European Federation of Pharmaceutical Industries and Associations

Position Paper

final – 12. November 2024

Enhanced Good Manufacturing and Distribution Practices (GMDP) Inspection Efficiency

Executive Summary

EFPIA member companies support effective regulatory inspection systems for overseeing compliance with regulatory requirements to ensure that patients have confidence in the medicines available. The pharmaceutical industry is globally networked, and emerging risks must be controlled such as falsification of medicines. Therefore, there has been an increased cooperation between regulatory agencies with respect to implementation of risks-based approaches by sharing intelligence, inspection activities and results and to conclude confidentiality agreements between agencies and Mutual Recognition Agreements (MRA) between governments to recognise inspection results. Despite these cooperations, an increase in the number of inspections including duplication at manufacturing sites has been observed.[1,2] This creates diversion of resources who could focus on higher risk areas in the entire supply chain.

Fédération Européenne
d'Associations et d'Industries
Pharmaceutiques

Neo Building
Rue Montoyer 51
1000 Bruxelles (Belgium)

T +32 2 626 25 55
F +32 2 626 25 66
www.efpia.eu
info@efpia.eu

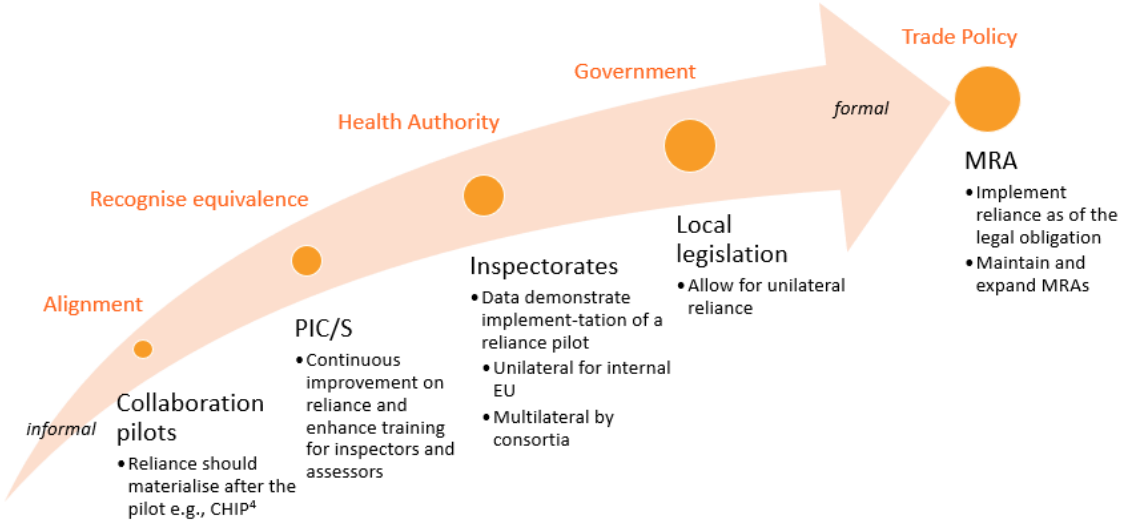
TVA
BE.418.762.559

Proposals

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

1. **Continued and focused regulatory agency collaboration**
   - To drive harmonisation and optimise use of global inspection resources
   - For domestic inspectorates to act as the primary overseeing body, and building or make use of appropriate legal pathways towards unilateral or mutual reliance

Fig 1: Pathways to reliance on domestic inspections overcoming likely perceived legal hurdles



Implement prior knowledge to reduce inspections, length and topics

2. **Harmonised GMP and GDP standards**
   - To support consistent interpretation of regulatory requirements.

3. **Harmonised regulatory inspection processes**
   - Implement effective risk-based procedures for faster provision of information, and better use of resources, covering e.g., the Inspectorates' certification process, Inspection planning and documentation incl. standard data packs for on-site / document inspections, deficiencies and reports using standard terminology for the categorisation of observations and reporting templates with comparable content, public data bases with up to date GMP/GDP certificates certifying compliance of an inspected site.

The EMA and PIC/S already provide guidance on elements of this in the Compilation of Union Procedures on Inspections and Exchange of Information[3]. Full utilisation of the process by regulatory agencies together with continued collaboration globally will allow GMDP inspections to be increasingly focused and optimise the use of resources.

Lessons learned from pilot projects and from health emergencies and crisis e.g., pandemic, led authorities to apply continuous oversight using different inspection modes in addition to the on-site inspections, like remote inspections, hybrid inspections, document-only inspections. This results in the opportunity to implement such risk-based approaches as routine procedures.

