European Federation of Pharmaceutical Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2020 Data

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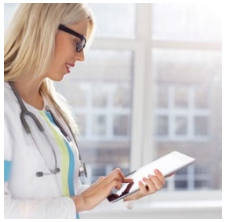
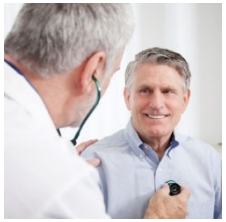
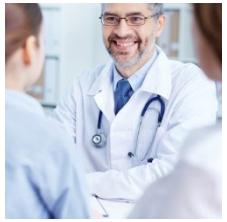




Summary

EFPIA'S ANNUAL INSPECTION SURVEY

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 / ISO-certifications
- Continue to promote reliance, collaboration and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections / ISO-certifications
- 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

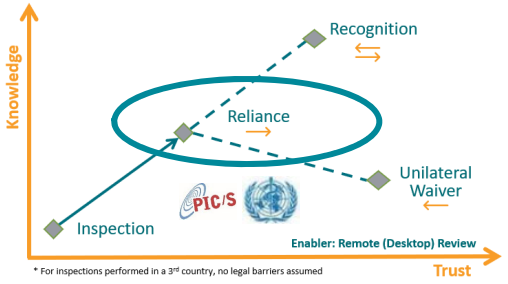
Scope

- Regulatory GMP/GDP inspections & related ISO-certifications for regulatory purpose
- Manufacturing sites and commercial affiliates
- Inside and outside the Regulatory Authority's own borders (domestic and foreign)
- All tools, that are used or combination from them: on-site, virtual, or paper-based inspections as well as reliance/recognition approaches

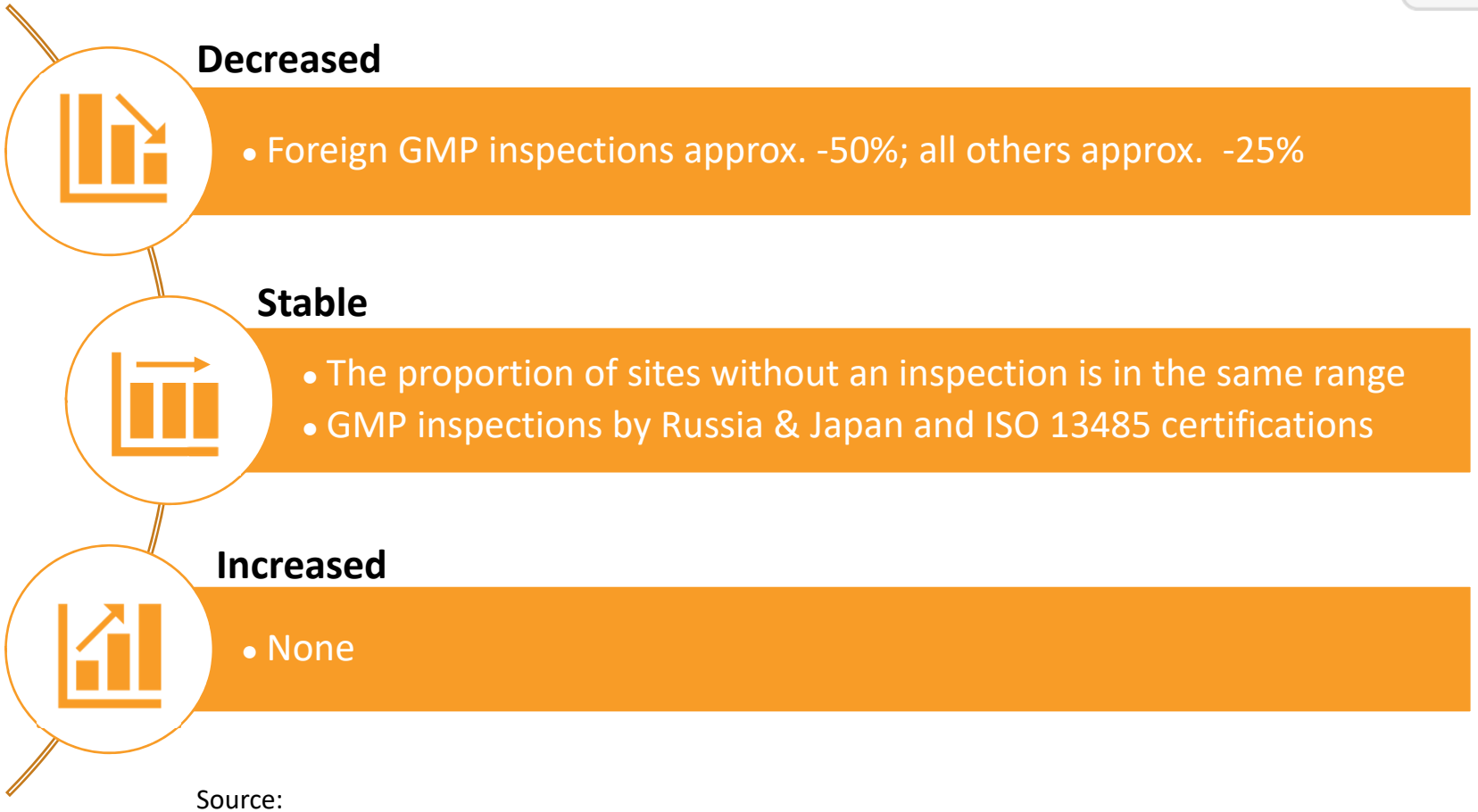
Note: 'foreign inspections' are inspections performed in a 3rd country to the inspectorate

Key Message

- **Regulatory oversight was maintained supporting public health**
  - Virtual approaches helped as an enabler and have a role
  - But companies report delay of approval by pushing back scheduled PAIs
- **Gain efficiency in the use of tools**
  - Combined use of virtual / on-site hybrid may be valuable
  - Standardise the package of documents to streamline efforts
  - Follow a clearly defined schedule, with an inspection endpoint
- **Increasing use of reliance will be beneficial**
  - Enabled by waivers, recognition and using various tools
  - Experience demonstrated feasibility and value in decision making



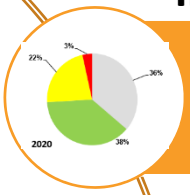
Situation in 2020 was Impacted by the Pandemic



Source:
25 Global research-based pharmaceutical companies (EFPIA members) and
8 Local companies from APIFARMA, Portugal (3) and Farmindustria, Italy (5)

Collaboration Opportunities Between Agencies Suggested by the Data Analysis

Inspecting

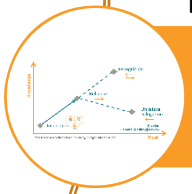


- **Agencies are maintaining strong oversight of domestic sites** - Although there were 50% fewer foreign inspections, number of sites without an inspection at all was similar to previous years

Cooperation

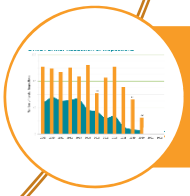
- **Opportunities for efficiency gains** in inspections exist as 51% foreign inspections are performed by a PIC/S inspectorate in a country, where the inspectorate is also a PIC/S member

Reliance



- **Unilateral reliance** is possible e.g., n-Nitrosamine, BREXIT, COVID-19
- Unfortunately, foreign inspections target sites in countries with well recognised inspectorates

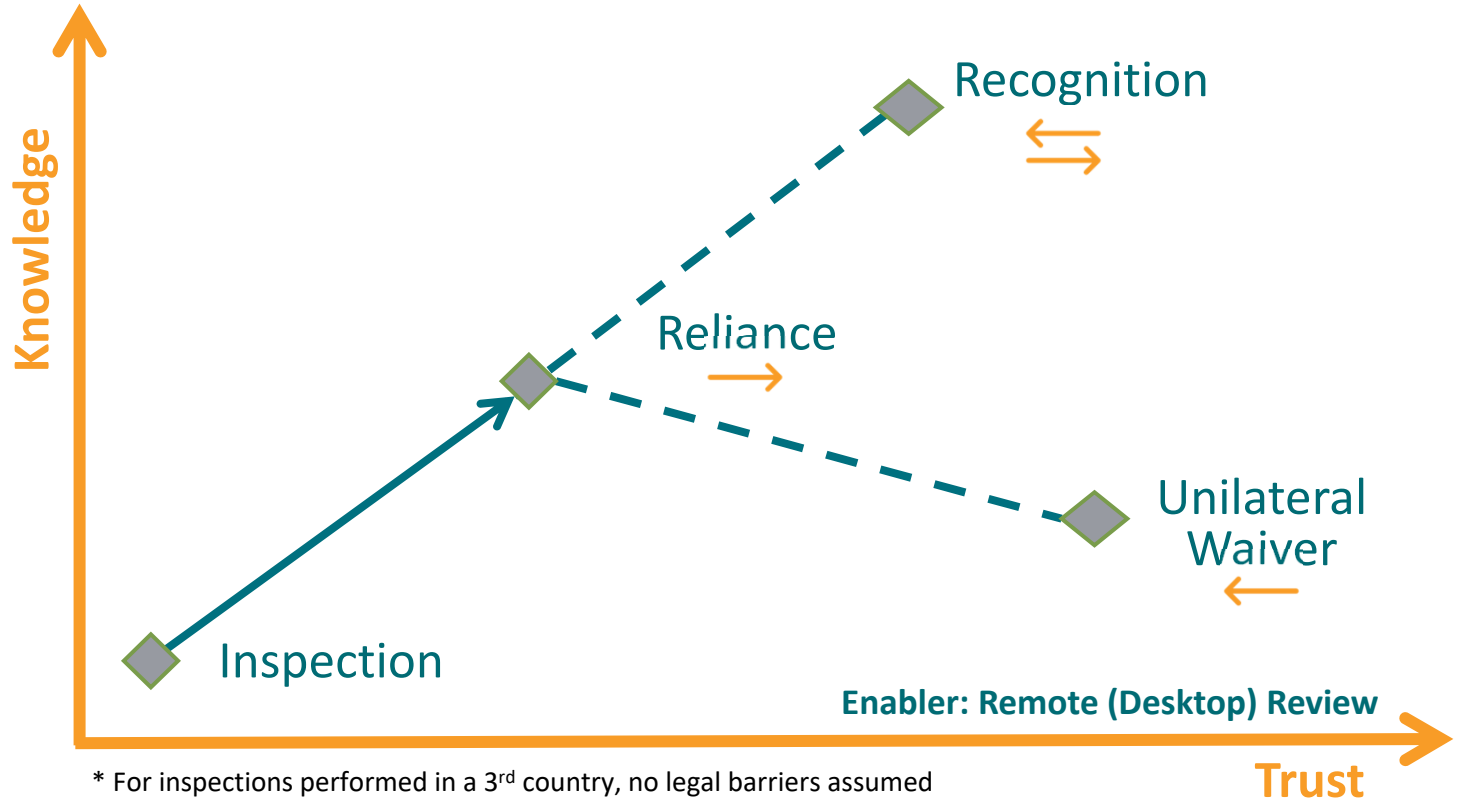
Recognition



- **Benefits of MRAs** are gradually becoming apparent, with the data showing fewer inspections; PAI by US in EU are still conducted (10 in 2020)

COLLABORATION, RELIANCE, DELEGATION

Pandemic Showcases Demonstrate Opportunities Towards an Ideal State



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

Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TRS 1033, Annex 10,* **2021,** 237-267.

- **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

Convergence of Good Manufacturing Practice (GMP) standards and Related Inspections, IFPMA Position paper, January 2020
S. Rönninger, P. Gough, V. Davoust, **Opportunities for Saving Resources in the Regulatory Inspection Process: Mutual Recognition Agreements (MRA) Example EU/US,** *Pharm. Tech. Japan*, 35, **2019,** 15-25..

COLLABORATION, RELIANCE, DELEGATION - MRA

Reflections on Further Opportunities to Leverage MRAs

EU / US

- We understand the challenges but expect the timeline to be met for recognition of inspections for Vaccines
- Opportunities for FDA to recognise PAI by US in EU and UK as this is included in the MRA

EU / Canada

- We welcome the inclusion of APIs and inspections in 3rd countries

EU / Japan

- We see opportunity for Japan to leverage the MRA also in context of the submissions
  https://www.pmda.go.jp/files/000222303.pdf

Opportunity for future EU / UK MRA?

- The current trade agreement fall short on elements typically agreed in a MRA
- We see a large opportunity waiving import testing requirements to reduce duplication of efforts, environmental footprint etc.

