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European Federation of Pharmaceutical Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2018 Data

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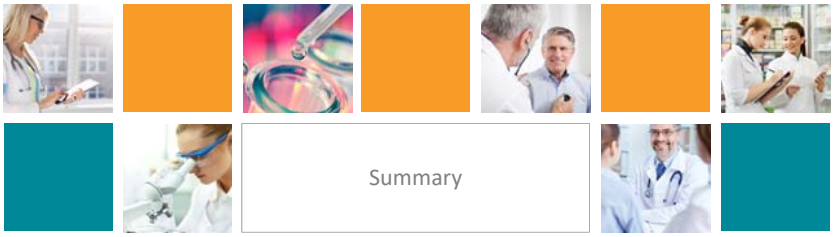

Summary

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Background and History

- **History**
  - The annual inspection survey was initiated in 2003 with the intent to gather data regarding inspections activities in the research-based industry
- **Intention**
  - Monitor trends and new focus areas of GMP/GDP inspections
  - Continue to promote reliance, collaboration and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections
  - Materialise the benefits of PIC/S membership in optimizing use of inspection resources with a harmonized risk-based approach for inspections while maintaining patient safety
- **Scope**
  - Regulatory GMP/GDP inspections & related ISO-certifications for regulatory purpose
  - Manufacturing sites and affiliates
  - Inside and outside the Regulatory Authority's own borders

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Survey Outcomes 2018

- **The highest number of foreign inspections reported in the 2018 survey are**
  - US, Russia followed by Japan, Turkey, Brazil, Mexico, Republic of Korea, EU, Belarus and Peru
- **Reportable trends from the survey compared with the previous year**
  - Decrease
    - Foreign inspections by US (-15%), Turkey (-35%), Russia (-40%), Brazil (-45%), EU (-51%)
    - Companies reported that Brazil, Canada, Israel and US waived inspections
  - Increase of
    - Foreign inspections by Australia, Chinese Taipei
    - The number of inspections requiring follow up; especially at affiliates (100% more)
- **Number of foreign inspections* indicated an increase**
  - Based on data from 22 research-based pharmaceutical companies

* Foreign inspection: inspection conducted outside of the inspectorate's own country/region
Domestic inspection: inspections conducted in the inspectorates own country/region

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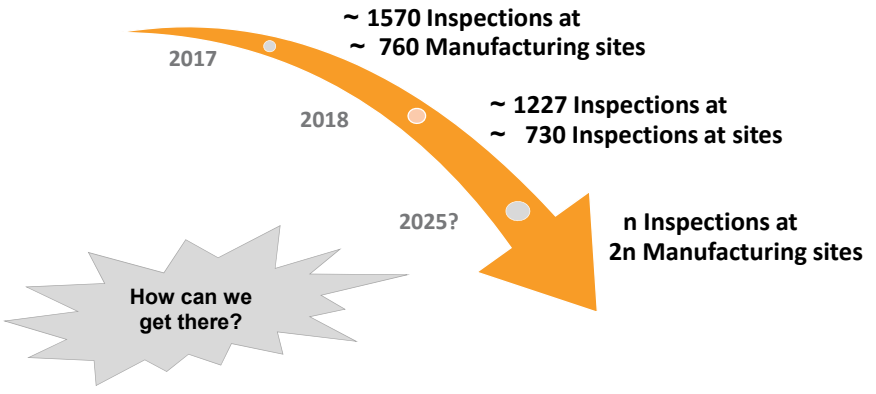
The Ideal State is in Average One Biannual Inspection by the Local Inspectorate



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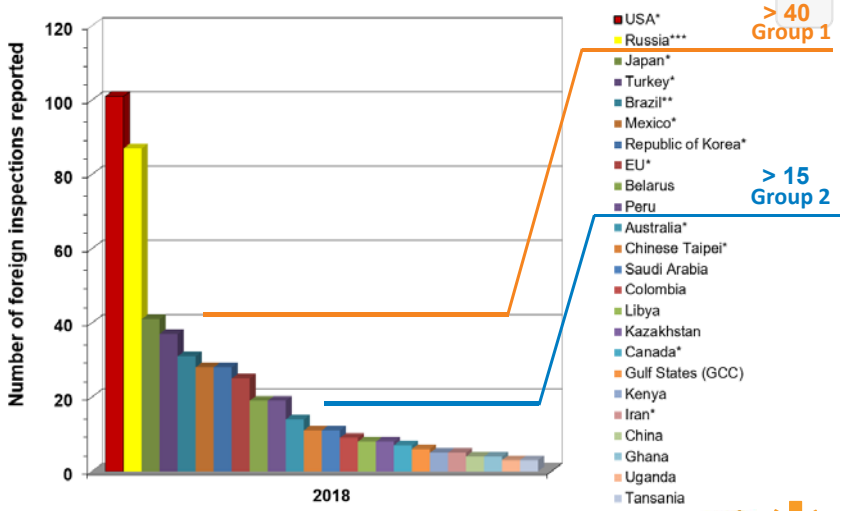
Number of Foreign Inspections

ordered by country (>1 inspections; EU as one entity)



