationale for the final classification of a site
- **Drafting of observations with input from inspected facility -** to facilitate understanding of GMP requirements and accuracy of findings
- **Harmonizing risk assessment and classification of observations -** to enable comparability of findings between jurisdictions with different laws and standards

Uniformity in the reporting of inspection findings would be of tremendous value to global health authorities, industry, and the public because it would permit informed comparisons of the relative compliance statuses of different facilities or the same facility at different points in time. This in turn would enable better informed risk-based decision-making on the basis of unambiguous and transparent inspection results.

Although establishing procedures and creating the tools necessary for uniform reporting would initially require health authorities to dedicate additional resources to their inspection efforts, once these measures are in place, there would be immense increases in efficiency for health authorities. Once standardized, internal systems for the monitoring and management of inspections can be aligned and, if desired, even communicated with those of other regulatory authorities. Additionally, with a clearer understanding of the meaning of inspection results, and thus the compliance status of the operations ongoing at a facility, health authorities may dedicate their scarce inspectional resources to those facilities that need the greater regulatory oversight. Most significantly, uniform reporting of inspection findings would facilitate mutual recognition of inspections, which would greatly

[1] *This position paper should be understood in the context of harmonization of GMP requirements and inspection processes in the EU, protection of exchanged trade secrets, confidential commercial information and sufficiency of conflict of interest rules and procedures in the EU. The text is also included in the PhRMA White Paper: Mutual Recognition of Drug GMP Inspections by U.S. and European Regulators' as addendum and was submitted to FDA 15th May 2015.*

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increase the number of facilities for which regulatory authorities have up-to-date compliance information.

EFPIA and PhRMA believe that the inspection report template described by the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) (together "PIC/S") is the most appropriate means for the standardized reporting of inspection findings. It provides for inspectors' observations to be summarized and provides a basis for the harmonized classification of inspected sites.

Standardised inspection report template

There are numerous and substantial benefits for both regulators and industry in standardizing the format of inspection finding reports and establishing clear timelines for report issuance. (Our proposal regarding these timelines is set forth in Annex II.) Regulators would be better able to assess the scope, potential issues and strengths identified, and the final outcome of all inspections, even those conducted by inspectors from another jurisdiction with unfamiliar laws and regulatory practices. This increases transparency and reliability of inspection findings, which would assist regulators in planning risk-based inspections and ensuring they are not using limited resources to inspect facilities with strong compliance records.

EFPIA and PhRMA understand that some health authorities may be legally required to use a specific format for their inspection reports. Even so, we have experience with each of the formats used in different jurisdictions and believe they allow for sufficient modification such that the proposals we advance below could nevertheless be adopted in those jurisdictions.

The following aspects are regarded helpful and should be expressed as elements of a standardized inspection report:

- The report should include a summary and conclusions, including a finding of whether the company operates in compliance with good manufacturing practice (GMP).
- To assist other health authorities in not dedicating excessive scrutiny to aspects of a site's operations that are fully compliant, and in the interest of a balanced findings, the report should include a description of the areas in which the manufacturing site is performing well and in compliance with current GMPs.

An **ideal standardized inspection report** should include the following information in general:

- **Inspected Site(s)**
  - Name and full address of the inspected site (including a DUNS-Number)
  - Activities performed by the company / Site Master File (SMF) Assessment
  - List of annexes attached (e.g. list of observations)

- **Administrative Details**
  - Inspection date(s)
  - Name of the agency performing the inspection
  - Inspection reference number(s), if applicable
  - The reason for the inspection
  - Name applied legal and regulatory standards (e.g. WHO, EU-GMP, US)
  - Name of Inspector(s) and expert / assessor
  - References to relevant Site and Product Regulatory Licences
  - A reference to the previous inspections at the site by the inspecting authority and other regulatory parties (the latter information could be obtained from the company)

- **An Executive Summary of the Current Situation**
  - Short description of the inspected operations and further activities of the site not in the scope of the inspection
  - Any relevant future changes to business
  - Short description of the critical and major issues identified with the inspected operations
  - Short description of strengths of the inspected operations
  - Initial conclusion with the overall risk ranking of the inspected operations
  - Preliminary statement as to whether or not the company operates in accordance with GMP requirements

- **Annexes**
  - List of observations with risk ratings and, if a corrective action is expected, an indication of that fact
  - Samples taken, if any

As a longer-term goal over the next five years, EFPIA and PhRMA believe that it would be extremely beneficial for global health authorities to agree to and mandate one standardized template for the inspections by all participating regulatory agencies. In addition, the use of a common language (e.g. English) in inspection reports would greatly assist all health authorities. In the nearer term, it could be helpful if at least the summaries of inspection reports could be provided in English.