Wasting Resources

Inspections in 3rd Countries

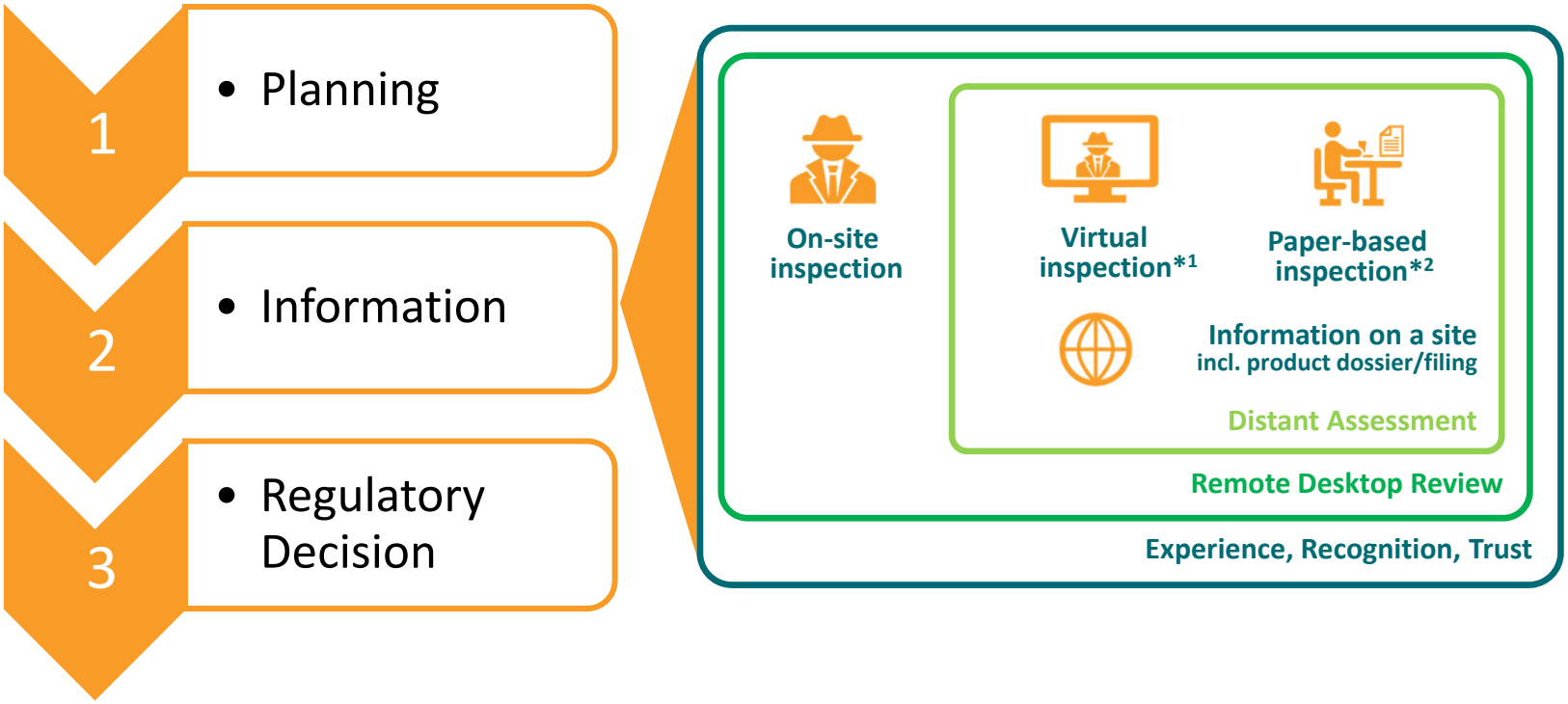
- Available information for an informed decision
- When equivalent standards are applied locally (e.g. inspectorate is member of PIC/S)
- Travel time limits effectiveness

Import testing

- Destroying medicines which cannot be delivered to patients
- Impacting shelf life by delaying delivery to patients by 1-2 m
- Supporting environmental pollution
  - Redundant tests (e.g., using solvents, energy)
  - Resources for storage (e.g., cold chain)

https://www.ifpma.org/tag/import-testing/

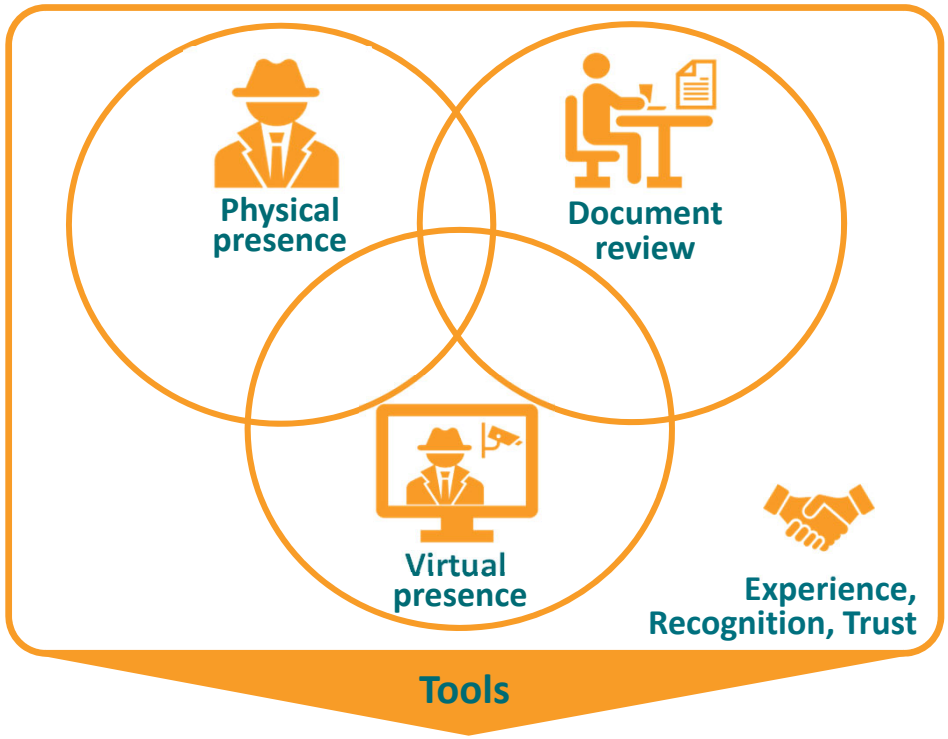
Process to Confirm GMP Compliance Enabled Through Different Tools



*1 Virtual inspections are e-technology enabled; This mimics an on-site inspection (1) in format and overall time frame.
Sometimes this may be called '*remote*' or '*distant*' or '*Real Time Remote*' '*inspection*' or '*assessment*'
*2 Sometimes this may be called '*desk assessments*', or see **Remote Interactive Evaluations of Drug…,** FDA , Guidance for Industry, FDA-2020-D-1136, April 2021

Agencies are using different Inspection Tools, Sometime in Combination

They are not Equivalent - Each has Pros and Cons



EFPIA Observations on Virtual Inspections: They can Confirm Compliance*

Applying e-tools has the ability to confirm compliance

- Providing that the legal decision is filed to guarantee continuous patient access

Scheduling among different time zones can be managed

- Virtual inspections are taking more time currently

Involvement of local affiliates in foreign virtual inspections

- Direct contact - site inspector needed

Using e-tools and securing communication

- Challenges with finding documents and that they are not always self-explanatory

* No evidence, that legislation in the EU does prevent virtual assessments beeing the basis for a legal decision as an 'inspection' e.g., EMA *Guidance related to GMP/GDP and PMF distant assessments* https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-related-gmp/gdp-pmf-distant-assessments_en.pdf

Industry and Regulators are on a Learning Curve Applying Virtual Tools

Each inspection is different

- Some technological / privacy limitations
- Mixed feeling if a virtual inspection is more or less stressful than an on-site inspection

Opportunity to work with defined agendas

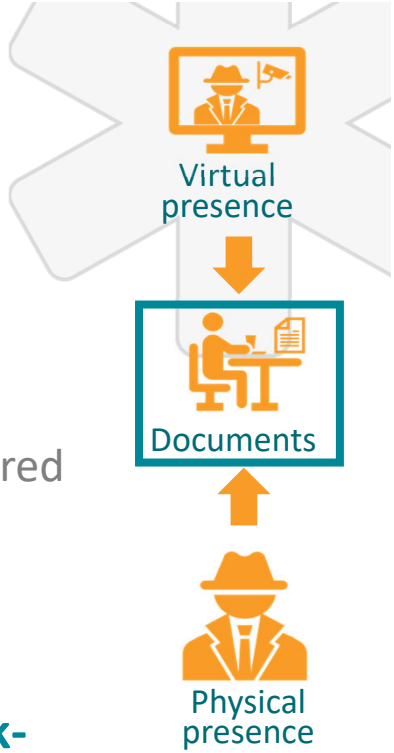
- Some agencies do not report when the inspection has ended (e.g., Russia)

Longer time for preparation when hosting virtual inspections

- More documents are requested in advance

INSPECTION PROCESS AND TOOLS – LEARNING CURVE

Predictable Preparation Efforts are Needed to Foster Efficiency of the Inspection Process



- **Regarding documentation provided**
  - Electronically saved documents shall be made available on a secured location
  - English is the acceptable language for inspectorates
  - Inspectors can clarify content in a virtual set up
- **Successfully passed previous inspection should drive the risk-based inspection approach**
  - Companies should be informed, if reliance was used (also for PAI)
- **Accelerate regulatory decisions on site compliance status**
  - Standardise the package of documents (e.g. within PIC/S) asked to be sent to inspectors for whatever inspection tool is used

- Type (paper/virtual/on-site)
- Inspection frequency (→ 5y?)
- Drive for reliance
- Level of detail
- Length
- etc.

INSPECTION PROCESS AND TOOLS – PAPER-BASED INSPECTIONS

Documents

Standardise the Package of Documents to Streamline Efforts for all Inspection Types

- **Inspectors can be more focused and effective**
- **Companies can be more focused and effective**

Requested to deliver in more than 50% of the paper-based inspections are

1. **SMF[1]**
2. **APQR[1]**
3. **List of inspections[1]**
4. Detailed Process validation data[2]
5. Process Validation status[2]
6. SOP Change Control[3]
7. SOP Complaint handling[3]
8. Copy Batch Record[3]
9. List Variations[2]
10. List Recalls[2]

For consideration by PIC/S

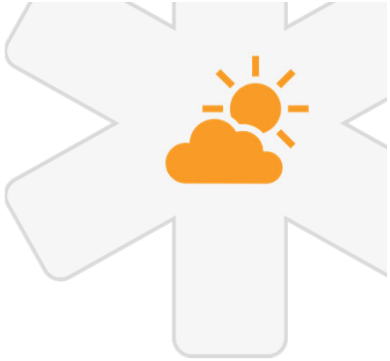
Proposal for requested documents[1]
- SMF
- APQR[2]
- List of inspections
- Site Quality Manual (PQS)

1 Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, EFPIA, *Position Paper*, **19. May 2014.**
2 **APQR included most lists requested e.g., variations, complaints, recalls, deviations**
3 Principles are included in the Site Quality Manual (PQS)[1]

SEPARATE SURVEY: 270 DATA POINTS (01.JAN.2019 - 31.JUNE.2020) PROVIDED BY 11 COMPANIES

COLLABORATION, RELIANCE, DELEGATION

Potential Strategies Towards the Future



Plan inspections based on risk

Consider

- Basics: compliance history, product criticality, etc.
- Coordination of inspections among agencies
- Expired GMP certificates may impact regulatory procedures
- Flexibility by using alternative tools including virtual inspection (also for PAIs) instead of postponing
- Coordination of certification audits by different notified bodies (note: privacy agreements)
- Support by a tool to coordinate inspections worldwide (e.g., by PIC/S)

Evolve the traditional on-site approach

Adopt

- A hybrid approach with a focused on-site presence
- A clear, defined and followed timetable
- Using surveillance inspection to build in PAI elements, as applicable
- Allowing reliance on domestic inspections for license renewals or use virtual tool especially in 3rd countries

Build reliance

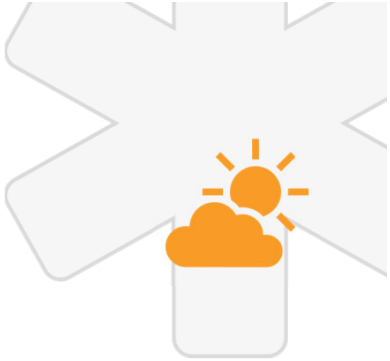
Leverage

- Complete inspection history
- Reliance on domestic inspections especially if performed by PIC/S members
- Regional certificates (e.g. EAEU)
- MRAs: implement and extend

Example for a Future State: A Pragmatic Approach of Flexibilites for Inspection Supports Business Continuity

- **Virtual and paper-based inspections successfully confirm compliance**
  - No change in number and/or severity of observations had been reported
  - No significant differences in the perception of GMP-, GDP-inspections nor ISO certification audits are reported by companies
- **Companies (>90%) did not observe changes in inspection observations**
  - Individual companies reported shifts in observations towards e.g., Quality System areas, risk-assessment thoroughness, documentation accuracy, documentation practices
  - Companies were asked about drug shortage prevention measures - no particular challenges reported
- **Recommendation**
  - Opportunities to follow a clearly defined and executed schedule of an inspection including a defined endpoint

Making the Inspection Processes More Efficient



Applying virtual tools allow for a better communication than sending documents

- Can performing compliance assessments using virtual tools fully replace on-site inspections?
- While on-site inspection by local inspectorates is a key asset, virtual inspection could be promoted wherever possible and/or pertinent

Opportunities for a better risk-based approach

- Some inspectorates and notified bodies are coming very often to inspect the same sites
- If regulators and industry get more used to applying virtual tools it could allow saving of resources

Industry Vision for the Future: Risk-based Approaches by Inspectorates Implementing Reliance

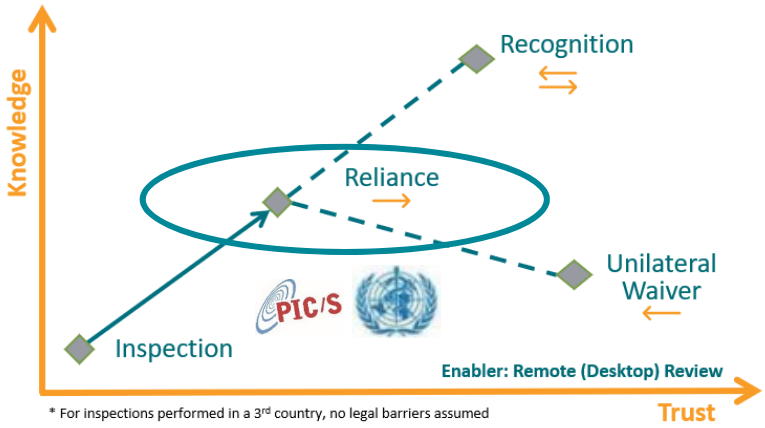
Ensure continued engagement on reliance approaches…

- Manage the anticipated peak of on-site inspections in near term
- Leverage domestic inspections to explore reliance pathways incl. PAI
- Improve planning, scheduling, coordination and execution of inspections
- Agile solutions using different tools and/or combinations rather than overloading sites with postponed on-site inspections
- Prefer the virtual tool e.g., for surveillance inspections especially in 3rd countries - experience will further evolve over time

…for timely approvals speeding access to medicines

Reliance

The Ultimate Goal for an Efficient Inspection System?



Additional References

Guidance for regulators incl. inspectors

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- 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
- WHO, **Good regulatory practices in the regulation of medical products,** WHO Technical Report Series, *1033, Annex 10,* **2021**, 237-267.