*Inspectorate is a PIC/S member **PIC/S Applicant ***PIC/S Pre-Applicant

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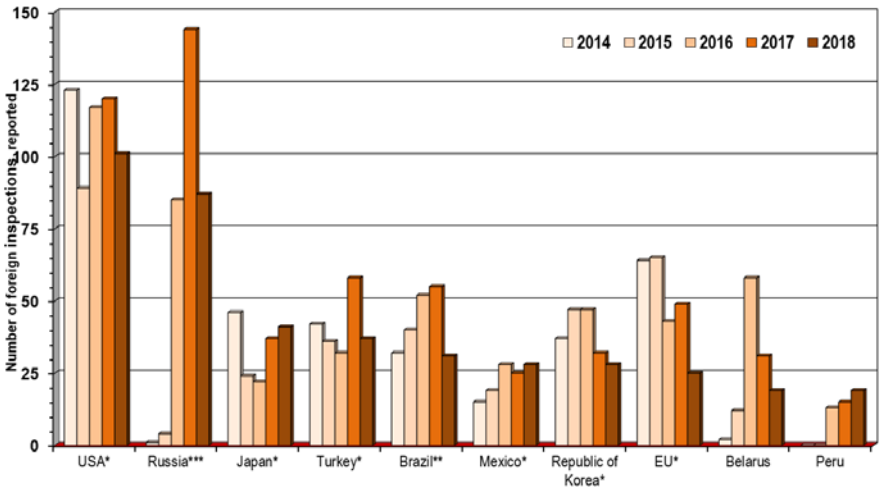
Number of Foreign Inspections by Country



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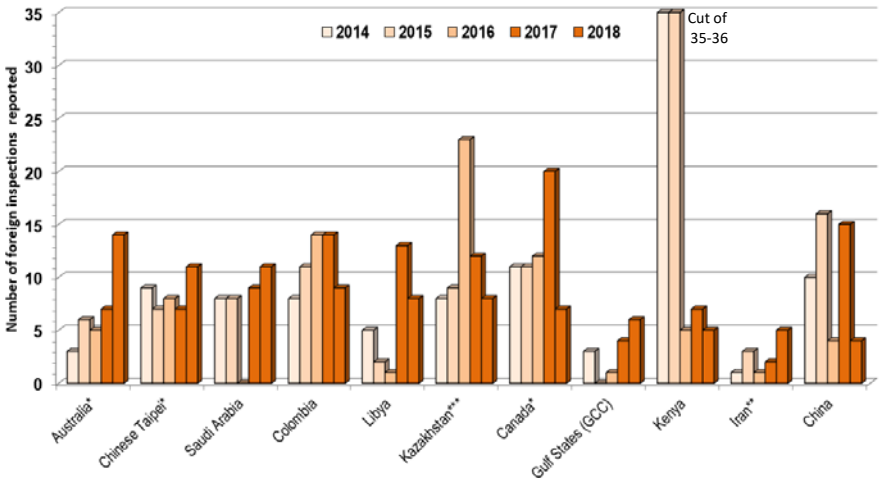
Number of Foreign Inspections by Country



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Survey Data Underline PIC/S is Facilitating Cooperation and Reliance

% of the reported foreign inspections are performed in countries, where the inspectorate is a PIC/S member

18%

PIC/S PRE-APPLICANT inspectorates

2017: 17%

5%

PIC/S APPLICANT inspectorates

2017: 20%
The decrease is due to a higher number of inspectorates with an applicant status in 2017

52%

PIC/S MEMBER inspectorates

2017: 34%
39% in 2018, when subtracting out the progress of applicants to member stage (Iran, Mexico, Turkey)

Note: Applicants and Pre-Applicants still need to demonstrate that they are equivalent and no GMP information is exchanged while they are in the accession / pre-accession process.