Informed drafting of observations

Daily wrap-up meetings in which the inspectors provide information on the findings being made as the inspection progresses should be provided. Inspectors should also communicate all observations at least verbally at the closing meeting and discuss them thoroughly with site personnel. The discussions at the daily wrap-up and closing meetings would help to educate the regulated industry and would significantly decrease the risk of misunderstanding and permit any errors to be corrected before the inspectors' findings are finalized in the written inspection report.

We note that some health authority inspectors provide personnel from the inspected site with the opportunity to review all written observations in draft form prior to finalization. This is a best practice that enables findings to be fully understood and helps to ensure the observations can be appropriately addressed in the inspected sites' responses.

EFPIA and PhRMA are aware that the ability of inspected sites to understand and act upon the findings made during inspections is occasionally impaired because the manner in which the findings are drafted, and the lack of communication with the site with regard to those findings, makes it difficult to understand the concern expressed by the inspectors. Accordingly, we wish to provide some suggestions with regard to the drafting of observations.[2]Industry gets the greatest benefit from observations if they:

- Carefully document the facts and provide the objective evidence (i.e. include the basic information necessary to establish who, what, when, where, and how)
- Explain the significance of the observation to product quality and patient risk (i.e. severity, probability, and detectability)
- Are succinct and clear
- Cross-reference other observations, if appropriate
- Consider the frequency of observation (e.g., "X out of Y occurrences," show a pattern or practice, etc.)

Most health authorities must link the observations made in their inspection reports to the enabling legislation of their jurisdictions. To facilitate the comparison and understanding of observations made by different regulators at the same site, however, it would be useful to have a way to link those observations to a universal set of GMP requirements. We believe that the best way to do this would be through a comparison chart of the local regulations with the chapters and annexes of the PIC/S GMPs.

[2] *For details see: PI 031-1/29-7-2009" and the "PIC/S inspection report format" PI 013-3/25-9-2007.*

Harmonised risk assessment and classification of observations

EFPIA and PhRMA also suggest that inspection reports indicate the criticality level of each observation, as defined below; to connect the compliance issue with the potential impact to patient safety. We suggest using a globally harmonized approach based on the principles of Quality Risk Management set forth in ICH Q9.

- **Critical observation (Risk level 1):**
  - A deficiency that has produced, or leads to a significant risk of producing a product which is harmful to the user or patient, **and/or**
  - The manufacturer has engaged in fraud, misrepresentation, or falsification with respect to the product or supporting data.

- **Major observation (Risk level 2):**
  A non-critical deficiency that:

  - Has produced or may produce a product that does not comply with its marketing or manufacturing authorization and/or established specifications;
  - Indicates a major non-compliance (e.g. a repetitive or permanent departure from a GMP provision or regulatory expectation);
  - Indicates a failure to follow satisfactory procedures for release of batches or a failure of the authorized person or quality unit to fulfil their required duties; or
  - Is a combination of individual deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

- **Other (minor) observation (Risk level 3):**
  - A deficiency that cannot be classified as either critical or major but which indicates a departure from GMP (e.g. isolated instances of non-compliance).

We believe that including “recommendations” is optional and should consist of any other notes the inspector may wish to offer with respect to best practices to potentially improve any procedures or processes. These recommendations should not be considered observations, and no formal response from the company would be required.

Harmonized definitions of observation classification would assist with consistent decision-making and evaluation of inspection observations by inspectors. This already is well established best practice in many countries in which inspectorates are organised into smaller local entities and oversight and country-wide coordination is provided on a national level (e.g. Germany and Japan).