Scientific Papers

- S. Rönninger, P. Gough, V. Davoust, **Opportunities for Saving Resources in the Regulatory Inspection Process: Mutual Recognition Agreements (MRA) Example EU/US,** *Pharm. Tech. Japan***,** 35, **2019,** 15-25.
- 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
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- 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 2018 https://www.efpia.eu/media/361849/_efpia-2018-reg-inspection-survey_public-summary.pdf

Industry Position Papers

- EFPIA: Annual Regulatory GMP/GDP Inspection Survey's https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/regulatory-affairs/
- EFPIA: **Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency**, 19. May 2014.
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- IFPMA **Infographic**: https://www.ifpma.org/wp-content/uploads/2018/02/GMP_IFPMA_02-20-2018-WEB.pdf
- IFPMA: **Points to consider for virtual inspections,** 2021 https://www.ifpma.org/tag/gmpgdp-inspection/

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Contributors to the EFPIA Inspections Survey 2020

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- Grünenthal GmbH
- GlaxoSmithKline
- Johnson & Johnson
- Lundbeck
- Merck
- MSD
- Novartis
- Novo Nordisk
- Pfizer
- Roche
- Sanofi (incl. Pasteur, Genzyme)
- Servier
- Teva
- UCB
- Vistin Pharma

National Trade Associations

- Farmindustria (5 companies in Italy)
- Apifarma (3 companies in Portugal)

European Federation of Pharmaceutical Industries and Associations

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BACK UP

Supporting Data and Details

Collaboration, Reliance, Delegation

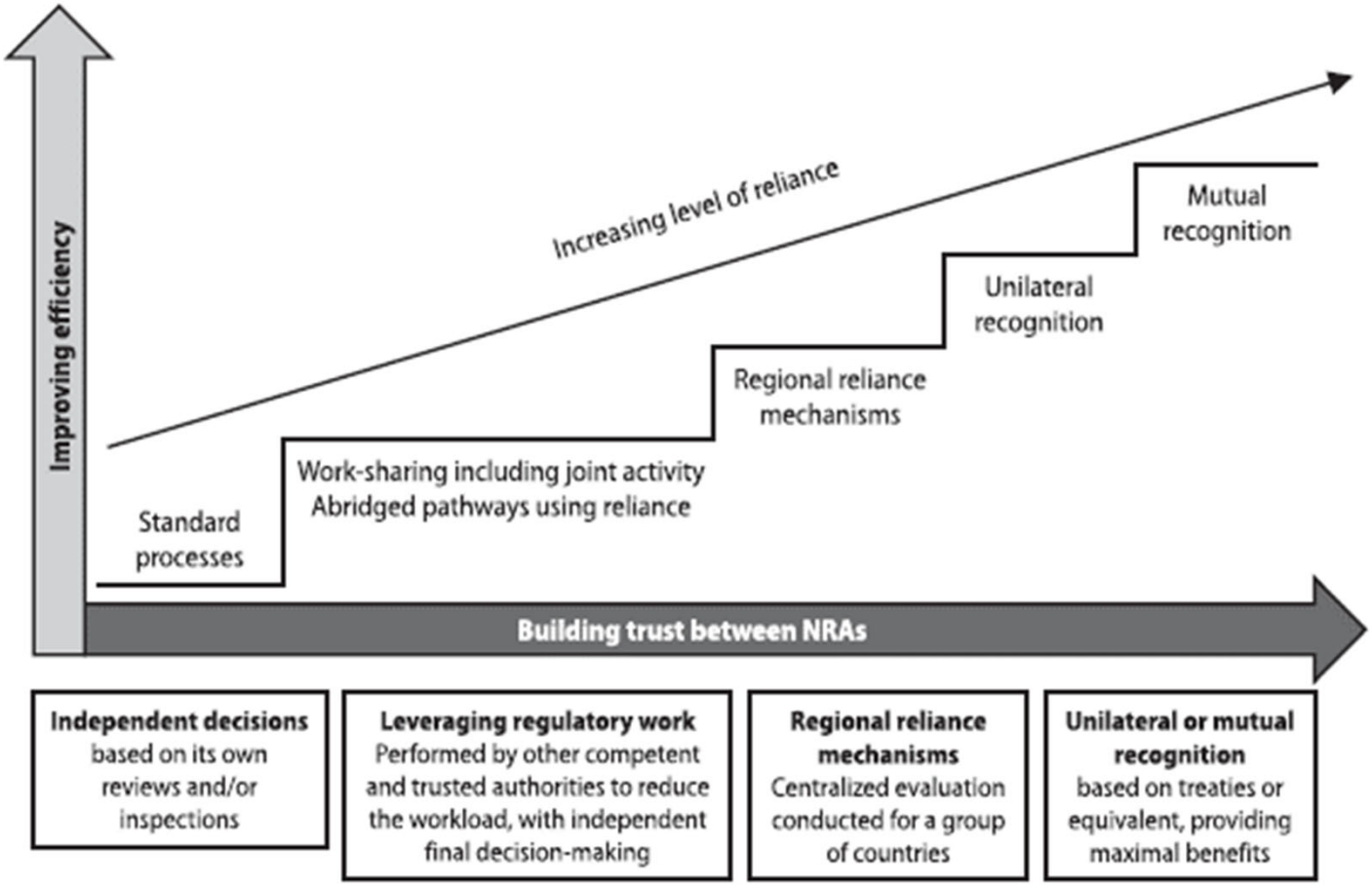
Survey Data and Trends

1. Foreign Inspections (incl. MRA EU/US)
2. Domestic Inspections
3. Paper-based Inspections
4. Inspection process and tools
5. Location of Manufacturing sites
6. Resource Considerations

Collaboration, Reliance, Delegation

COLLABORATION, RELIANCE, DELEGATION

WHO now Recommends the Key Concepts of Reliance



Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TSR 1033, Annex 10,* **2021**, 237-267**.**

WHO now Recommends the Key Concepts of Reliance
Glossary

Recognition — must

- Acceptance of the regulatory decision of another regulator or trusted institution
- Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority
- Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement

Reliance — may

- The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision
- The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others

Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TSR 1033, Annex 10,* **2021**, 237-267 – chapter 4: glossary

COLLABORATION, RELIANCE, DELEGATION

A Simple and Qualitative Tool for Inspection Planning

Elements

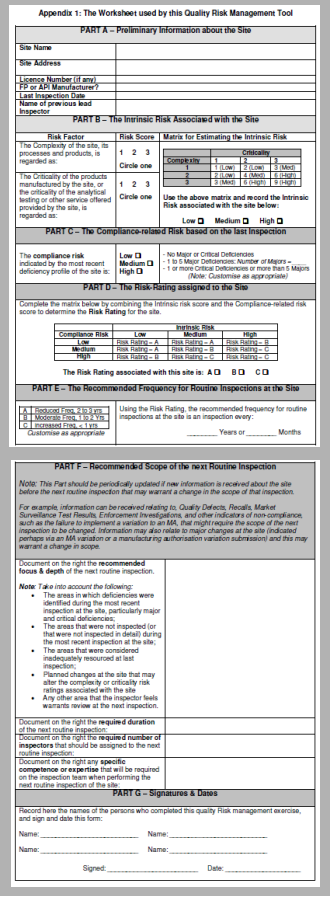
- Knowledge of the GMP compliance status of the site
- Footprint of critical and major deficiencies
- Type of inspection i.e., routine, for cause, pre-approval

Hazards to consider

- **Intrinsic risk**
  - Complexity of site, Processes and Products, Criticality to availability
- **Compliance-related risk**
  - GMP/GDP / CMC, regulatory status (incl. e.g., number of deficiencies)

Output

- Risk ranking ('Quality metrics')
- Inspection frequency
- Required number of inspectors and competence / expertise
- Scope, focus, depth & duration of the next routine inspection



Appendix 1: The Worksheet used by this Quality Risk Management Tool

PART A – Preliminary Information about the Site

Site Name	
Site Address	
Licence Number (if any) FP or API Manufacturer?	
Last Inspection Date	
Name of previous lead Inspector	

PART B – The Intrinsic Risk Associated with the Site

Risk Factor	Risk Score	Matrix for Estimating the Intrinsic Risk
The Complexity of the site, its processes and products, is regarded as:	1 2 3 Circle one	Criticality: 1 / 2 / 3 Complexity 1: 1 (Low) / 2 (Low) / 3 (Mod) Complexity 2: 2 (Low) / 4 (Mod) / 6 (High) Complexity 3: 3 (Mod) / 6 (High) / 9 (High)
The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:	1 2 3 Circle one	Use the above matrix and record the Intrinsic Risk associated with the site below: Low ☐ Medium ☐ High ☐

PART C – The Compliance-related Risk based on the last Inspection

The compliance risk indicated by the most recent deficiency profile of the site is:	Low ☐ Medium ☐ High ☐

- No Major or Critical Deficiencies
- 1 to 5 Major Deficiencies; *Number of Majors –*
- 1 or more Critical Deficiencies or more than 5 Majors

(Note: Customise as appropriate)

PART D – The Risk-Rating assigned to the Site

Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the **Risk Rating** for the site.

Compliance Risk	Intrinsic Risk: Low	Medium	High
Low	Risk Rating – A	Risk Rating – A	Risk Rating – B
Medium	Risk Rating – A	Risk Rating – B	Risk Rating – C
High	Risk Rating – B	Risk Rating – C	Risk Rating – C

The Risk Rating associated with this site is: A ☐ B ☐ C ☐

PART E – The Recommended Frequency for Routine Inspections at the Site

A Reduced Freq, 2 to 3 yrs B Moderate Freq, 1 to 2 Yrs C Increased Freq, < 1 yrs *Customise as appropriate*	Using the Risk Rating, the recommended frequency for routine inspections at the site is an inspection every: _____ Years or _____ Months

PART F – Recommended Scope of the next Routine Inspection

Note: This Part should be periodically updated if new information is received about the site before the next routine inspection that may warrant a change in the scope of that inspection.

For example, information can be received relating to, Quality Defects, Recalls, Market Surveillance Test Results, Enforcement Investigations, and other indicators of non-compliance, such as the failure to implement a variation to an MA, that might require the scope of the next inspection to be changed. Information may also relate to major changes at the site (indicated perhaps via an MA variation or a manufacturing authorisation variation submission) and this may warrant a change in scope.

Document on the right the **recommended focus & depth** of the next routine inspection. ***Note:** Take into account the following:* • The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies; • The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site; • The areas that were considered inadequately resourced at last inspection; • Planned changes at the site that may alter the complexity or criticality risk ratings associated with the site • Any other area that the inspector feels warrants review at the next inspection.	
Document on the right the **required duration** of the next routine inspection:	
Document on the right the **required number of inspectors** that should be assigned to the next routine inspection:	
Document on the right any **specific competence or expertise** that will be required on the inspection team when performing the next routine inspection of the site:	

PART G – Signatures & Dates

Record here the names of the persons who completed this quality Risk management exercise, and sign and date this form:

Name: _____ Name: _____

Name: _____ Name: _____

Signed: _____ Date: _____

Fulfill the Legal Requirement for 'Inspection'

EudraGMDP

efpia

PIC/S **RISK-BASED INSPECTION PLANNING**, PIC/S GUIDELINE PI 037-1, 1 JANUARY 2012

Content of GMP Inspection 'Reliance Assessment Report'

Information from the site	Scope of the inspection	Reliance statement	Basis for the assessment
• Name and address of the manufacturing site (SMF) • Further details e.g., building number/GPS location/UFI (SMF) • Name and contact details (SMF) • GMP compliance statement by the site	• Specific products/dosage forms within scope, as applicable • Activities within the scope e.g., - manufacture of API - non-sterile finished product - sterile finished product - biological finished product - packaging - distribution - importation	• Name of the hosting NCA • Basis on which country reliance has been established (e.g., MRA, PIC/S, WHO Global Benchmarking tool)	• List of reviewed documentation - incl. GMP Certificate / inspection report • Confirmation that products and activities of interest are covered • Verification of the accuracy of the Information reviewed (e.g. verification of translation)

Regulatory Decision

Assessment of the outcome and rationale

COLLABORATION, RELIANCE, DELEGATION

Inspections by a Local Inspectorate can be More Efficient and Mature than an Inspection from a 3rd Country

Prerequisite

- High quality standards embraced and supported by the local government
- Evaluation of national regulatory systems by an independent control / maturity metrics e.g., PIC/S member inspectorates, WHO Global Benchmarking Tool

Advantage

The local inspectorate has

- Flexibility regarding coming back and following up on issues
- Knowledge on the site specific history
- Insight on culture i.e., do/don'ts in the local area
- Optimisation of resources
- Benefit from improved inspection logistics e.g., no language barrier, less travel / environmental friendly

Transparency

- A non-compliant local site may put the integrity of the local inspectorate at risk
- Direct access for feedback on CAPAs
- Inspectorates may not like to see their local manufacturing sites in the headlines

Survey Data and Trends

Lessons Learned from the Data 1/2

- **More than 50% of the inspections are reported at sites located in the EU**
  - We are assuming that research based manufacturers have a very strong European presence above any other country or region
- **Evolution of number of foreign inspections versus manufacturing sites is back to the baseline from 2006**
  - The inspection rate for foreign inspection was continuously reduced till 2012 with the Russian driven peak in 2016/2017 and dropped in 2020
- **We understand there are opportunities for a better risk-based approach as some inspectorates are coming very often inspecting to the same sites e.g.,**
  - Russia (11), Japan (9), Turkey (6), Brazil (3), US (3)
- **We understand some inspectorates are usually showing up with more than 2 inspectors at a site e.g., EMA, Japan, Singapore, US.**
  - This can be for training purpose or including a CMC-reviewer