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MRA US/EU

Opportunities: Efficient MRA Implementation Can Drive Reduction of Inspections

EU has decreased foreign inspections in US since 2014

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MRA US/EU

Challenges With Implementation

- **Not all provisions of the current MRA are implemented**
  - Inspections called pre-approval inspections (PAI) in the US – *currently paused*
  - Recognition of inspections of manufacturing sites in 3rd countries – *pending*
  - Biological products, if registered by CBER – *no recognition by some offices in FDA*
  - Medicinal Products in the EU with a Medical Device registered as 'Combination Products' in the US – *different terminology leads to discrepancy in applicability*
- **Unexpected consequences on EU GMP-certificates**
  - They are required for 3rd country registration and import
  - FDA (CDER only) may issues a product specific GMP statement under special circumstances – *initiative started*
- **Initiating efforts towards expanding the MRA to include**
  - Waiving of import testing after inspection of manufacturing sites in a 3rd country
  - GMPs for Advanced Therapy Medicinal Products (ATMPs) / Cell and Gene Therapies (CGTs)

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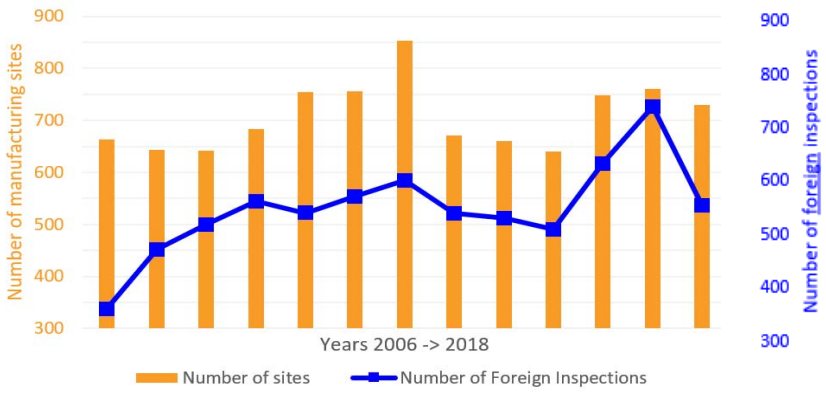
Evolution of Number of Foreign Inspections Versus Manufacturing Sites



Back to the baseline from previous years?

SHARE REPORTS FROM REGULATORY INSPECTIONS

Assessment of WHO Recommendations Supporting the Ideal State

Recommendations to Industry

1. In support of transparency, companies should consent to the sharing of full information amongst regulators and procurement agencies on inspections.

- **The survey showed that industry implemented the ICDRA recommendation**
  - Industry is prepared to share inspection reports, usually redacted
  - Full information is shared upon request, where Intellectual Property is preserved

NRA: National Regulatory Authorities
ICDRA: International Conference of Drug Regulatory Authorities (by WHO)

SHARE REPORTS FROM REGULATORY INSPECTIONS

Assessment of WHO Recommendations Supporting the Ideal State

- **Industry support the ICDRA 2018 recommendations on risk based inspections and regulatory collaboration**

Recommendations to Member States

1. NRAs should embed the use of reliance procedures in their regulatory decision processes relating to inspections.
2. NRAs should monitor foreign inspections and support desk-top assessments with defined conditions

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Recommendations to Member States

1. When sharing assessment or inspection reports, Member States should share unredacted reports, where possible, which is important to build trust and to optimize reliance on outcomes from other regulators.

NRA: National Regulatory Authorities
ICDRA: International Conference of Drug Regulatory Authorities (by WHO)

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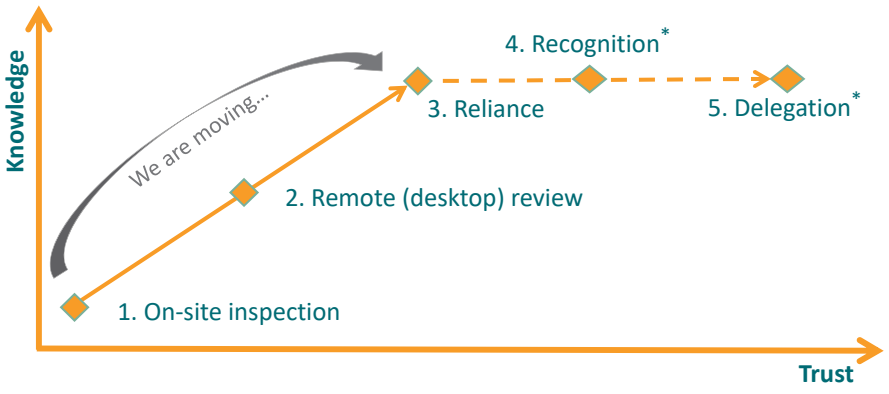
An Approach Towards the Ideal State



