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European Federation of Pharmaceutical Industries and Associations

Position Paper

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Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency

Executive Summary

EFPIA supports effective regulatory inspection systems for overseeing compliance with regulatory standards and medicinal products' quality, and to ensure that patients have confidence in the medicines they take. The pharmaceutical industry has become increasingly global and new risks have emerged such as falsification of medicines. As a consequence there has been an increased cooperation between regulatory agencies with respect to implementation of risks-based approaches by sharing intelligence, inspection activities and results. Despite this cooperation, an increase in duplication of inspection oversight at manufacturing sites[1] has been observed. This creates potential shortage of inspection resources to focus on higher risk areas of the supply chain.

EFPIA proposes that effective and balanced risk based regulatory oversight, allowing for improved resource utilisation, can be further enhanced by:

1. **Continued regulatory agency collaboration**
   - To drive harmonisation and optimise use of global inspection resources;
   - For domestic inspectorates to act as the primary overseeing body, and by mutual recognition of each other's systems or reliance of inspection outcome.
2. **Harmonised GMP and GDP standards**
   - To support consistent interpretation of regulatory requirements.
3. **Harmonised regulatory inspection processes** including:
   - Inspectorates certification process,
   - Inspection planning and documentation: standard data packs for on-site and paper-based inspections for faster provision of information, and better use of resources,
   - Risk based approach to inspection,
   - Inspection findings and reports: standard terminology for the categorisation of observations and standard reporting template,
   - Sharing of inspection results in database,
   - Globally accepted GMP/GDP certificate format to document compliance of an inspected site.

The EMA and PIC/S already provide guidance on elements of this in the Compilation of Community Procedures on Inspections and Exchange of Information, including the *´Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers´*. Full utilisation of the process by regulatory agencies together with continued collaboration globally will allow GMP/GDP inspections to be increasingly focussed and optimise the use of resources.

[1] EFPIA supporting data are available for presentation upon request

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1. Continued regulatory agency collaboration

EFPIA believes a balanced level of oversight is best achieved through well coordinated domestic regulatory inspections based on harmonised and standardised processes. These inspections shall take into account internal, supplier and 3rd parties audits managed by industry, and provide evidence on the status of the quality management system and compliance. This is the fundamental way to support patient's safety.

The research-based pharmaceutical industry supports domestic regulatory inspections, which are regarded as an efficient instrument to verify that medicinal products are manufactured and supplied in compliance with the relevant quality standards and regulatory filing. The content of such filings are similar in each country as they are usually submitted by industry based on a core document.

In recent years industry has seen an increasing number of inspectorates starting to perform their own foreign inspections. This has led to an increase in the number of inspections per site with limited additional value compared with the oversight provided by the domestic agency. This could be avoided by a coordinated approach and mutual reliance of regulators concerning each other's domestic regulations and inspections.

EFPIA recommends that:

- In the short-term, associations of inspectorates (e.g. PIC/S) are encouraged to continue their international training program, work in building trust and facilitating collaboration between agencies. Inspectorate resource management may be optimised through avoiding consecutive inspections on the same site and use of risk principles for scheduling inspection (see PIC/S PI 037-1)
- In the medium-term, industry and regulatory authorities should work together towards harmonised and standardised GMP/GDPs and inspection processes. Existing tools can be promoted and enhanced and new tools might be developed to support this, including the Site Master File (SMF), WHO-CPP, ICH guidance.
- Longer-term options could include mutual reliance and acceptance of a general GMP/GDP certification system, and international accreditation for regulatory inspectorates under the umbrella of an internationally recognised body.

2. Harmonised GMP and GDP standards

Harmonised standards would improve the consistency of implementation and interpretation of such standards across the globe. This may prevent new expectations evolving in an ad-hoc manner, sometimes beyond the written GMP/GDPs. The risk-based and life-cycle approaches as promoted by ICH Q9 and Q10 should also increase trust between parties to better manage the inspection activities. Opportunities for harmonisation and trust building between regulatory agencies may support concepts based on mutual reliance. Ultimately this will enable optimal use of regulatory agency inspection resources, focussing on the highest risks without compromising patient safety.

With the growing number of foreign inspections, there is increased variability among inspectorates and need for industry to adapt inspection management processes

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accordingly. Harmonisation among inspectorates would lead to efficiency for industry and authorities by strengthening global collaboration and harmonisation in the framework of e.g. ICH, WHO and/or PIC/S. There are opportunities for enhanced mutual reliance of GMP/GDP certificates based on inspection observations, reports, responses as well as sharing and coordination of inspection logistics. It is EFPIA's intention to encourage harmonisation of inspections' process introducing the concept of oversight by cooperating competent domestic inspectorates.

EFPIA member companies sometimes observe inconsistent or diverging interpretation of regulation by inspectors. Occasionally inspectors ask for requirements beyond written standards, i.e. not mandatory recommendations or guidance not yet effective. Opportunity should be given to address such issues in an open, scientific discussion between the company and the inspector. This includes different understanding of an inspector with the commitments approved in the regulatory filing. It should be accepted that companies ask for clarification over divergent interpretations of the respective legal references, and in case an observation is made. Short-term benefits will result from an optimised use of resources, reduced costs and through a harmonised and consistent interpretation of GMP/GDP standards across regions taking into account local obligations. Industry is supportive of such initiatives as this will leverage both, management of inspection activities and control of risk to patients.