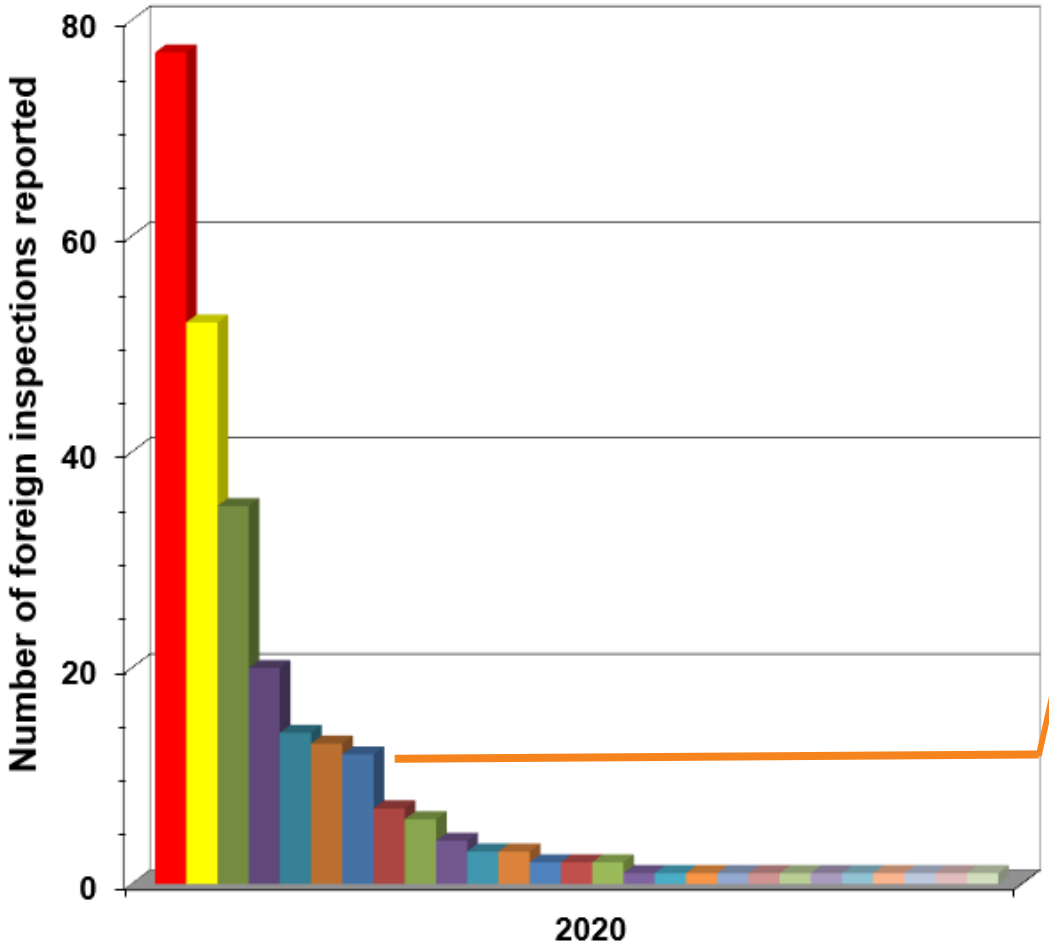
Lessons Learned from the Data 2/2

- **Inspections**
  - Although there were significantly fewer foreign inspections (approx. -50%) the number of sites with inspections remains comparable to previous years
  - Inspections from domestic inspectorates seem to be more effective to uncover issues as more follow-up investigations are reported
  - Pre-approval inspections, especially when paper-based, may be understood as a bureaucratic act in the registration process
- **Certification Audits**
  - Certification audits are shorter in duration than regulatory inspections
    - Assumption: do they know the site and look in updates only?
  - Notified body certifications are reported several times at the same site (up to 9)
    - Then product wise certification is a requirement this may drive to duplication the oversight of the Quality System (for devices) at a specific manufacturing site

Foreign Inspections
(incl. MRA EU/US)

Number of Foreign Inspections at Manufacturing Sites

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



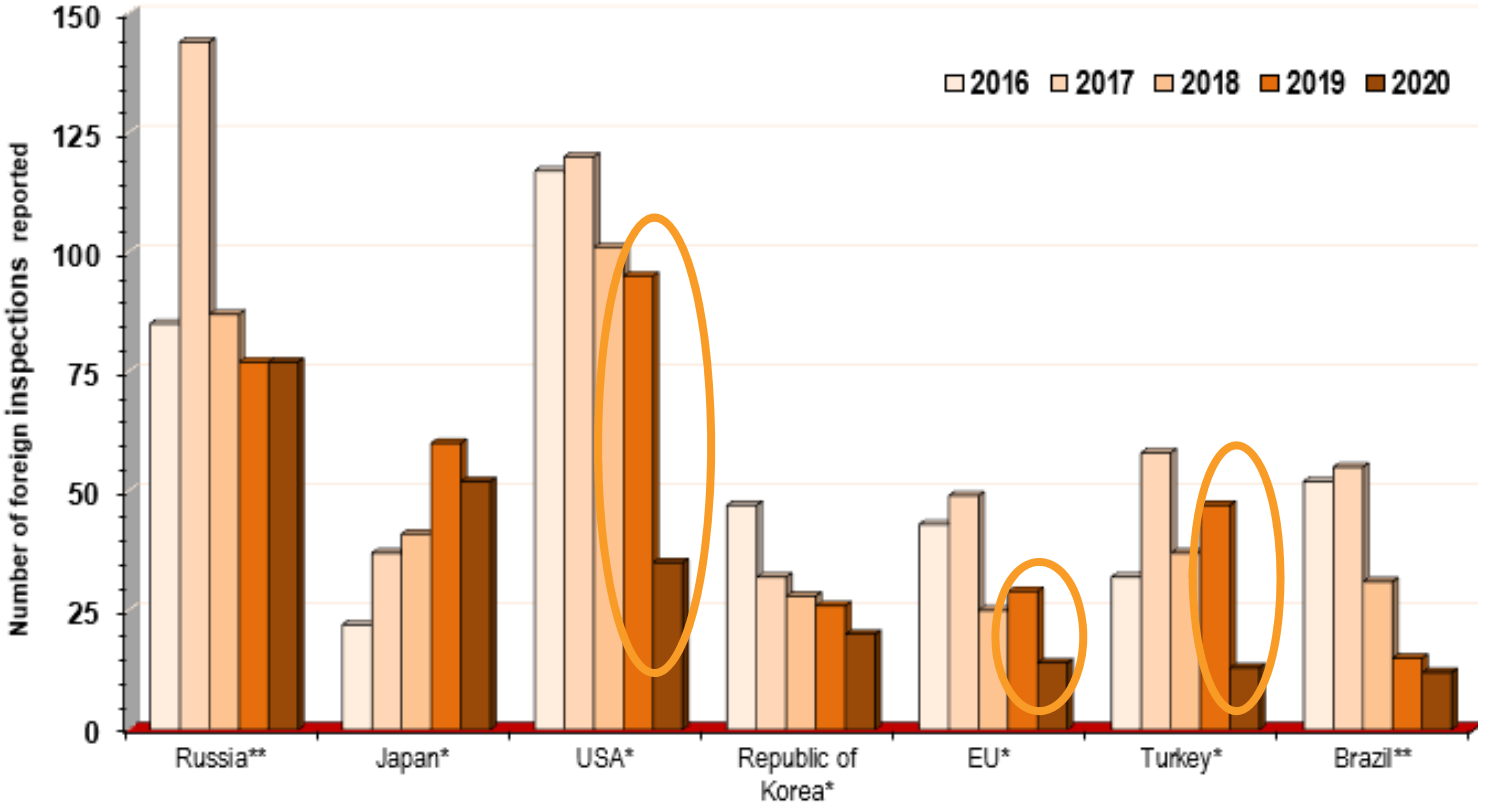
Performed by

- Russia**
- Japan*
- USA*
- Republic of Korea*
- EU*
- Turkey*
- Brazil**
- Belarus
- Mexico*
- Canada*
- Australia*
- Kenya
- China
- Chinese Taipei*
- Gulf States (GCC)
- Bosnia Herzegovina
- Colombia
- EAEU
- Indonesia*
- Jordan
- Saudi Arabia
- Singapore*
- South Africa*
- Uganda
- Ukraine*
- United Arab Emirates
- Vietnam

> 12

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

Number of Foreign Inspections by Country - A Year Like No Other



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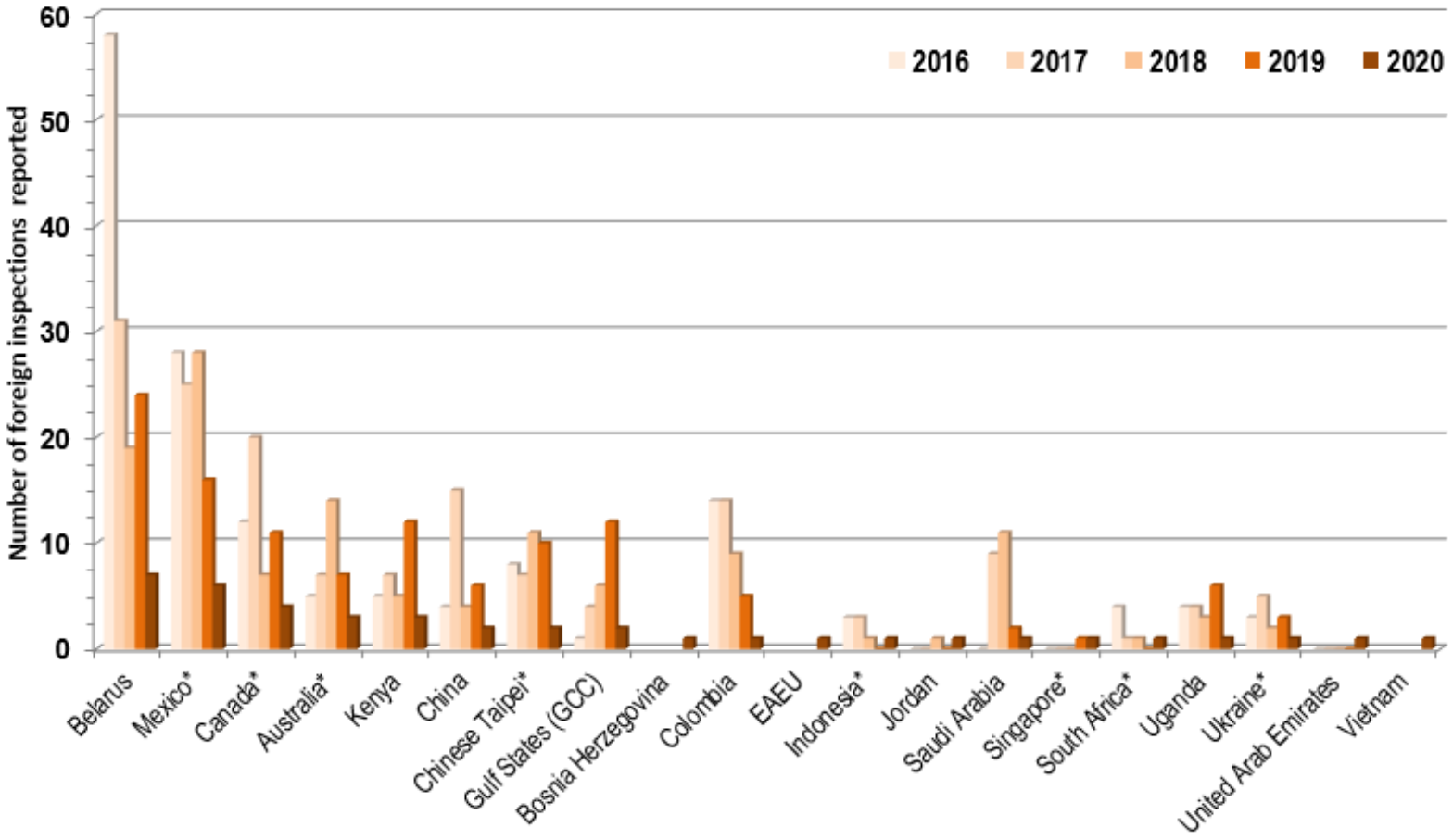
Number of Foreign Inspections by Country - A Year Like No Other: 2020 Reduces Compared to 2019



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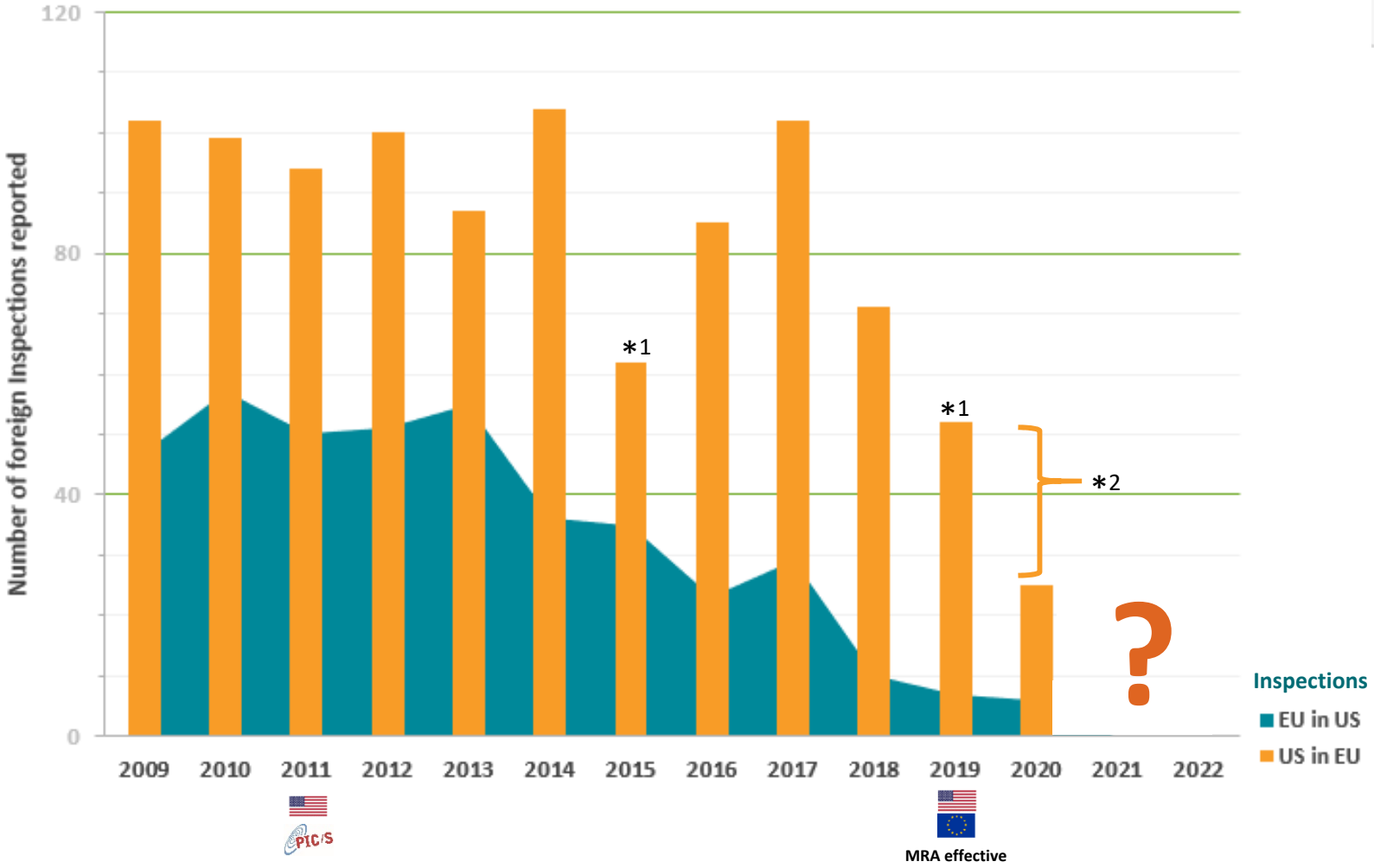
Full EU / US MRA Implementation Could Leverage Further Benefit