- Risk-based inspection planning PIC/S guideline PI 037-1, 1 January 2012
- GMP-Inspection reliance, PIC/S guideline PI 048-1, 1 June 2018
- Classification of GMP Deficiencies, PIC/S guideline PI 040-1, 1 January 2019

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*For inspections performed in s 3rd country, no legal barriers assumed

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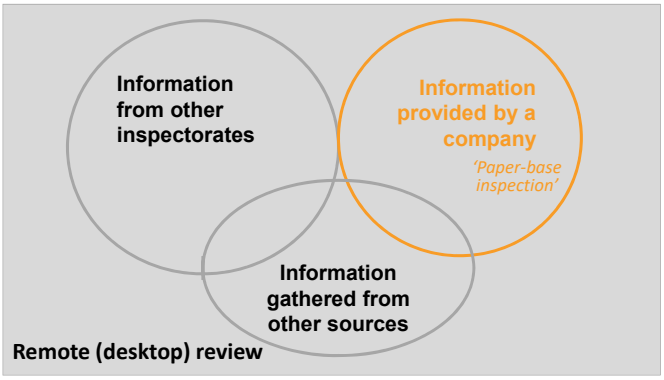
TERMINOLOGY

Remote (Desktop) Review - Paper-based Inspections



Remote (desktop) review (PIC/S)
PIC/S, GMP Inspection reliance, Guideline No PI 08-1, 01. June 2018
- Confirming GMP compliance through remote (desktop) inspection, where appropriate, without undertaking an onsite inspection

Paper based inspections
11/22 companies reported in the survey
- Providing documents to an inspectorate, without an on-site inspection

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REMOTE (DESKTOP) REVIEW - PAPER-BASED INSPECTIONS

Talking Points to Optimise the Use of Opportunities in the Inspection Process

A Companies suggest a remote (desktop) review according to PIC/S* as an alternative to a requested for an on-site foreign inspection

B Remote (desktop) review according to PIC/S* should be considered as alternative to a foreign inspection

Companies could submit standardised documentation package

- May include, and may be limited to SMF, APQR for product in scope, valid GxP certificates and/or WHO CPP, manufacturer's licence, list of inspections / inspections reports (e.g. EIR-US only) and companies responses.
- All other documents would be available to be reviewed on site by the local inspectorate

* Remote (desktop) review: PIC/S, GMP Inspection reliance, Guideline No PI 08-1, 01. June 2018

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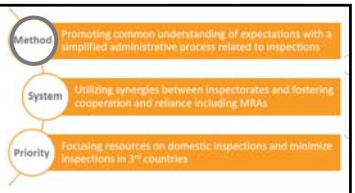
STRATEGIC INTENTION ON INSPECTIONS

Optimise the Effectiveness of Inspectional Oversight of GMP/GDP Operations

- **Method** – Promoting common understanding of expectations with a simplified administrative process related to inspections
- **System** – Utilizing synergies between inspectorates and fostering cooperation and reliance including MRAs
- **Priority** – Focusing resources on domestic inspections and minimize inspections in 3rd countries

OTHER REFLECTIONS ON CONTINUOUS IMPROVEMENT

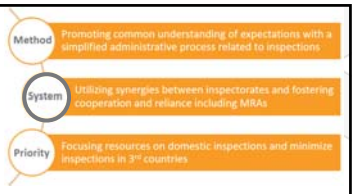
Inspection Method



- Basing regulations, rules and practices on science principles and incorporating risk-based approaches
- Sharing knowledge and looking for opportunities in the existing legal framework rather than creating 'new' fragmented GMP/GDP guidelines in the EU
- Assessing new products and technologies in the context of the existing understanding of GMP requirements and oversight
- Alignment on documentation requirements prior to an on-site inspection and/or for a paper-based inspection as part of remote (desktop) review

OTHER REFLECTIONS ON CONTINUOUS IMPROVEMENT

Inspection System

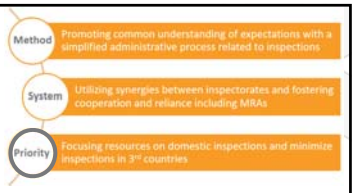


- **Sharing good practice and aligning on a common interpretation of GMP/GDPs**
  - Classification system for observations (PIC/S*)
- **Encouraging trust and dialogue among inspectors**
  - Maximise effectiveness of existing harmonisation forums e.g., PIC/S, ICMRA, ICH, WHO, APEC
  - Facilitate education
- **Fostering reliance and recognition towards delegation**
  - Maturity level of authorities (e.g., PIC/S, WHO, MRA US/EU)
  - Leverage the benefit from reliance on inspection outcomes

