

# Regulatory Authority Inspection Comparison

Regulatory inspections can be a source of uncertainty for many organisations. This guide will give you an insight into what to expect during a regulatory inspection. The differences in the approach taken by three of the main regulatory authorities and PIC/S, as the co-operative body of 56 Regulatory Authorities, are explored in detail. Whilst some differences still remain, it is clear that the focus on Quality Culture and Quality Management Maturity is common.

## US FDA

- There are 3 general categories of inspections:
  - **Surveillance** (also called routine or post-market) inspections, are conducted to generally determine or monitor a firm's compliance with regulatory requirements. Surveillance inspections are prioritised using a risk-based model ([5014-1Rev-1-Risk-BasedSiteSelection-7-12-2023.pdf \(fda.gov\)](#)).
  - **Pre-approval**, pre-market, or pre-license inspections, are conducted as part of the review of an application to market a new product.
  - **For-cause** inspections are prompted when there is reason to believe a facility has serious manufacturing problems, or to investigate a specific complaint that has come to FDA's attention. These are prioritised over surveillance inspections.
- FDA's approach to domestic inspections is typically unannounced site visits. Foreign inspections usually allow for 10-12 weeks advance notice. However, in 2022, FDA launched an initiative to increase the number of unannounced inspections for foreign countries, focussing on regions associated with a historic pattern of quality challenges/non-compliance and in countries where the FDA have a team of local inspectors (e.g. India and China). For general guidance see [Regulatory Information | FDA](#).
- FDA may occasionally perform remote inspections but typically prefer to inspect on-site.
- Investigators follow the Investigations Operations Manual Chapter 5 & 8 [Investigations Operations Manual | FDA](#)
- For Foreign Inspections, investigators follow the guidance for Establishment Inspection, Chapter 3: [Foreign Inspections | FDA](#)
- FDA also follow Compliance Programs based upon product profile types, e.g. [Compliance Programs \(CBER\) | FDA](#) (biologics) and [Drug Compliance Programs | FDA](#) (pharmaceuticals).
- Additional general guidance on FDA inspections can be found at [Pharmaceutical Inspections and Compliance | FDA](#)
- FDA will issue a "Notice of Inspection" (FDA Form 482 for domestic firms in the US) upon arrival to the most Senior level of site authority. For Foreign Inspections, FDA Form 482 is not issued, except for inspections of U.S. military blood banks in foreign countries.
- For CBER-regulated biologics, the lead CMC reviewer (often with aseptic manufacturing/microbiology expertise) leads the inspection and is likely to have significant product and process background information leading into the inspection, allowing them to focus inspection areas on high-risk areas. This is not usually the case for small molecule facility inspections.
- Investigators will often use a methodical approach by asking questions that lead to another question, "peeling the onion".
- The inspection usually runs as follows:
  - Introduction detailing the purpose of the inspection.
  - Facility tour.
  - Document review is a big focus for FDA investigators, more so than other inspectorates.
  - Daily closing meetings to discuss findings and confirm agenda for the next inspection day. There will be opportunities for the site to rectify potential findings before the conclusion of the audit.
  - End of inspection close-out that may include inspectional findings on FDA 483.
  - The site will then have 15 days to formally reply with a holistic and comprehensive corrective and preventative action plan to address all observations.
- Following review of responses / CAPA, the agency will determine if the facility is in compliance with applicable laws and regulations and classifies the inspection. The **three classifications** are:
  - **No action indicated (NAI)** – no objectionable conditions or practices were found.
  - **Voluntary action indicated (VAI)** – objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action.
  - **Official action indicated (OAI)** – regulatory and/or administrative actions are recommended.