3. Harmonised regulatory inspection processes

Inspectorates certification process

Global accreditation systems are in place specifying requirements for the competence of bodies performing inspections and for the impartiality and consistency of their inspection activities, e.g. as laid down in ISO 17020. Although a voluntary certification of an inspectorate is required for PIC/S membership, a longer-term option might include inspection authorities working together towards an international accreditation process under the umbrella of an internationally recognised body (e.g. WHO).

Inspection planning and documentation

EFPIA member companies see an increasing number of requests to submit more and more detailed documentation to regulatory agencies prior to an inspection and/or for paper-based inspections. Companies have to deal with agency specific requests and questionnaires resulting in administrative issues, which are regarded as resource intensive with no added value. Translation into local language is occasionally requested which can create some misunderstanding.

Standardised preparation documentation packages are recommended for faster provision of information, better facilitation and use of resources. Standard documentation packages might help to tailor inspections with regard to their depth, breadth and duration or trigger waiving of an inspection. EFPIA suggests using existing reporting tools:

- Site related: **Site Master File (SMF)** according to PIC/S for information about the site, including the facilities, products, validation concepts, people and organisation.

- Product related: **Annual Product / Annual Quality Reviews** of product(s) within the scope of inspection. These include information about recalls / withdrawals, product complaints, change control and validation assessments.
- Quality System related: **Quality Manual** with an appropriate overview of the Quality System and its elements implemented at the site.
- Additional compliance information: valid GMP/GDP-certificates for the site; list of inspections, list of internal audits and number of customer / contractor audits.

In the medium-term, industry requests more standardised inspection processes. Standardised documentation packages might be prepared and transmitted in a way similar to the concepts used for regulatory eCTD submissions (acc. ICH M2). Confidentiality would have to be addressed in a proper way.

Inspections conduct: risk based approach

Industry has observed consecutive GMP/GDP inspections at the same site while many other sites are not being inspected due to lack of resources. EFPIA member companies have noted that there is virtually no difference in process between a product specific or system based inspection, or whether it is performed by a foreign or domestic authority. In all cases, about 80% of the time is spent on topics already covered during other inspections of the same site. Inspection time is generally distributed as follows: 30% on a ´plant tour´, 30% on quality management and about 20% on quality control. The remaining ~20% is used to address country specificities and processes (e.g. batch release, contracts).

Improved coordination processes and application of risk based approaches might allow either waiving foreign inspection or optimising the time such valuable resources can use to inspect more sites.

Inspection observations and reports

While the ranking of inspection observations is different across agencies, there is a high level of convergence in the naming of the findings, i.e. 'critical´, ´major´ or ´minor', and the ´recommendations´ (e.g. Community procedures, EU-NCA, TGA, PIC/S, TGA, Health Canada, and Switzerland). Similar naming conventions are applied by industry for their rating of audit observations. EFPIA supports initiatives aimed at standardising the terminology used and international codification of observations. We support the PIC/S concepts to issue documents promoting consistency (e.g. through aide memoires, Q&As). Industry is willing to contribute and to provide feedback to such publications. Furthermore we would welcome inspection findings to be substantiated by their respective legal references. Positive findings should also be cited in reports.

A statement of conformity on the inspection outcome is expected but not always provided at the conclusion of an inspection. The overall outcome of an inspection should be clearly stated in inspection reports. We understand that today some inspectorates prefer a non-standardized verbal assessment. In the medium-term standardised inspection reports should include an unambiguous conformity statement on the overall outcome of an inspection. Sharing of standardised inspection reports and companies responses can be a longer-term opportunity, if confidentiality is addressed in a proper way. The outcome of an inspection and the company's responses could be shared as a statement in inspection databases.

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Sharing of inspection results in databases

EFPIA appreciates the establishment of a database on inspection results. The EudraGMP database is considered as a source of compliance / non-compliance information of sites inspected globally. We encourage regulatory agencies from outside the EEC and MRA countries to participate and use this platform. Furthermore we suggest supplementing the databases with information on the global product number (ISO IDMP) as soon as it is implemented.

GMP/GDP certificates

Certificates are needed for registration purposes and required for receiving a licence to operate in many countries. Industry sees a need for such certificates to be issued in a timely manner after the successful completion of an inspection and to include all the relevant information to access markets. Certification systems have proven to be efficient in other areas (e.g. narcotics, aviation industry, nuclear power industry). PIC/S member inspectorates have the opportunity for alignment, as other inspectorates are issuing and/or relying on WHO CPP certificates (acc. Chapter 3ff). As a longer-term option, EFPIA advocates the use of a globally accepted GMP/GDP-certificate format to demonstrate compliance of an inspected site; such certificates should further become available from a public database.

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