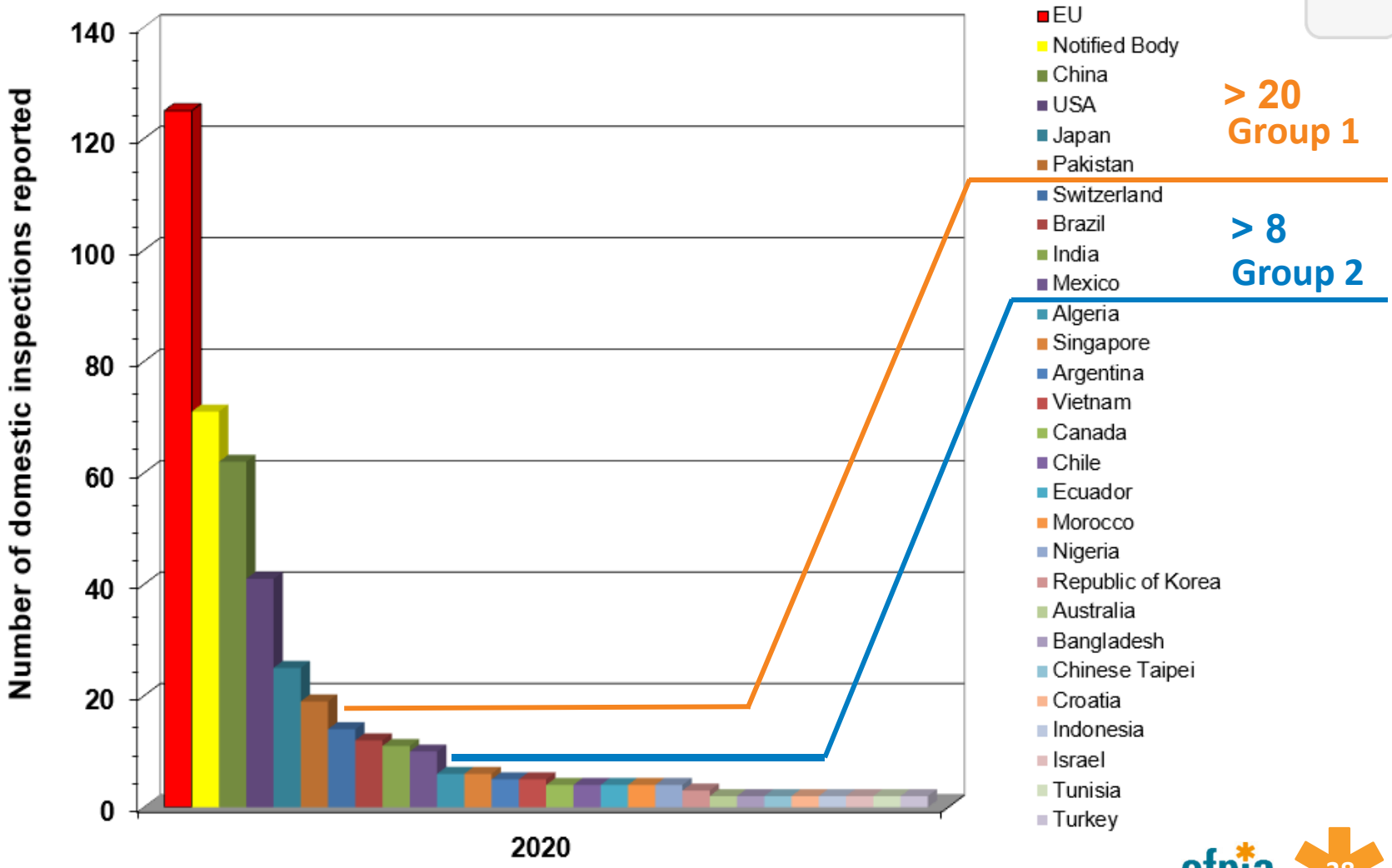
*1 Government shut down in US >20 days

*2 Effect may only result from the general reduction of foreign inspections in 2020 (~50%)

Domestic Inspections

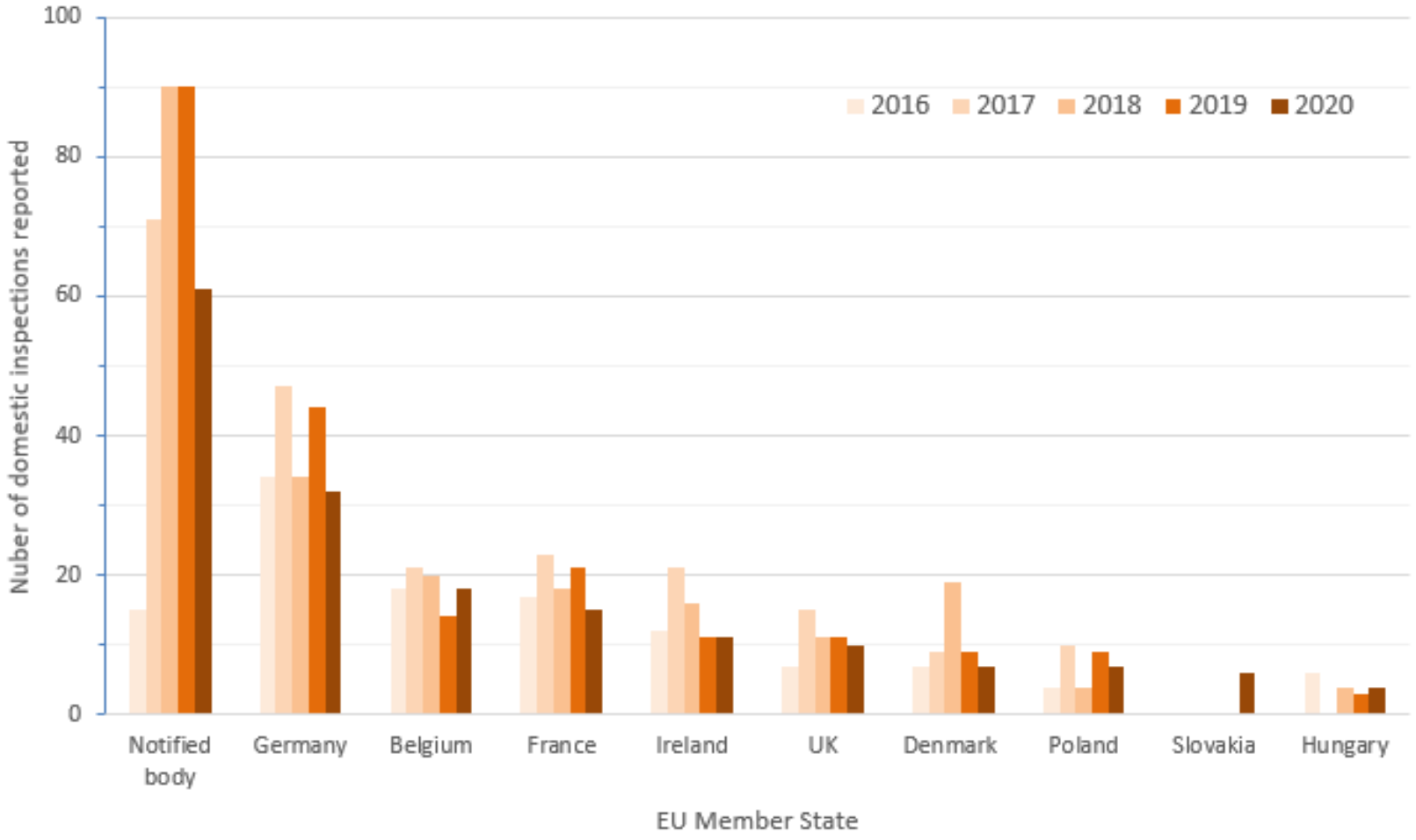
Number of Domestic Inspections

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

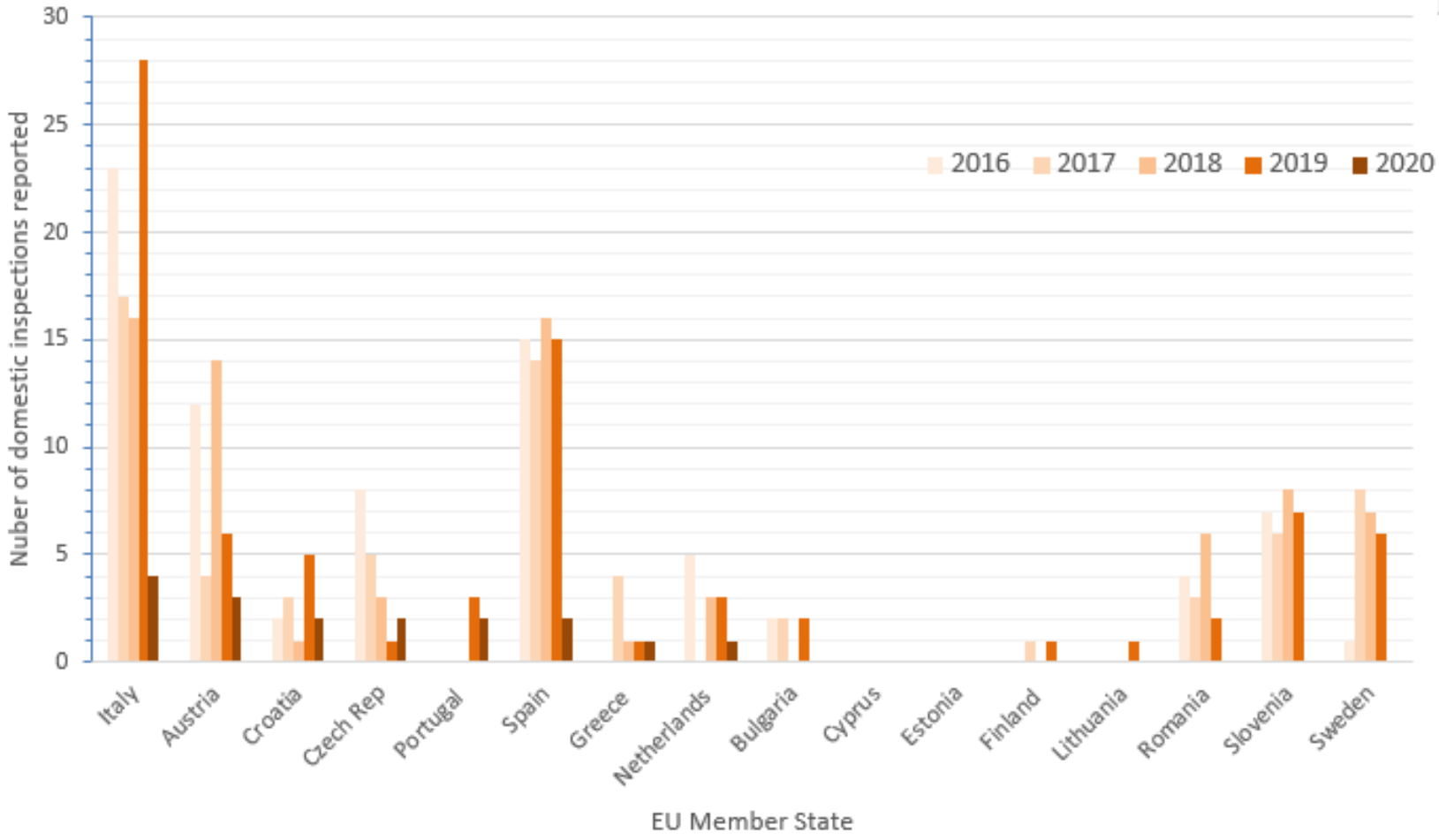


Only listed if more than 1 domestic inspection (12)