### EMA

- EMA initiate inspections for Centrally Authorised product. The EMA contracts out inspections to different Member States.
  - Inspectors allowed to conduct the Inspections are identified as European Experts and their CVs are available on the EMA website along with their Declarations of Interest: European experts | European Medicines Agency (europa.eu)
  - Sites to be inspected often receive reasonable notice, usually 4 weeks in advance of the inspection.
  - Inspections are likely to be risk based and assess compliance:
    - to EU GMP EudraLex - Volume 4 - European Commission (europa.eu)
    - to EU GMP Q&As Guidance on good manufacturing practice and good distribution practice: Questions and answers | European Medicines Agency (europa.eu)
    - to ICH guidelines ICH Official web site: ICH
    - to EMA's CHMP/CVMP guidelines on Quality.
    - In addition, they may lean heavily on the PIC/S Aide memoires Publications (picscheme.org)
  - The primary aim of the inspector is to determine if the quality systems are effective, in compliance with GMP and determine if products comply with their marketing authorisation.
  - EMA will often be direct with questions to get to the “core” issue instead of asking questions that lead to other questions.
  - The inspection will be in line with the process detailed in the Compilation of Union procedures Compilation of Union procedures on inspections and exchange of information | European Medicines Agency (EMA) (europa.eu), previously known as the Compilation of Community procedures.
  - Compliance to the Compilation of Union Procedures is ensured through the Joint Audit Programme Joint Audit Programme | European Medicines Agency (europa.eu)
  - Prior to the inspection, the inspector is likely to review products manufactured / imported by the company being inspected, the previous inspection report, the marketing authorisations and any variations pending approval or recently approved.
- The inspection usually runs as follows:
    - Opening meeting during which the inspector will outline the purpose and scope of the inspection and identify up front some of the key documentation likely to be required during the inspection.
    - A concise company presentation should include the management structure of the organisation, the status of CAPA from previous inspections by this competent authority and an overview of any significant changes in facilities, equipment or personnel since the last inspection.
    - Opening meetings should be attended by senior management – this gives a good initial impression and demonstrates understanding of Eudralex Volume 4 Chapter 1 PQS.
    - A facility tour, usually following the logical flow of materials through the facility, will be expected. In some cases, a rapid plant tour may be followed by a more detailed tour focussing on specific areas of interest. Inspectors will speak directly to individuals executing the operation being observed to assess competency and understanding. This should not be seen as a negative, this is inspectors trying to understand the process and operational activity.
    - Document review will cover the whole suite of documentation supporting batch release.
    - Observations are likely to be discussed as they arise to ensure the facts are established with key personnel and subject matter experts.
    - A final closing meeting will be held to discuss deficiencies observed and their classification. Timelines and requirements for progression through to closure of the inspection will also be outlined.
  - A formal report will be issued in a standard template good-manufacturing-practice-gmp-inspection-report-union-format\_en.docx (live.com). Observations are classified as:
    - **Critical** – significant risk of producing a product which is harmful
    - **Major** – does not comply with MA, deviates from GMP, failure of a QP to fulfil their legal duties, a combination of several ‘other’ deficiencies
    - **Other** – not critical or major but a departure from GMP
  - Following review of the company responses, if acceptable, a GMP certificate will be issued within 90 days.

### UK MHRA

- MHRA have been operating a risk-based inspection programme since 2009. The GMP risk rating of a site is based on the compliance report, internal information about previous inspection history and organisational changes.
  - New sites, high risk formulations (e.g. Biological, Sterile), and previously non-compliant sites will be prioritised.
  - MHRA require the site to complete a GMP pre-inspection compliance report before an inspection, unless it is a triggered inspection, which are only notified at short notice.
  - Guidance for completing a pre-inspection compliance report, including compliance report templates, can be found on the MHRA website <https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice>
  - The pre-inspection compliance report requests information on all changes since the last inspection as well as an overview of personnel, products, processes, facilities, equipment, data integrity and any upcoming changes that the regulator should be aware of\*.
  - Prior to the inspection, the inspector is also likely to review products manufactured / imported by the company being inspected, the previous inspection report, the marketing authorisations and any variations pending approval or recently approved.
  - The approach of MHRA is closely aligned to that of EMA in that the primary aim of the inspector is to determine if the quality systems are effective, in compliance with GMP and if products comply with their marketing authorisation. Inspectors will often ask the same questions to different personnel – this is to gain confidence that approaches are consistent.
  - MHRA will also ensure compliance with Brexit specific requirements and, in the case of sterile or low bioburden products (either manufactured or imported), focus will be on compliance with revised Eudralex Volume 4, Annex 1 requirements.
  - The actual inspection will follow the same flow as for an EMA inspection.
    - Opening meeting to include a concise company presentation. Attendance by senior management creates a good impression and indicates an understanding the Eudralex Volume 4 Chapter 1 PQS.
    - A facility tour – prepare for this in advance, walking the route with relevant SME's before the inspection. Do not miss out ancillary areas such as plant rooms where critical utilities are housed.
    - Documentation review, returning to areas of interest on site if required. Ensure documents are provided in a timely manner and that they have been reviewed by an SME prior to sharing with the inspector – this ensures the SME is familiar with the document and is aware of any supporting documentation which may be referenced and requested for review.
    - Close out meeting – as observations will be discussed as they arise during the inspection, the close out meeting is not the time to discuss at length, or challenge, observations.
- A post inspection letter will be sent to the site confirming any deficiencies found, sites will respond to the inspector directly with a proposed CAPA plan including timelines. If accepted, the site will receive a GMP or GDP certificate with the final inspection report. Guidance on the approach to take for responses can be found at: Guidance on responding to a GMP/GDP post inspection letter – GOV.UK ([www.gov.uk](http://www.gov.uk))
  - An unacceptable response may lead to compliance escalation. Sites that are poor but where there is no immediate evidence of a critical deficiency are referred to the **Compliance Management Team** where the Inspectorate will support companies to achieve compliance.
  - If the threshold for regulatory action has been met, the **Inspection Action Group** (IAG) will manage the formal action against the Site or Product licences. More information on IAG can be found here: Inspection Action Groups – GOV.UK ([www.gov.uk](http://www.gov.uk)) The Inspection Action Group are multi-disciplinary team which meet to discuss inspection reports of sites where critical deficiencies have been identified. This is the highest level of escalation.
  - In 2022 a pilot program was launched for GMP/GDP remediation supervision by **Compliance Monitors** (independent consultants trained by MHRA) to reduce the burden in IAG. More information can be found here: Compliance Monitor process (Part 1) – An introduction – MHRA Inspectorate ([blog.gov.uk](http://blog.gov.uk))