Conclusion

It is time now: Several pilots[4] and public health emergencies (e.g. pandemic) have demonstrated the possibility to accept the inspection outcome of different inspection modes such as e.g., remote inspections or unilateral reliance on domestic inspections by trusted authorities right away. EFPIA member companies see opportunities to improve the regulatory inspection processes of the manufacturing and distribution of medicinal products. Efficient risk-based and life-cycle approaches to inspection should focus on how to best control the risks to patient safety and quality of medicines. Inspectorates may optimise tools and guidance based on e.g., ICH Q9 (R1) to guide reliance.

Continued and focused regulatory agency collaboration can be achieved by working together to harmonise, standardise and implement GMDP inspection principles and related processes including inspection outcomes. Reliance on each other's domestic inspections and certificates is the goal. Using existing platforms and tools, such as EudraGMDP and elements provided by PIC/S and WHO should facilitate information sharing and reliance. Harmonised regulatory expectation on innovative approaches used in development, manufacture, and supply of medicines such as manufacturing platform technologies, artificial intelligence/machine learning, agile manufacturing, continuous manufacturing, and new technologies, e.g., viral vector platforms and mRNA can enhance the quality and performance of the manufacturing, distribution and industrialisation processes.

Environmental and sustainability aspects (less water, energy, worker safety etc.) are regulated outside the GMPs/GDPs and should be kept separated of GMP/GDP inspections.

All above points for consideration would be well included in the guidance documents by EMA resulting from future EU General Pharma legislation and upcoming guidance under discussion.

We recommend staying aligned with existing principles, allowing for advances of risk-based approaches while keeping flexibilities to regulatory submission/ filing, approval, certification, and reporting processes. Furthermore, regulatory requirements shall be used if there is something to regulate and not outsource to – for-profit - standard setting and certification organization (e.g., ISO standards).

Annex

1. Continued regulatory agency collaboration towards reliance

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, convergent quality standards and regulatory applications. The content of such application is similar in each country as they are usually submitted by industry based on one core document.

EFPIA member companies believe a risk-based and balanced level of oversight is best achieved through well-coordinated domestic regulatory inspections based on convergent and standardised principles for processes overcoming perceived legal hurdles. This is the fundamental way to support patient's safety. To enhance knowledge, regulatory inspections can also consider results of internal, supplier and 3rd parties audits managed by industry, which may provide evidence on the status of the quality management system and compliance.

However, year after year industry has seen an increase in number of inspectorates performing foreign inspections on their own. This has led to an increase in the number of inspections per site with limited additional value compared to the oversight provided by the domestic agency[2]. We have an opportunity to increase efficiency by a coordinated approach and unilateral reliance of regulators concerning equivalence of each other's domestic regulations and inspections processes.

EFPIA recommends that:

- In the short-term, PIC/S as a not-for-profit Swiss association (inspectors only) are encouraged to continue their harmonisation efforts and international training programs, including for assessors, and should continue to facilitate collaboration between agencies. Inspectorate resource management may be optimised through deferring inspections on the same site and use of risk-based principles for scheduling inspection (see PIC/S PI 037-1)[5] and implementation and expansion of Mutual Recognition Agreements to also reduce the environmental footprint (CO_2 emissions[2]) during traveling. This includes inspections announced as pre-approval as reliance QMS/PQS processes are equivalent covered by the domestic inspectorate. Different inspection modes may allow to significantly shorten inspection time and resources by focusing on the specific questions a reviewer may have communicated to the inspector.
- In the medium-term, industry can support regulatory authorities to continue work together towards convergent and perhaps standardised GMP/GDPs and inspection processes. Existing effective tools can be promoted and enhanced. New tools might be developed and implemented and accepted in support, including standardised document packages for inspection preparation to shorten the inspection time spent on-site, like Site Master File, etc., see Section 3.
- Longer-term options could include full trust in local authority inspectorates' local GMP/GDP certification system based on an international accreditation for regulatory inspectorates under the umbrella of an internationally recognised body (e.g., PIC/S or WHO).