*Classification of GMP Deficiencies, PIC/S guideline PI 040-1, 1 January 2019

OTHER REFLECTIONS ON CONTINUOUS IMPROVEMENT

Inspection Priority



- **Fully deploying the US/EU MRA to maximise benefits**
- **Harmonized documentation package for desk assessments and/or inspection preparation**
- **Sharing results of inspection outcomes among regulators and by industry**
- **Promoting reliance of outcomes from domestic inspections**

OTHER REFLECTIONS ON CONTINUOUS IMPROVEMENT

Expected Benefits

- **For Industry and Regulators**
  - Globally aligned GMP/GDPs principles
  - Facilitate access to innovation
  - Resource-efficient inspection processes
- **For Patients**
  - Assurance of Quality and optimised regulatory oversight
  - Accelerate Time to Market
  - Get access to new and innovative medicines

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Additional References

- **Guidance for inspectors**
  - PIC/S, A recommended model for risk-based inspection planning in the GMP environment Guideline, *Guideline PI 037-1*, 01. Jan 2012
  - PIC/S, GMP Inspection reliance, *Guideline No PI 048-1*, 01. June 2018
  - PIC/S, Classification of GMP Deficiencies, *Guideline No PI 040-1*, 01. January 2019
- **Scientific Papers**
  - A. Meshkovskij, S. Rönninger, National GMP Inspection Practice for Biotech Pharmaceuticals: Commonalities, Differences, Opportunities, CIS GMP News, 2018, *1*, 26-31. https://gmpnews.net/magazine/gmpnews-eng-2-1-2018/#page/26
  - H. Jin, N. Carr, H. Rothenfluh, TGA, Medicines Regulations: Regulating Medicines manufacturers: Is an onsite inspection the only option?, *WHO Drug Information*, 31/2, 2017, 153-157.
  - EMA, WHO, TGA, US-FDA, EDQM,Council or Europe, ANSM, DMA, HPRA AIFA, MHRA, Report on the International Active Pharmaceutical Ingredient Inspection Programme 2011 – 2016, March 2018, 1-13.
  - S. Rönninger, J. Berberich, V. Davoust, P. Kitz, A. Pfenninger, Landscape of GMP/GDP inspections in research-based pharmaceutical industry, Part I: Data, *Pharm. Tech. Europe*, January, 2017, 6-10. http://www.pharmtech.com/gmpgdp-inspection-landscape-part-i-data ; Part II: Considerations and Opportunities, *Pharm. Tech. Europe*, February, 2017, 5-9. http://www.pharmtech.com/gmpgdp-inspections-landscape-part-ii-considerations-and-opportunities
  - A. Meshkovskij, S. Rönninger, GMP Inspection practice: a case for global benchmarking, convergence and mutual reliance/recognition, *The GMP News, 2017*, 2-9 (Rus).
  - EFPIA Annual Inspection Survey, results 2017 https://www.efpia.eu/media/361849/_efpia-2017-reg-inspection-survey_public-summary.pdf
- **Industry Position Papers**
  - EFPIA: Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, 19. May 2014.
  - EFPIA / PhRMA: A Concept for Harmonized Reporting of Inspections, 29. May 2015; *addendum of the PhRMA White Paper: 'Mutual Recognition of Drug GMP Inspections by U.S. & European Regulators'*, 15. May 2015. http://www.efpia.eu/uploads/EFPIA_Position_Paper_A_Concept_for_Harmonized_Reporting_of_Inspections_final.pdf
  - IFPMA: Convergence of Good Manufacturing Practice (GMP) standards and Related Inspections, 9. June 2017 https://www.ifpma.org/wp-content/uploads/2017/06/IFPMA-Position-on-GMP-Convergence-Final-_9June2017.pdf
  - IFPMA Infographic: https://www.ifpma.org/wp-content/uploads/2018/02/GMP_IFPMA_02-20-2018-WEB.pdf

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Contributors to the EFPIA Inspections Survey 2018

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- GlaxoSmithKline
- Johnson & Johnson
- Merck
- Merck Sharp & Dohme
- Novartis
- NovoNordisk
- Pfizer
- Roche
- Sanofi (incl. Sanofi Pasteur)
- Servier
- Teva
- UCB

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