\*MHRA expectation is that an Interim Compliance Report should be submitted between inspections following significant change or as requested by the inspector. Inspectors will assess the significance of changes reported and may move the planned inspection period based on the risk presented by the changes. However, the risk rating will only be changed after a subsequent inspection. Keeping the inspectorate updated via this report demonstrates a proactive approach to compliance and quality.

### PIC/S

- The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a co-operative arrangement between Regulatory Authorities in the field of GMP of medicinal products for human or veterinary use.
- Unlike ICH, only regulatory authorities can become a member of PIC/S.
- PIC/S presently comprises 56 participating authorities coming from all over the world (Europe, Africa, America, Asia and Australasia) and is increasing in number:
  - Argentina
  - Australia
  - Austria
  - Belgium
  - Brazil
  - Bulgaria
  - Canada
  - Croatia
  - Cyprus
  - Czech Republic (SUKL & ISCVBM)
  - Denmark
  - Estonia
  - Finland
  - France (ANSM & ANSES)
  - Germany (BMG & ZLG)
  - Greece
  - Hong Kong
  - Hungary
  - Iceland
  - Indonesia
  - Iran
  - Ireland
  - Israel
  - Italy
  - Italy Veterinary
  - Japan (MHLW & PMDA)
  - Korea
  - Latvia
  - Liechtenstein
  - Lithuania
  - Malaysia
- PIC/S also partners with EDQM / PhEur, EMA, UNICEF and WHO.
- PIC/S aims to facilitate networking between participating authorities, harmonise inspection procedures worldwide by developing common standards and providing training opportunities to Inspectors.
- Compliance: To join PIC/S, Competent Authorities must be able to apply an inspection system comparable to that referred to in this Scheme and 'whose requirements and procedures could ensure the proper implementation of the Scheme and contribute to its effective operation'.
- GMP / GDP: The development and promotion of harmonised GMP standards and guidance documents has been key for PIC/S – these common standards are critical to allow members to accept inspection results / have equivalent GMP systems.
- It is the role of the Sub-Committee on Harmonisation (SCH) to establish best inspection practices and harmonise the interpretation of GM(D)P to ensure consistency in inspection / audit practices.



- Malta
  - Mexico\*
  - Netherlands
  - New Zealand
  - Norway
  - Poland
  - Portugal
  - Romania
  - Saudi Arabia
  - Singapore
  - Slovak Republic
  - Slovenia
  - South Africa
  - Spain
  - Sweden
  - Switzerland
  - Taiwan
  - Turkey
  - Thailand
  - Ukraine
  - United Kingdom (MHRA & VMD)
  - USA
- Currently the following working groups are active in harmonisation projects:
    - ☐ Classification of deficiencies
    - ☐ Revision of Annex 1
    - ☐ Revision of Annex 2
    - ☐ Data Integrity
    - ☐ PI 006-03
    - ☐ PIC/S Blood Guidance
    - ☐ Controlling Cross-Contamination in Shared Facilities
    - ☐ PIC/S Aide Memoire on Tissues and Cellular Therapy Product Inspections
  - Inspectors are increasingly referencing PIC/S when inspecting sites within countries which are members of PIC/S but are not supplying the US / EU and therefore do not strictly need to comply with EU GMP / US CFR's. For example, the revised Eurdralex Volume 4 Annex 1 has been fully adopted by PIC/S members therefore manufacturing facilities within these countries are required to comply with the revised Annex 1 regardless of whether the product they manufacture is for supply to the EU / UK.