Number of reported Domestic Inspections by EU Member States 1/2



Number of reported Domestic Inspections by EU Member States 2/2



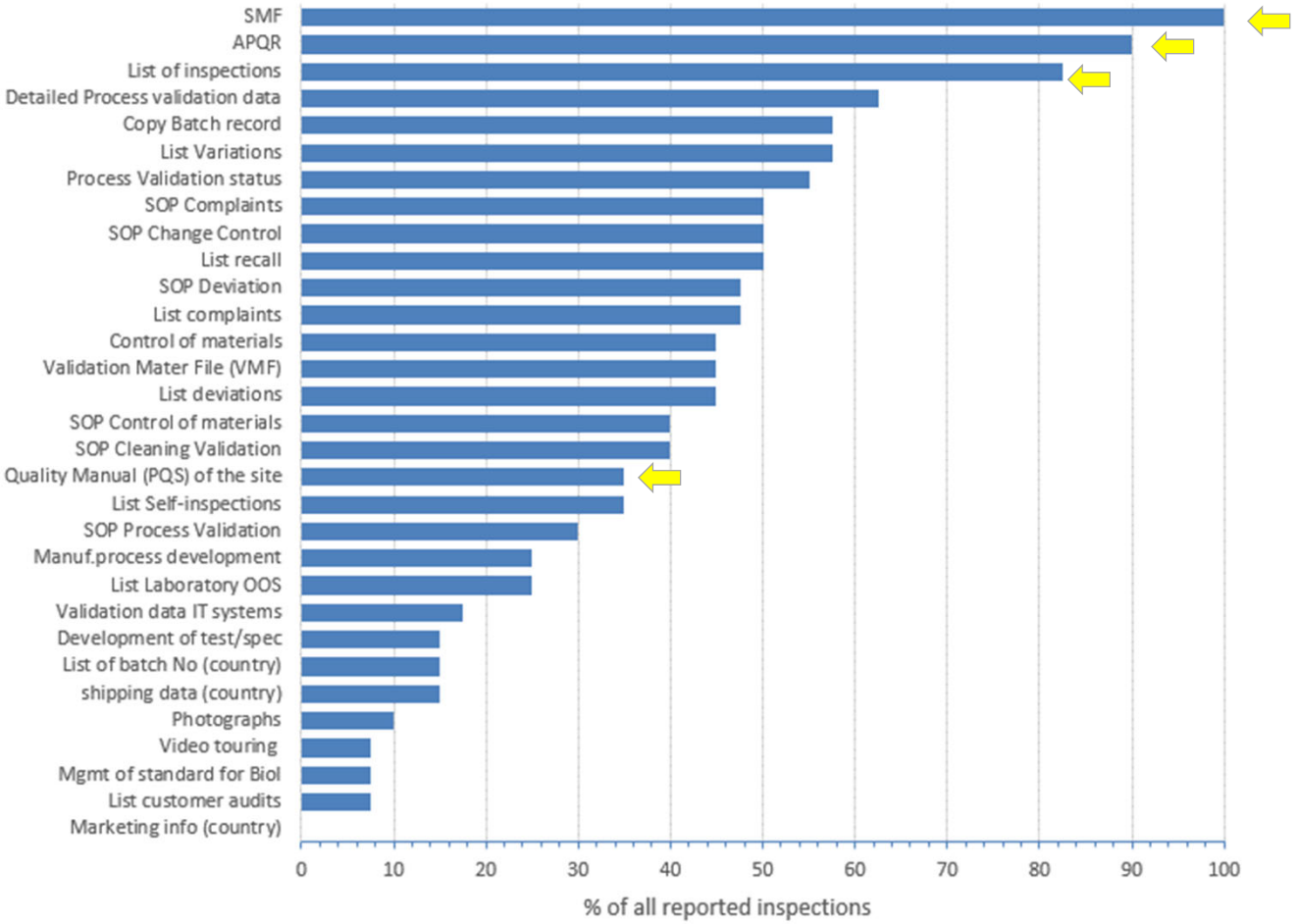
Paper-based Inspections

SURVEY DATA AND TRENDS 3: PAPER-BASED INSPECTIONS

How often is a Document Type Requested

Most countries

Documents



Number of documents to be submitted

- **Min** 1
- **Mean** 10
- **Average** 34
- **Max** 700

Considered as primary documents to be asked in paper-based inspections (see Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, EFPIA, *Position Paper*, **19. May 2014**

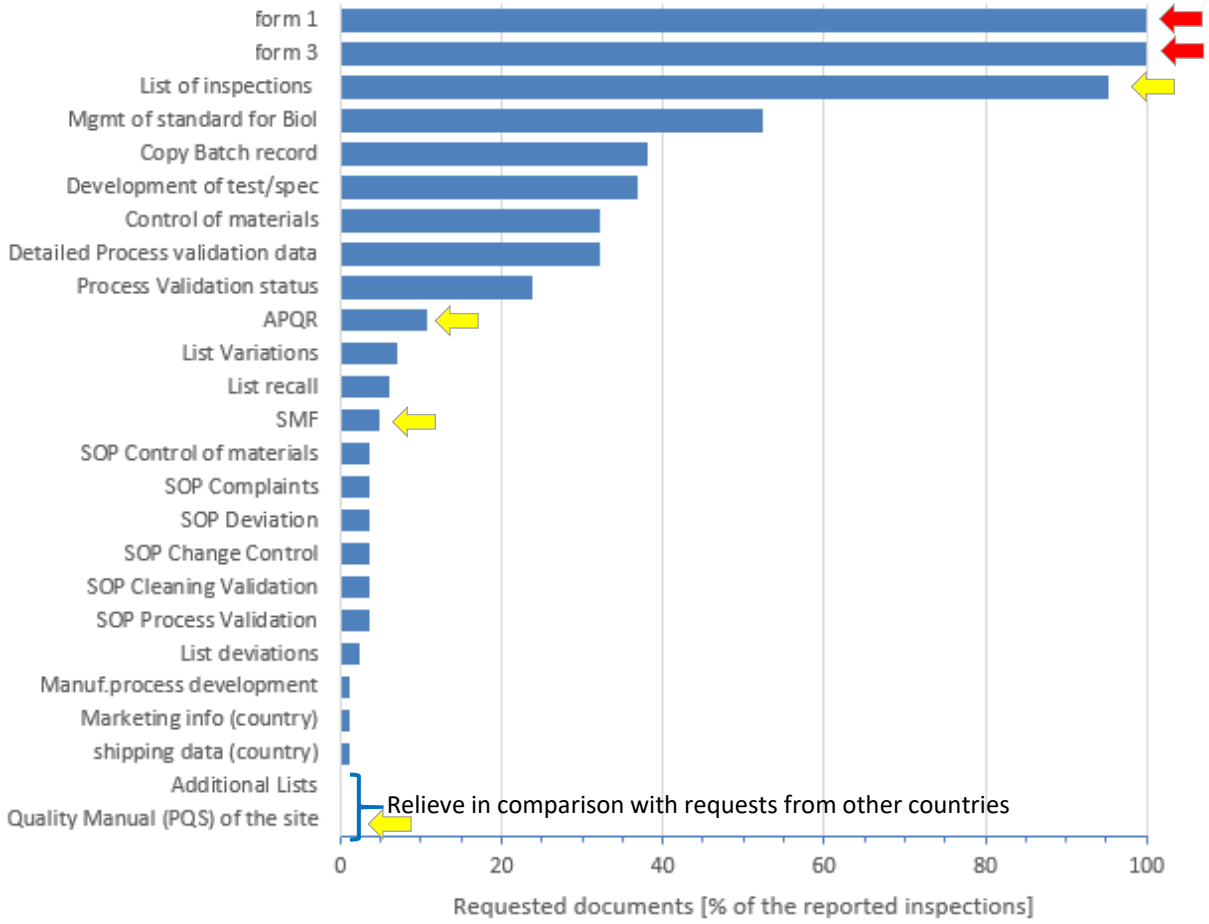
SEPARATE SURVEY: 270 DATA POINTS (01.JAN.2019 - 31.JUNE.2020) PROVIDED BY 11 COMPANIES

SURVEY DATA AND TRENDS 3: PAPER-BASED INSPECTIONS

Documents

How often is a Document Type Requested

One specific example



Number of documents to be submitted

- **Min 2**
- **Mean 8**
- **Average 15**
- **Max 200**

Agency's regulatory requirement

Considered as primary documents to be asked in paper-based inspections (see Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, EFPIA, *Position Paper*, **19. May 2014**

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SURVEY DATA AND TRENDS 3: PAPER-BASED INSPECTIONS

Information Provided by the Site can Follow a Commonly Agreed Standard for Paper Based Inspections

Documents

Site	• Site Master File (SMF)*
Product	• Annual Product Quality Review
Pharmaceutical Quality System	• Site Quality Manual
Additional information	• List of inspections / audits

Adobe Acrobat Document

Enhanced GMP/GDP Inspection Efficiency, EFPIA, Position Paper 19. May 2014.

Adobe Acrobat Document

Optimising the GMP paper based Inspection Process EFPIA, Position Paper 26. June 2019.

*EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE, PIC/S PE 008-4, Annex 1, January 2011

Inspection process and tools

Examples of Inspection at one Manufacturing Site of Different Companies

Site in country	Domestic inspections	Foreign inspections	Sum	Foreign inspectorates
Denmark	2	**7**	9	Japan (3), Russia (2), Brazil (1), Turkey (1)
Germany	6	**3**	9	Russia (2), Turkey (1)
Denmark	2	**6**	8	Japan (3), Brazil (1), GCC (1), US (1)
Slovenia	7	**1**	8	Russia (1)
Denmark	0	**7**	7	Australia (1), Japan (3), Brazil (1), Russia (1), Turkey (1)
Switzerland	4	**3**	7	Belarus (1), Russia (1), Turkey (1)
Austria	3	**3**	6	Russia (3)
Belgium	3	**3**	6	Turkey (1), Russia (1), US (1)
France	1 (+2*)	**3**	6	Russia (1), Turkey (1), US (1)
US	2	**4**	6	EMA (1), Japan (1), Republic of Korea (1), Russia (1),

Top 6 and more inspections at one site if reported by the companies

- Domestic inspections only by
  - China: 3 sites with 7 inspections and 2 sites with 6 inspections
  - Belgium: 1 site with 5 inspections + 1 Notified Body
  - Japan: 1 site with 6 inspections
  - Saudi Arabia: 1 site with 6 inspections
  - Switzerland 1 site with 7 inspections (6 by Notified Body)
  - US: 1 site with 12 inspections (9 by Notified Bodies)

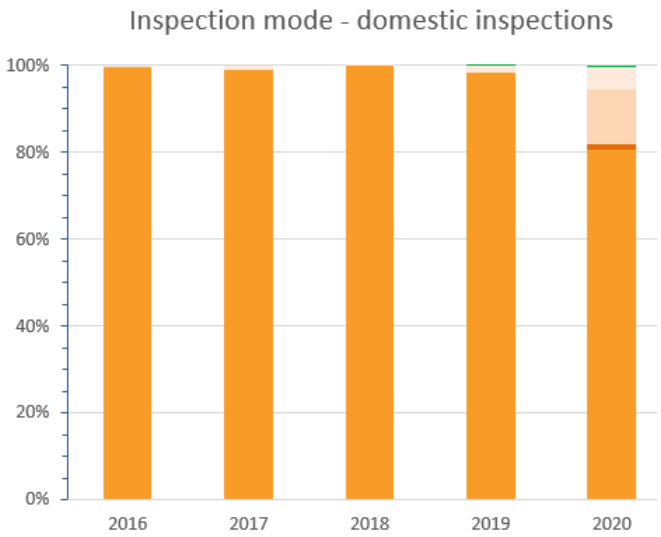
Consideration: *Notified body certifications are reported site several times (up to 9) at the same site. Then product wise certification requirement may drive to duplication in the oversight of the Quality System (for devices) at a specific manufacturing site*

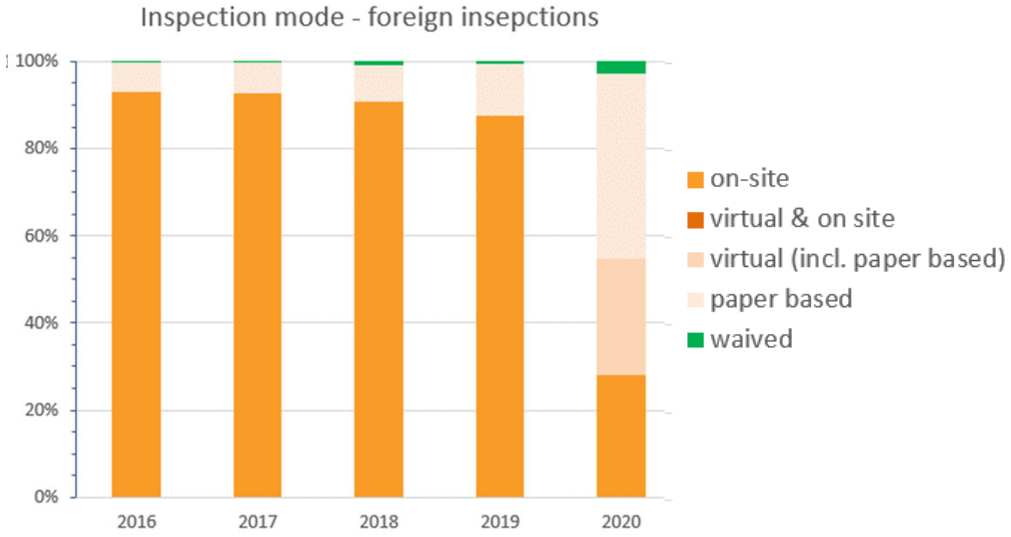
* **Countries with opportunities for a better risk-based approach include**

- Russia (11)
- Japan (9)
- Turkey (6)
- Brazil (3)
- US (3)