2. Harmonised interpretation of GMP and GDP standards

EFPIA member companies sometimes observe inconsistent or diverging interpretation by inspectors of their established processes. Occasionally, inspectors may ask for requirements beyond regulatory guidance and laws, i.e. enforcing own 'best practice' recommendations or guidance not yet effective.
It is EFPIA's intention to encourage harmonisation of inspections' process introducing the concept of oversight by cooperating domestic, competent inspectorates. The growing number of foreign inspections drives variability in interpretations among inspectorates and the need for industry to adapt inspection management processes accordingly. Coordination among inspectorates would lead to efficiency for industry and authorities by strengthening global collaboration. There are opportunities for enhanced reliance on GMP/GDP certificates based on inspection observations laid down in inspection reports and responses. These can be supported by coordinated planning of upcoming inspections or even that a 3rd country inspectorate joins an inspection remotely for a specific part as of the agenda.

Harmonised guidance and Q&As would further improve the consistency of implementation and interpretation of such requirements 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 (R1) have increased trust between parties to better manage the inspection activities. Opportunities for harmonisation and trust building between regulatory agencies should continue in supporting concepts based on reliance. Ultimately, this will enable optimal use of regulatory agency inspection resources, focussing on the highest risks without compromising patient safety or product quality.

Opportunity should be given to address such issues in an open, scientific discussion between the company and the inspector. This includes differences in interpretation an inspector has with the commitments approved in the regulatory filing during the authorisations processes e.g., definition of the API starting material. Companies would welcome the opportunity to ask for clarification over divergent interpretations of the respective legal references, and in case an observation is issued[6] . Short-term benefits will result from an optimised use of resources, speed to market, and through a harmonised and consistent interpretation of GMP/GDP standards within and across regions considering local obligations. Industry is supportive of such initiatives as this will leverage both, management of inspection activities and control of risk to patients.

3. Towards reliance on regulatory inspection processes

Inspectorate certification process

Globally accepted stringent regulatory authorities can make a difference. There are already processes in place (e.g., PIC/S, WHO-GBT, ISO certifications) which facilitate this understanding. They are 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. We underline that a voluntary certification system of an inspectorate is already required for being a PIC/S participating inspectorate. A longer-term option might include inspection authorities

working together towards an internationally accepted accreditation process under the umbrella of an internationally recognised body (e.g., WHO). A valuable start is made establishing a ranking system of agencies under the Global Benchmarking Tool of WHO[7].

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 on-site inspection and/or for document inspection for both, routine and pre-approval inspections. Companies must deal with agency's very specific requests and completing dedicated questionnaires resulting in administrative burden, which are resource intensive with no added value for the patient. Translation from local language to the inspectorate language or into English is often requested which can create misunderstandings.

Therefore, we are recommending standardising the preparation packages to allow for faster provision of information, better facilitation, and focused use of resources. Such standard documentation packages might help to tailor inspections regarding their depth, breadth and duration or trigger deferring of an inspection. The answers to the EFPIA inspection survey demonstrated communalities among different inspectorates. As a result, we suggest the following documents as part of a standard package[2]:

- **Common documents requested in surveillance and pre-approval inspections (PAI)**
  - Site Master File
  - Annual Product Review
  - Quality Manual
  - Inspection History
  - List of Deviations
  - List of Major Changes
  - List of Recalls
  - List of Quality Agreements

- **Additional documents usually requested in PAI**
  - Process Flow Diagrams
  - Product Specifications
  - Validation Documents
  - List of countries where the product is approved
  - List of Laboratory OOS results

EFPIA suggests using safe and secure ways for document sharing with the regulators. Standardised documentation packages might be prepared and transmitted in a way like the concepts used for regulatory eCTD submissions (according to ICH M2/M8). Confidentiality and cyber security would have to be addressed in a proper way.

Inspections to conduct using enhanced risk-based approaches

Industry has observed consecutive GMP inspections at the same site(s) while many other sites are not being inspected due to lack of resources from the inspectorates. EFPIA member companies have noted that there is virtually no difference in process between a so called '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 resulting in similar observations[2]. Inspection time is generally distributed as follows: 30% on a ´plant tour´, 30% on quality management system implementation and about 20% on quality control and drug shortage management. The remaining ~20% is used to address country specificities and processes (e.g. batch release, contracts)[1].

Improved coordination processes and application of risk-based approaches might allow either deferring foreign inspections or optimising the time by focusing on subjects not yet inspected by other authorities. Valuable resources can then be used to inspect more sites not covered so far.

Inspection observations and reports

While the ranking of inspection observations is formally 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´. 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) and perform training for inspectors. Industry is willing to contribute and to provide feedback to such publications and training materials. Furthermore, we would welcome inspection findings to be substantiated by their respective legal references.