### Recommended Industry Approach to All Regulatory Inspections

- Sites should ensure inspection readiness at all times. If an inspection is due or delayed it may be prudent to perform an end-to-end audit of your facility, in addition to the regular self-inspection schedule.
- On receiving notification of a routine GMP inspections, sites should prepare by reviewing the previous inspection report and associated CAPA plan. If the inspection is by MHRA, a pre-inspection compliance report must be prepared and submitted. For all inspections, some information is likely to be requested prior to the inspection. Information should be accurate and provided to the inspectorate in a timely manner.
- For potential inspections by a regulatory authority new to the site, for example a PAI for launch of a product in the US, a gap analysis should be performed and, if time permits, a mock inspection can be extremely useful. Sites can utilise independent entities to act as the regulatory body or agency to assess the firm's current internal inspection readiness program or build an inspection readiness program.
- The gap analysis should focus on not only potential observations, but holistically review the differences between the regulatory guidance of the relevant authorities.
- Any gaps identified during a gap assessment / mock inspection should be addressed and corrected prior to the official inspection or have a robust CAPA plan documented in the QMS.
- It is recommended that inspection management, including proper communication, audit facilitation roles, and back room logistical support should also be included in readiness preparations. Delays due to retrieval of documentation or unavailable PPE to enter production areas, create a bad impression and breaks down trust between the host and the inspector.
- If the site is inexperienced at hosting regulatory inspections, consideration should be given to utilising external resources to aide running the back room.
- Site-wide training of personnel, particularly Subject Matter Experts and Area Owners, should be conducted to ensure personnel know what to expect and how to handle questions from inspectors. Utilising self-inspections to replicate this format is recommended so that answering questions factually and referring to site procedures / methods becomes standard practice.
- If no in-house experience of inspections exists, companies should consider independent entities, such as NSF, to assess the firm's current internal inspection readiness program or build an inspection readiness program. These activities should be proactive (ideally 2 to 3-months prior to any potential audit or inspection) and should "stress test" the entire process via a mock inspection.
- Mock inspections work best when they incorporate coaching / training sessions with Area Owners and key Subject Matter Experts.
- On an on-going basis, it is beneficial to gather regulatory intelligence of other firms which manufacture similar products to assess regulatory risk, industry trends and the FDA's current thinking - see FDA, EMEA and MHRA websites:

[Warning Letters and Notice of Violation Letters to Pharmaceutical Companies FDA](#)

[Inspections and compliance EMA Annual Report 2021 \(europa.eu\)](#)

<https://www.gov.uk/government/statistics/good-manufacturing-practice-inspection-deficiencies>

- This is also a good opportunity to update internal Risk Register / Risk Management Files to reflect any industry trends or regulatory intelligence findings relevant to your company.
- Remember to use your PQS to log deficiencies that you are aware of – inspectors are less likely to raise a deficiency for something you have already identified and recorded in your PQS (unless there is significant patient risk or a legacy issue was raised in the PQS after notification of inspection was received).