SURVEY DATA AND TRENDS 4: INSPECTION PROCESS AND TOOLS

The Use of Inspection Tools has Changed in 2020

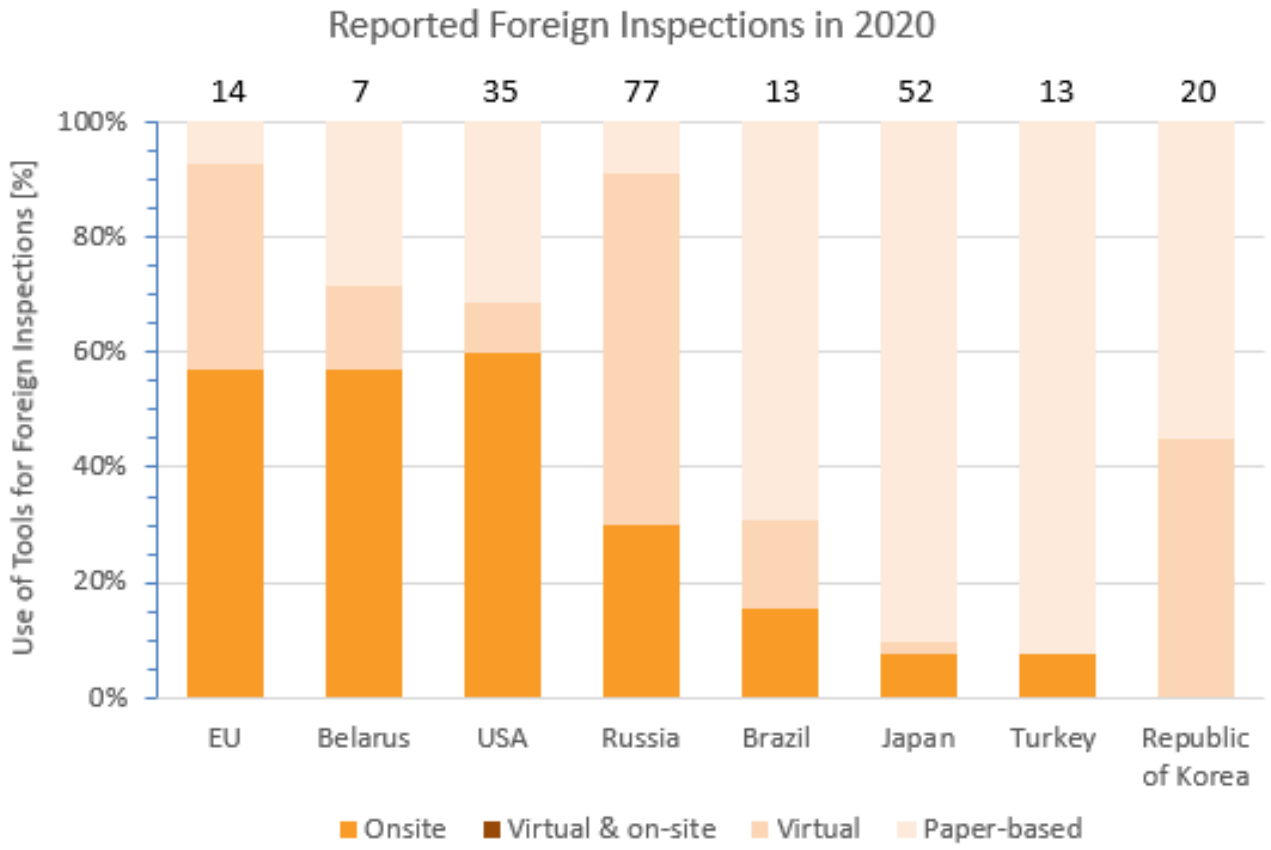




- > 80% of the domestic inspections have at least a partial on-site presence
- < 25% of the foreign inspections have been conducted with on-site presence

Inspectorates Vary in the Use of the Tools

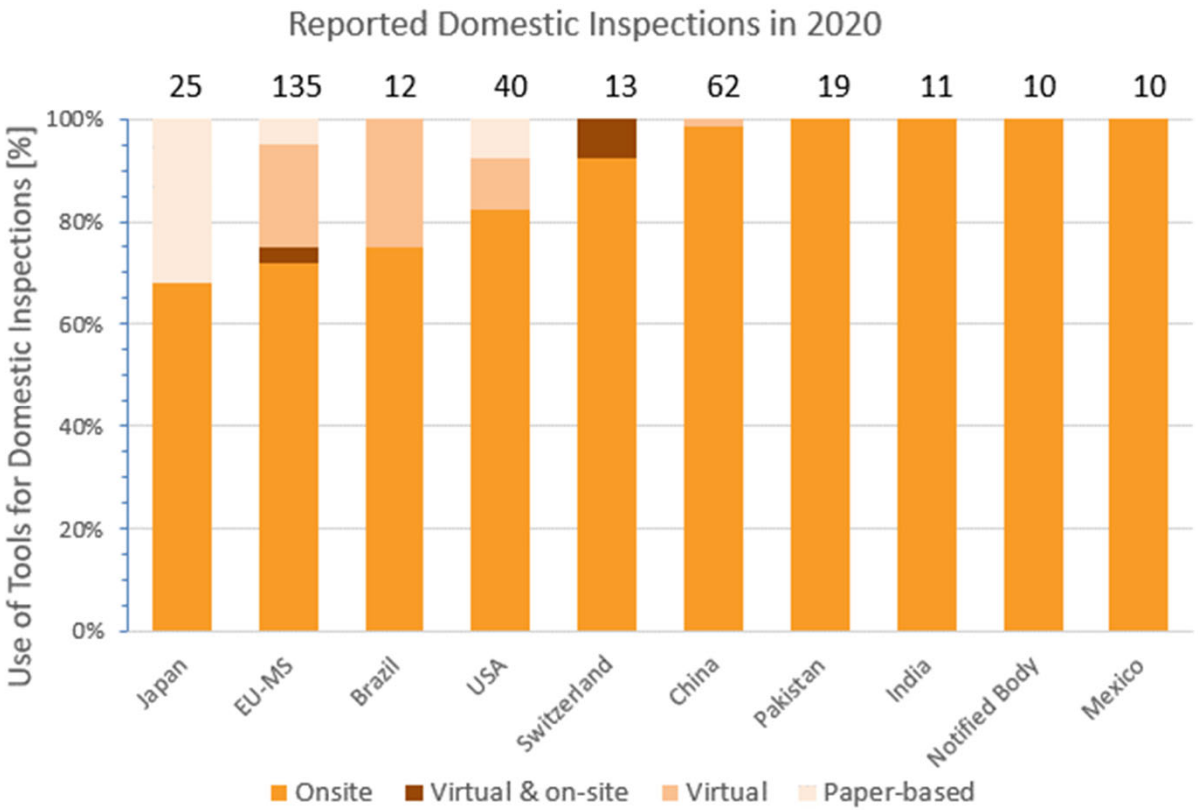
Example: Foreign Inspections



Note: no agency is reported to use a hybrid approach in foreign inspections

EU Member States* used Alternative Inspection Tools

Example: Domestic Inspections

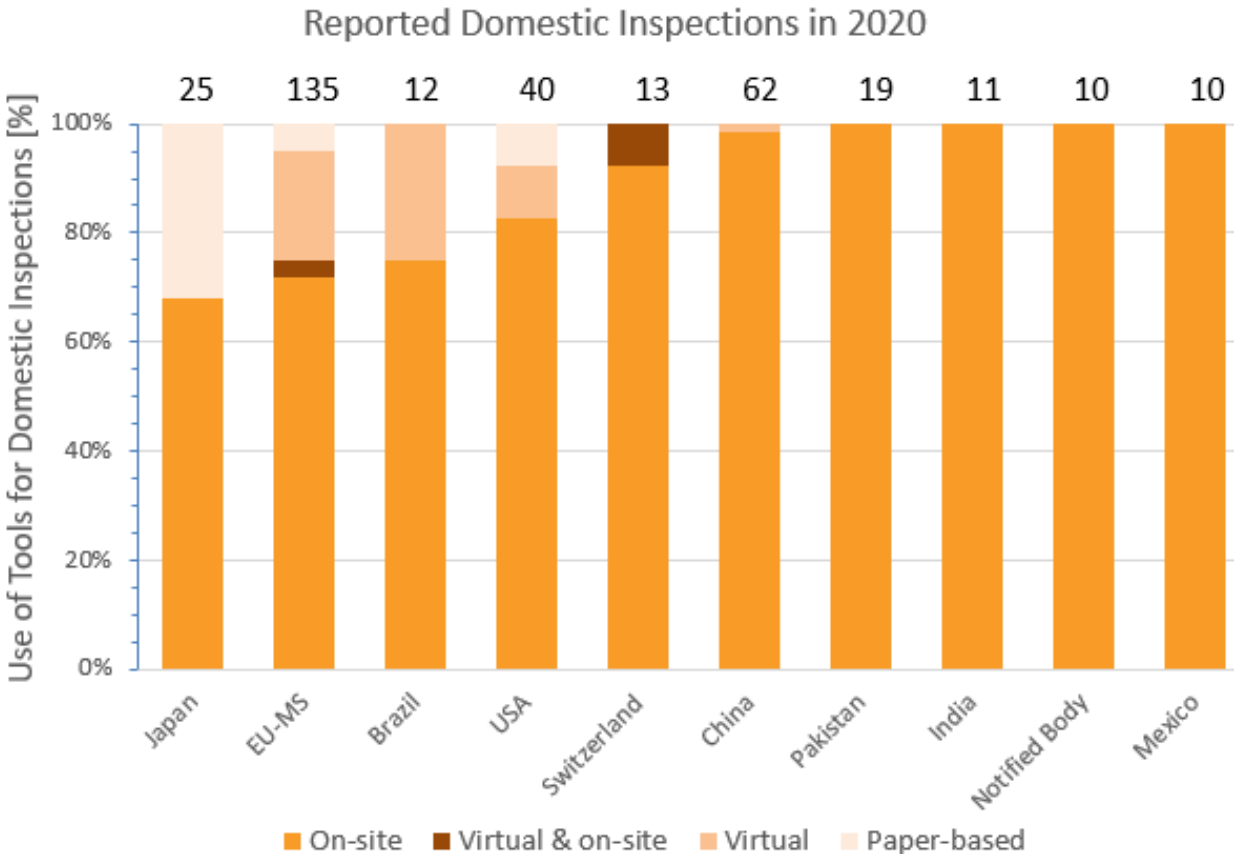


Experience with implementing the virtual inspection tool is reported by

- Belgium
- France
- Germany
- Ireland
- Notified Body
- Poland
- UK

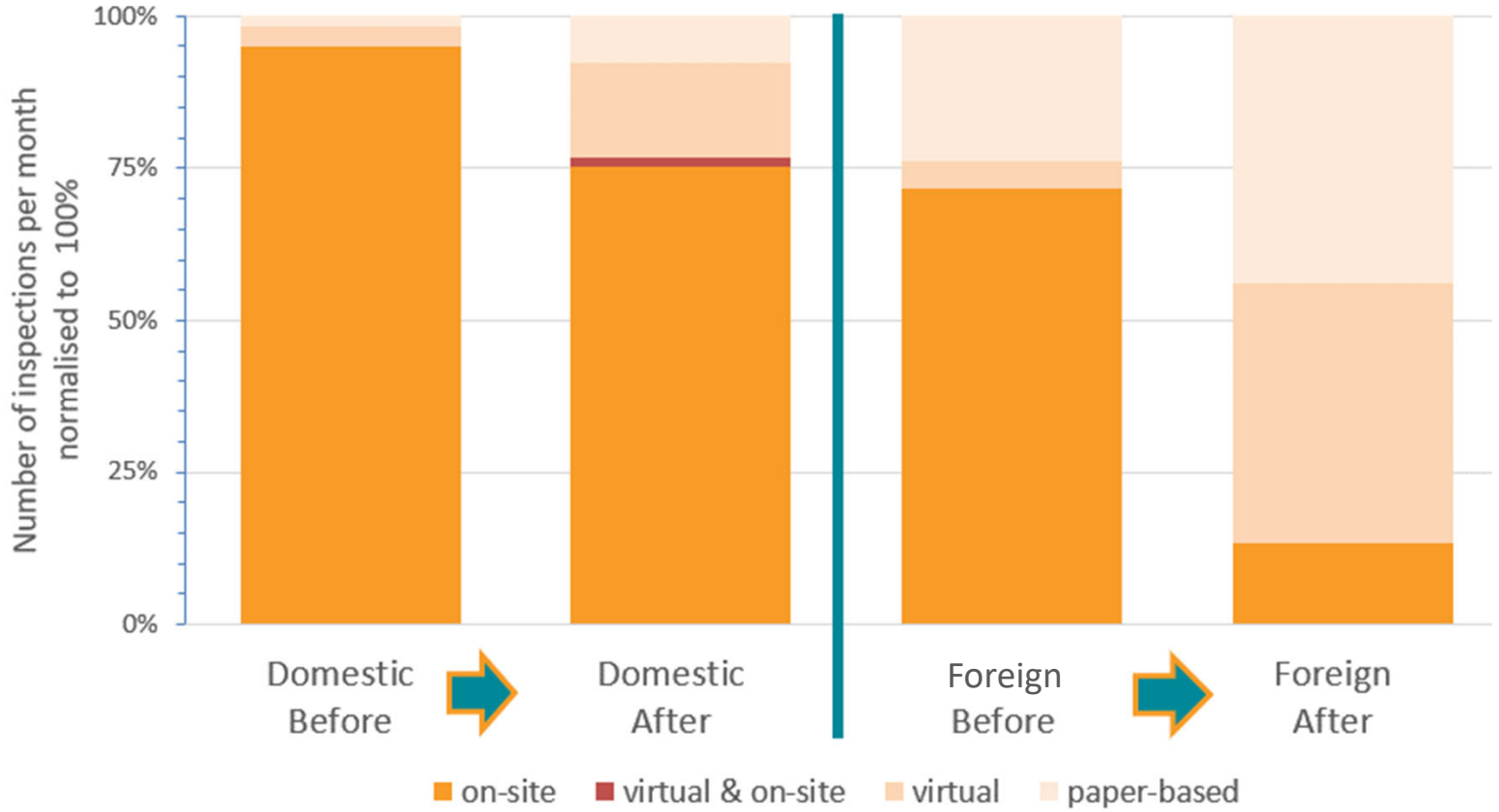
*UK counts as EU Member State in 2020

Domestic Inspectorates may not Adopt the Virtual Tool



* **Experience with implementing hybrids of virtual & on-site tool**
  * EU-MS
  * Switzerland