Annex I: Proposal for a standardised format for listing observations

Inspectional observations made by inspectors in many jurisdictions are already provided in a standardized format and in an order that roughly tracks the PIC/S GMPs. EFPIA and PhRMA believe this represents a good starting point for discussions with inspected sites and makes it easier to follow and understand the observations. We would suggest that the following headings, which broadly follow the chapters of the PIC/S GMP guide, should be adopted in a standardized inspection report:

- Pharmaceutical Quality System and Quality Management
- Personnel
- Premises, equipment, and level of computerized systems
- Documentation
- Production, including the level of process/product design and development (implementation of QbD, CPP/CQA identification, status of validation activities, etc.)
- Quality Control
- Outsourced activities
- Complaints and product recall
- Self-inspection[3]
- Distribution and shipment (i.e., Good Distribution Practices)

Annex II: Proposal for harmonising the inspection process

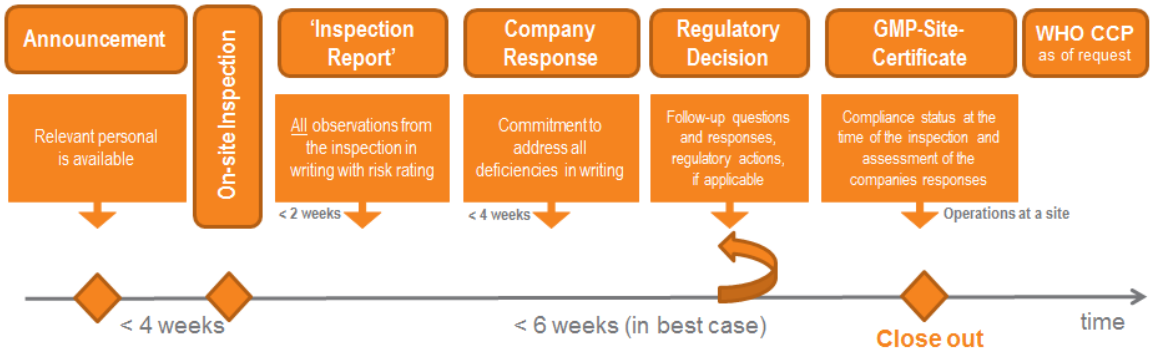
EFPIA and PhRMA believe that effective and efficient regulatory inspections are critical for ensuring compliance with regulatory standards by all drug/medicinal product manufacturers to assure the quality of these important products and give patients full confidence in the medicines they take.

As industry we understand that an "inspection report" is currently issued by individual health authorities at different times in the post-inspection process. Inspectors often either provide the list of observations in writing directly after the on-site inspection (e.g. US FDA 483 for "critical" and "major" observations) or two weeks following the inspection (e.g. EU "Inspection report"). Decision making based on the inspection findings is more varied, with numerous different regulatory systems in the various jurisdictions.

We believe that the following process for communicating of and responding to observations should be adopted in all participating jurisdictions and would permit greater harmonization in inspection and post-inspection processes (N.B. We recognize that amendments of existing legislation and regulatory policies may be necessary in many jurisdictions to achieve this outcome):

[3] *Evidence should be available during an inspection to show that self-inspections are conducted by the site following a pre-determined and risk-based frequency, but it is understood that the content of such self-inspections should normally remain confidential to the manufacturer in order to promote a culture of continuous improvement.*

Fig: Proposed process for communicating of and responding to observations



1. An announcement of the inspection is made to ensure availability of key staff at the site. (In some countries a prior announcement is a legal requirement.)
2. The ability to provide feedback on potential observations and the investigators' initial thoughts on the compliance status of the facility is provided at the end of the inspection and allow for clarification of misunderstanding or miscommunication.
3. The "inspection report" is issued within two weeks of the conclusion of the inspection, with all observations from the inspection in writing with risk rating. (If observations are only communicated orally at the closing meeting, there is an opportunity for potential misunderstanding and incorrect interpretations.)
4. The inspected site responds in writing to the observations within four weeks. In exceptional cases, authorities pose follow-up questions to the responses if they were not adequate or needed clarification. They may also take legal action, if needed.
5. To close out the inspection, health authorities deliver a "GMP-site-certificate" on the operations performed by the inspected site (including an updated "inspection report," as necessary).This should usually be issued within six weeks after the inspection, or if further investigations or legal actions may be necessary, in a timely manner with feedback to the site on the rationale for the delay.