### Focus on Culture

- All inspections focus on a company's understanding of GMP. Investigators will often ask multiple personnel the same question in different ways to confirm understanding of a particular topic and to get a feel for the quality culture on site. Therefore, it is important to get full clarity on the question being asked or requests for documentation during the inspection as often mis understanding can lead to unintentional unrelated findings.
- In all cases, regardless of the inspectorate:
  - Inspections focus on a company's understanding of GMP
  - The GMP's defined in CFR's and Eudalex reference the minimum standard that a medicines manufacturer must meet, the inspectorate will be looking for more where process or product risk necessitate a need for more.
  - Inspectors / Investigators will often ask multiple personnel the same questions to confirm understanding of a topic, consistency of approach and to get a feel for the Quality Culture on site.
  - Inspectors / Investigators are looking to verify the Quality Culture of an organisation and the willingness to cooperate during the inspection. This includes:
    - » **Knowledge** – process understanding and awareness of critical quality attributes.
    - » **Diligence** – everyone understands how their role contributes to product quality.
    - » **Vigilance** – clear guidance on what good looks like and on how to escalate issues when there is an issue.
    - » **Senior Management commitment** – visible and transparent decision making to encourage an open and honest culture. Senior management engagement in inspection activity demonstrates to the inspector that quality is not just Quality's responsibility.
  - As a manufacturer named on a Marketing Authorisation you have agreed to operate in compliance with the rules (CFR or Eudalex) and to be inspected. You have accepted an obligation under the law to answer Inspectors questions.
  - The inspectors / investigators expectation is that you will provide truthful, honest answers. If answers are found to be untrue the consequences are potentially severe. Any inspection is a sampling exercise and therefore a relationship based on trust between the inspector and the host is important in achieving a successful inspection outcome.
  - Any evidence of issues with integrity and dishonesty will not be tolerated and result in unfavourable inspection.

### Noteworthy Differences

US FDA provides more formality (e.g. Form 482 and Form 483) where the EMA does not.

US FDA uses a methodical line of questioning; EMA / MHRA is more direct.

UK MHRA has specific guidance in place for Out of specification: Out-of-specification investigations - GOV.UK ([www.gov.uk](http://www.gov.uk)) and Data Integrity: Guidance on GxP data integrity - GOV.UK ([www.gov.uk](http://www.gov.uk))  
Note: this guidance is largely but not fully incorporated into the PICS guidance: Guidance on Data Integrity ([picscheme.org](http://picscheme.org))

### Noteworthy Similarities

All are Science based.

All are becoming more focussed on Quality Management Maturity and the implication of Culture and Behaviours on the level of compliance.

All will consider the impact of operations / observation on the impact to patient supply.

All have become under-resourced in recent years leading to some significant gaps between inspections. Recruitment is active however, as a lot of inspectors / investigators are new in role, some areas of specialised expertise are low.

### Summary

- Prolonged delays between regulatory inspections are becoming common due to lack of resource within all regulatory agencies.
- It is strongly recommended that sites be proactive about inspection readiness. **Ian White, Executive Director at NSF** and former Expert Inspector at MHRA delivers an informative Webinar on preparing for a regulatory inspection – follow the link to register: [nsf.registration.goldcast.io](http://nsf.registration.goldcast.io)
- Sites can utilise independent entities to act as the regulatory body or agency to assess the organisations current internal inspection readiness program or build an inspection readiness program.
- Third party audits and mock inspections are great ways to obtain an independent review of the compliance of a site.
- Inspection preparation should include an end-to-end review including how the inspection will be managed e.g. backroom support and resource.
- Storyboards are a great way to summarise complex issues or a chronology of events, for example where multiple deviations have occurred for the same issue. However, be mindful that QMS documents should be able to be read as standalone documents and therefore the use of storyboards should be limited to complex issues.

- It is the sites responsibility to demonstrate compliance, not for the Inspector to prove non-compliance.
- The cGMP's are minimum requirements – increasingly Quality Culture and Quality Management Maturity is a focus of inspectors. See **Samantha Atkinson, Executive Vice President of NSF** discussing this at <https://bit.ly/4cdvOcY> and how to deploy QMM across global sites at <https://bit.ly/3WdME5v>
- Coaching of Senior Management, Subject Matter Experts and Area Owners is valuable in ensuring a successful inspection. NSF have a range of coaching packages, or we can prepare a bespoke package based on your needs, please email at: [healthsciences@nsf.org](mailto:healthsciences@nsf.org) for further information.
- Quality is not the responsibility of the Quality Department, this needs to be evident during an inspection.
- Inspections are an opportunity to strengthen your operations, demonstrate your commitment to compliance and quality, and identify opportunities for continuous improvement.

The NSF team includes a number of former FDA, EU and UK officials as well as industry experts – this combined global regulatory knowledge, alongside industry best practices, will help you achieve successful regulatory strategies and execution as well as sustainable and compliant quality systems.

If you would like to speak to NSF about an upcoming inspection, or would like our help preparing for a regulatory inspection, then please email at: [lifesciences@nsf.org](mailto:lifesciences@nsf.org)

### NSF

789 N. Dixboro Road Ann Arbor, MI 48105 USA  
[www.nsf.org](http://www.nsf.org)  
E: [info@nsf.org](mailto:info@nsf.org)