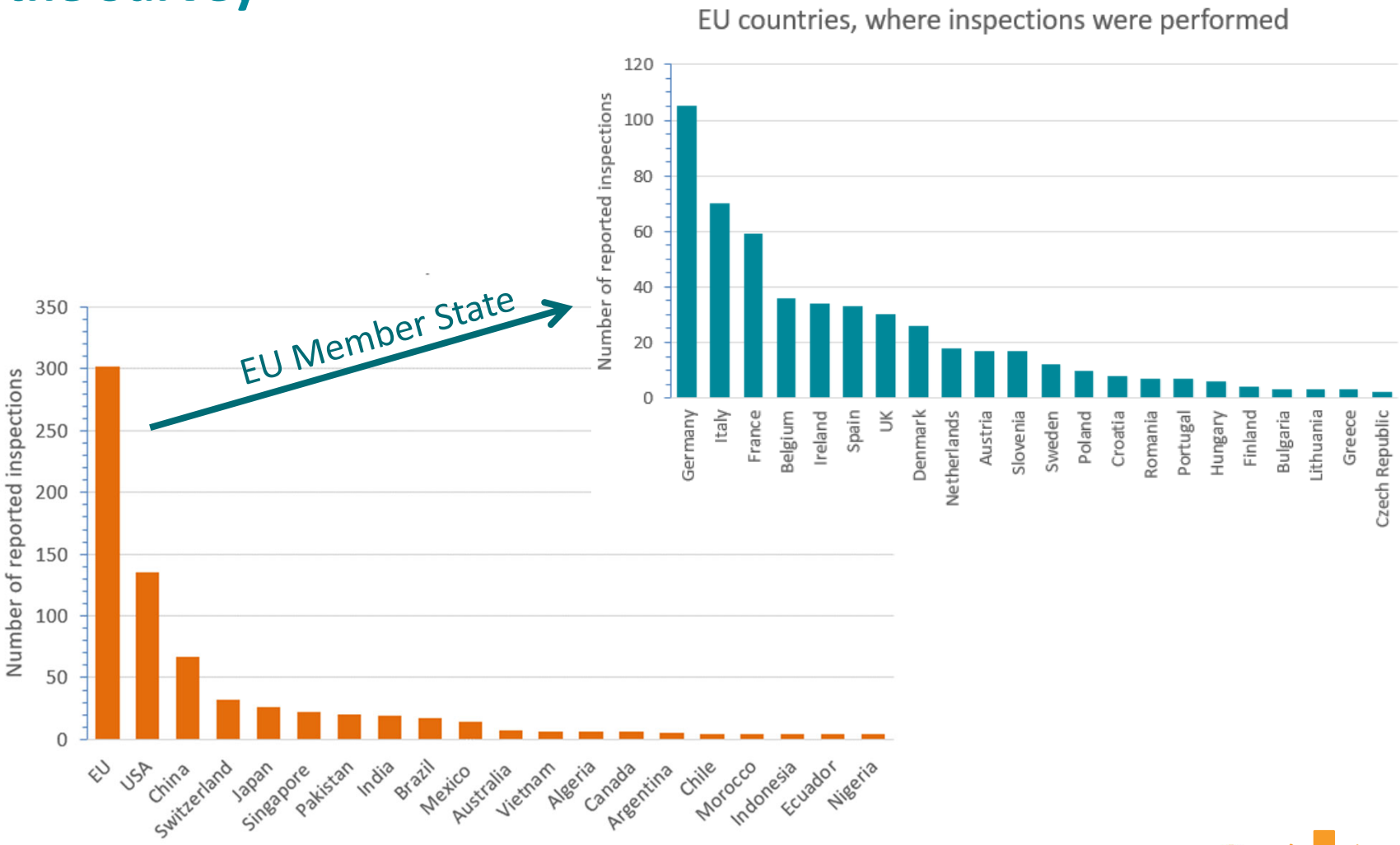
The Pandemic Restrictions Drove the Need for Agencies to use Alternative Approaches for Inspections at Sites and Affiliates



* A large percentage of the domestic inspections still occurred on site after the outbreak

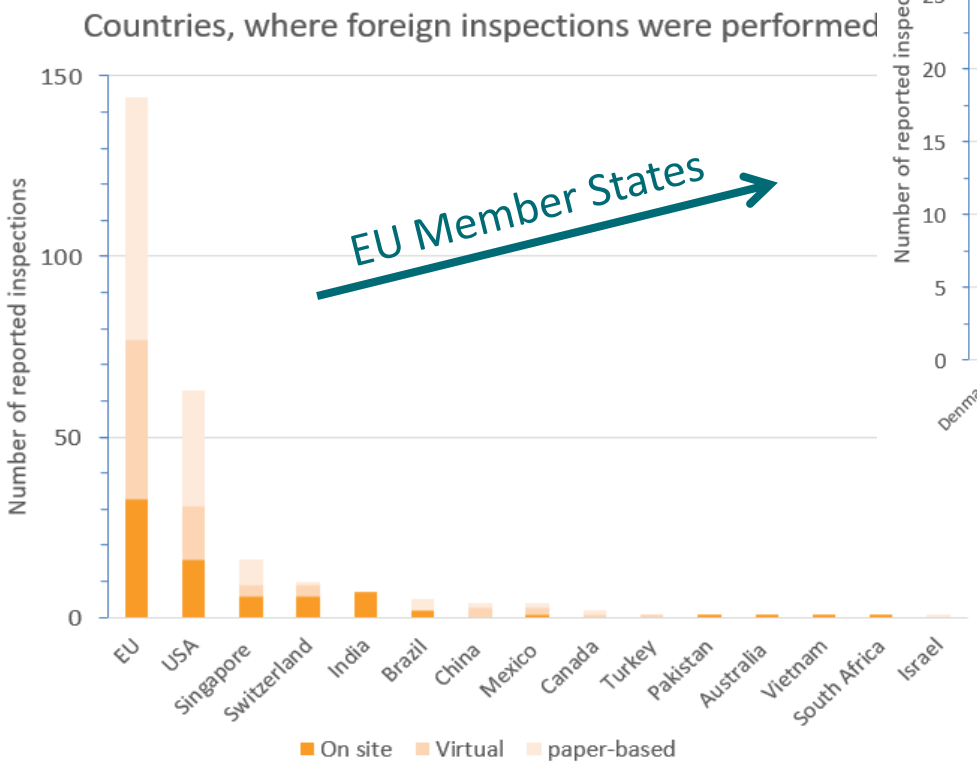
Location of Manufacturing sites

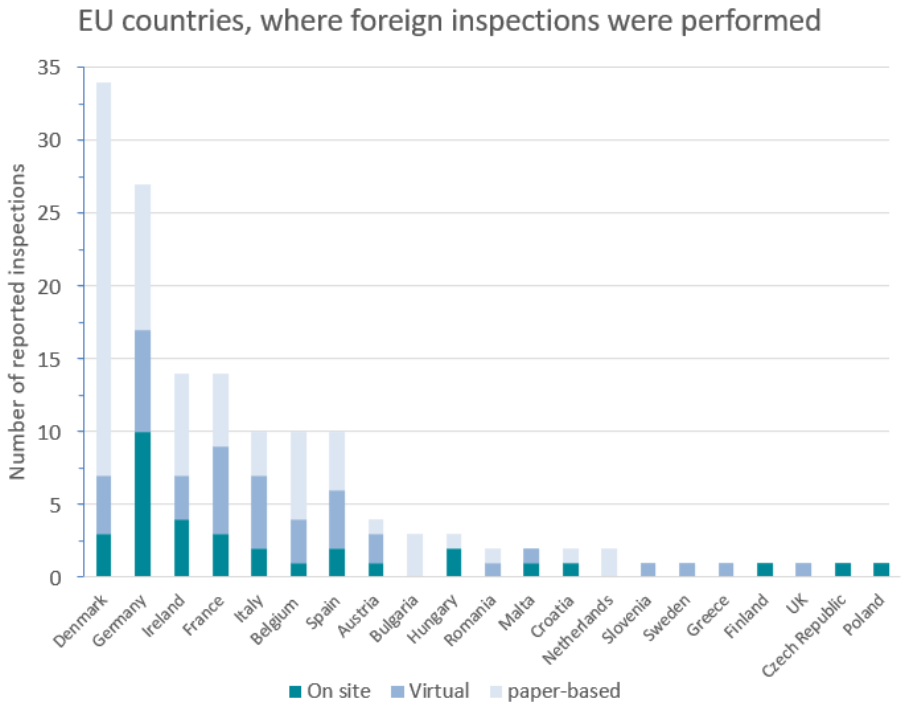
Locations of Manufacturing Facilities Included in the Survey



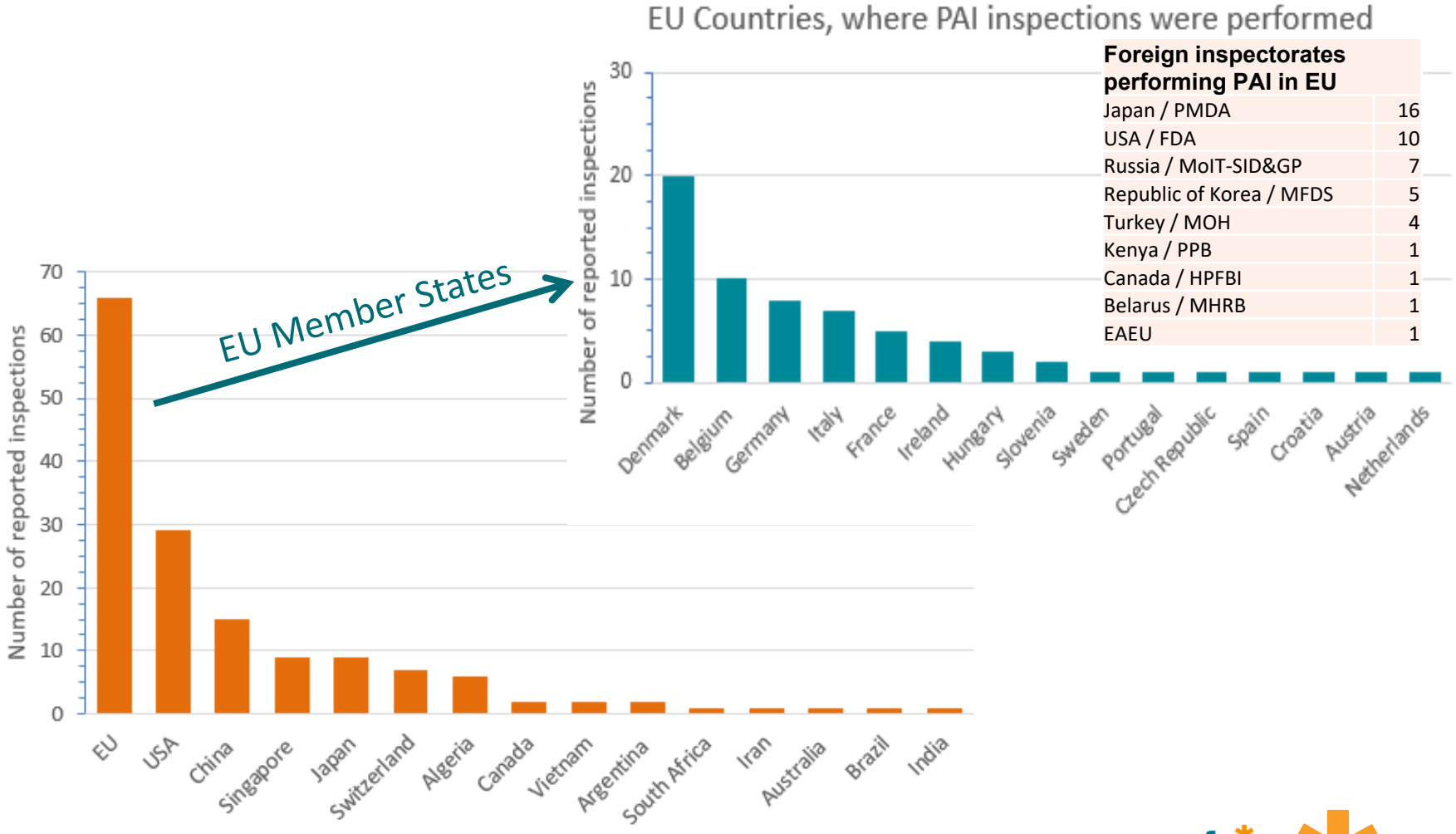
Countries listed with sites having > 4 inspections

Locations of Manufacturing Facilities Hosting Foreign Inspections





Locations of Manufacturing Facilities Reporting PAI Demonstrating where Innovative Products are Manufactured



Foreign inspectorates performing PAI in EU	
Japan / PMDA	16
USA / FDA	10
Russia / MoIT-SID&GP	7
Republic of Korea / MFDS	5
Turkey / MOH	4
Kenya / PPB	1
Canada / HPFBI	1
Belarus / MHRB	1
EAEU	1

Resource Considerations

Significant Resources Required

Example: Foreign on-site Inspection

Resources	Inspector	Industry
Preparation[1]	4 person days (experience from industry audits)	40 - 240 person days (average ~ 70) (due to specific requests by individual inspectorates)
On site[2]	8 person days (on average 2 inspectors 4 days)	60 - 144 person days (4 days, average ~ 112)
Post-inspection[3]	4 person days (experience from industry audits)	10 - 86 person days (average ~18)
Sum	16 person days	110 - 470 person days (average ~200) 115 - 500 k€ (based on ~131 €/h; average = 210 k€)
Travel	4 person days (2 inspectors 2 days in average)	0 - 150 k€ (0-150 k€; 6 (0-15) companies SME to travel to the site incl. overseas, considered to be approx. 10k€/SME: average ~60 k€)
Staff related	**20 person days**	**115 - 650 k€[3] (average ~270 k€)**

- **A wide range of cost**
- **Domestic inspections are less expensive than foreign inspections**

[1] Includes e.g., resources for translations, as applicable
[2] Excludes e.g., cost of interpreters
[3] Excludes e.g., direct costs (e.g., loss of productivity) and indirect costs (e.g., CAPA resolution, capital investments)

Estimating Average Cost of one On-site Foreign Inspection

	For what	Estimated Costs
1	**Estimated administrative cost of executing** **a) Staff costs** **b) Translation**	**115 - 650 k€** (average ~270 k€) **0 - 70 k€** (average ~30 k€)
2	**Estimated EU inspection Fee** Size of manufacturing sites having ~14 (2-30) unit operations	**55 - 865 k€** (average ~325 k€)
3	**Estimated associated costs** special cases, product changes etc.	**0 - 1250 k€** (average ~200 k€)
Sum	**Cost of an inspection varies a lot**	**170 - 2835 k€** (average ~825 k€)

Updated assessment based on more detailed data assessment

 Source: separate survey during 2020