Industry would welcome notification of positive, state of the art, improvements or even outstanding practices in inspection reports, that will be beneficial for the reliance and in building trust in the companies and among inspectorates.

A statement of conformity on the inspection outcome is expected but not always provided at the conclusion of an inspection. PIC/S and EMA have established a balanced risk-based approach by defining a proposed period when the next inspection should be performed which could be communicated as a ranking system and used as a metrics of the overall compliance assessment of the inspected site.[8] Anyhow, the overall outcome of an inspection should be clearly stated in inspection reports. We understand that as of today some inspectorates may prefer a non-standardized verbal assessment. In the medium-term standardised inspection reports may include an unambiguous conformity statement on the overall outcome of an inspection at the time the inspection was performed. 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 could be shared as a statement in inspection databases. In case an inspection report is documented in an agency internal or shared system the company's responses should be included.

Sharing of inspection outcomes

EFPIA appreciates the establishment of a database on inspection results. The EUDRA-GMDP database is considered as a reliable source of compliance / non-compliance information of sites inspected globally. We encourage regulatory agencies from PIC/S participating authorities to contribute, use and maintain this platform or establish a reference to allow reliance. Furthermore,

we suggest supplementing the databases with information on the global product number (ISO IDMP) as soon as it is implemented.

Supporting inspection readiness EFPIA member companies would welcome inspectorates and or PIC/S to publish annual updates of major observations to allow focused preventive actions and stay aligned with current interpretations of existing guidelines. Examples of best practices may include the publication by MHRA[9] , ANSM annual report or the availability of FDA 483 citations.[10]

Sharing known compliance gaps identified by companies

There can be the opportunity to access previous inspection reports. Independent from inspections, the industry can and do share known compliance gaps in the documents requested in surveillance and pre-approval inspections. Lists of deviations/Corrective and preventive actions as well as an appropriate Annual Product review are valuable sources of information[3].

GMP/GDP certificates

Certificates confirming GMP/GDP compliance are needed for registration purposes and in the variation process. They are 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. They should include all the relevant information to allow market access. EFPIA advocates the use of a globally accepted GMP/GDP-certificate format e.g., based on the PIC/S template[11] to demonstrate compliance of an inspected site at the time of inspection. They may also contain a compliance risk-ranking of the inspected site / processes similar as available for hygiene standards of restaurants in some countries, e.g. UK[12]. Such certificates should be retrievable from open access data bases e.g., EudraGMDP data base.

Innovations to drive advances in GMP/GDP

EFPIA member companies are committed and advocate innovative approaches for the development, manufacture and supply towards an optimised high quality of medicines. This includes:

- **Developing manufacturing platform technologies**

  This is covering end-to-end manufacturing processes from API to the medicinal product and associated information in the marketing authorization applications, for either chemical or biological molecules. The platform can be used to warrant the registration process as well as GMP and inspection aspects.

- **Implementation of Artificial Intelligence/Machine Learning in manufacturing**

  This would allow to optimize the quality and performance of manufacturing and distribution processes to be fit-for-purpose, risk-based, non-duplicative, globally aligned, and adequately tailored.

- **Implementation of agile manufacturing**

  The concept of Central and Decentralized Sites offers benefits as the Decentralized Site could rely on the Central Site for registration, inspection and GMP status, thus allowing supply of

medicines where the patients are in need. This would potentially reduce the number of inspections.

* **Adopting continuous manufacturing**

  This focus on the integrated system where two or more operations are directly connected. This leads to gains in efficiency, agility and flexibility on API and medicinal product manufacturing.

* **Introduction of new technologies and modalities**

  This includes viral vector platforms, mRNA technologies to drive new treatment options.

References

1 EFPIA annual inspection survey

2 EFPIA inspection survey 2023 data

3 EMA Compilation of Union procedures on inspections and exchange of information

4 Inspection pilots incl. e.g.: Access Consortium; CHIP (Collaborative Hybrid Inspection Pilot): EMA-inspection pilot 1/pilot 2

5 A recommended model for risk-based inspection planning in the GMP environment PIC/S PI 037-1, 01. January 2012

6 Proposed process to flag inspection inconsistencies, EFPIA Position Paper, September 2024

7 WHO Global benchmarking tool

8 A recommended model for risk based inspection planning in the GMP environment PI 037-1 and EMA

9 MHRA deficiency reporting

10 ANSM inspection practice

11 PIC/S Inspection report format PI 013-3, Annex 1, 25 September 2007

12 UK Food hygiene rankings