European Federation of Pharmaceutical Industries and Associations

# Annual Regulatory GMP/GDP Inspection Survey 2021 Data

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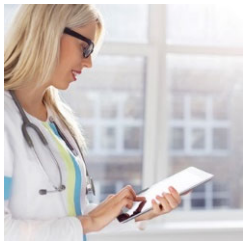
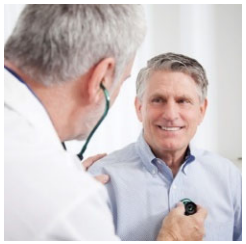





Presentation

# 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-certification audits
- Continue to promote reliance, collaboration and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections an ISO-certification audits
- Materialise the benefits of PIC/S and ICMRA membership in optimizing the use of inspection resources with a harmonized risk-based approach for inspections while maintaining patient safety

## Scope

- Regulatory GMP/GDP inspections and related ISO-certification audits
- Manufacturing sites and commercial affiliates worldwide
- Inside and outside the Regulatory Authority's own borders (domestic and foreign*)
- All tools used or combination from them: on-site and virtual presence, or document review as well as reliance/recognition approaches

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

## CONCLUSIONS OF THE 2021 EFPIA INSPECTION SURVEY

# The Pandemic is a Catalyst for Improving Ways of Working

*'The level of effort, formality and documentation … should be commensurate with the level of risk'* (ICH Q9)

**Tools**

- Increased use of alternative and effective tools
- An on-site inspection can not be fully replaced – *always needed?*
- Preferred: Virtual tool combined with on-site presence

**Method**

- Data show virtual tool and on-site inspection take similar inspection duration
- Keep an open mind applying risk-based approaches: use of the virtual tool, focus, frequency & duration
- Improvement opportunity: Sharing defined, focused set of documentation in advance

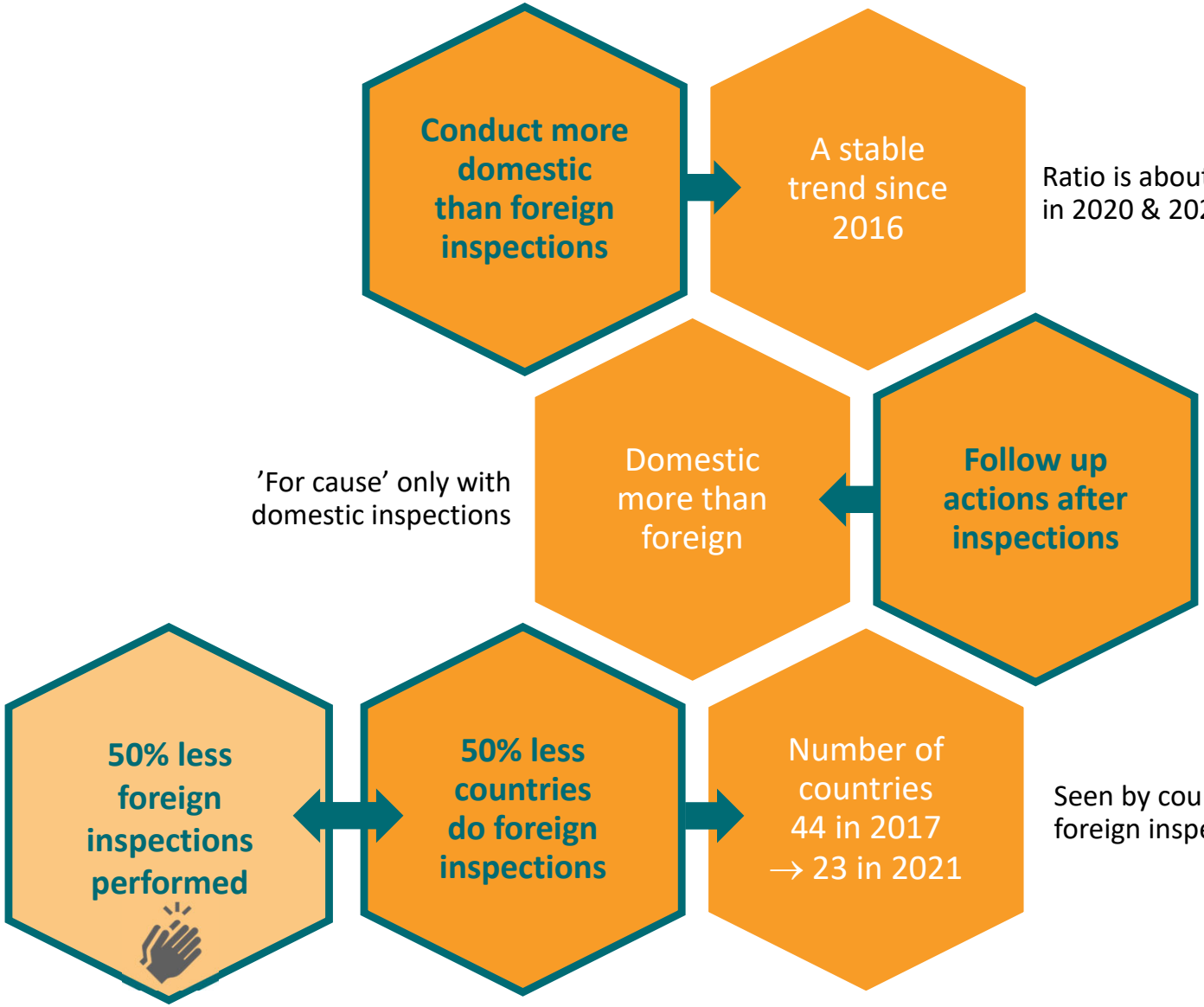
**Practices**

- Utilizing domestic inspections; jointly with 3rd countries?*
- Fully leverage and update existing MRAs; explore new MRAs
- Well founded reliance results in more knowledge and improves decision making

**Data / Recommendations**

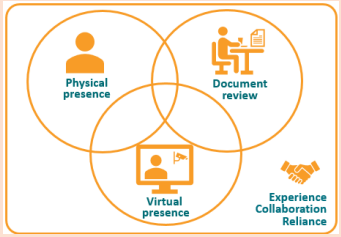
*e.g., ICMRA or EDQM 'hybrid' approaches i.e., with more than one inspectorate

# General Trends



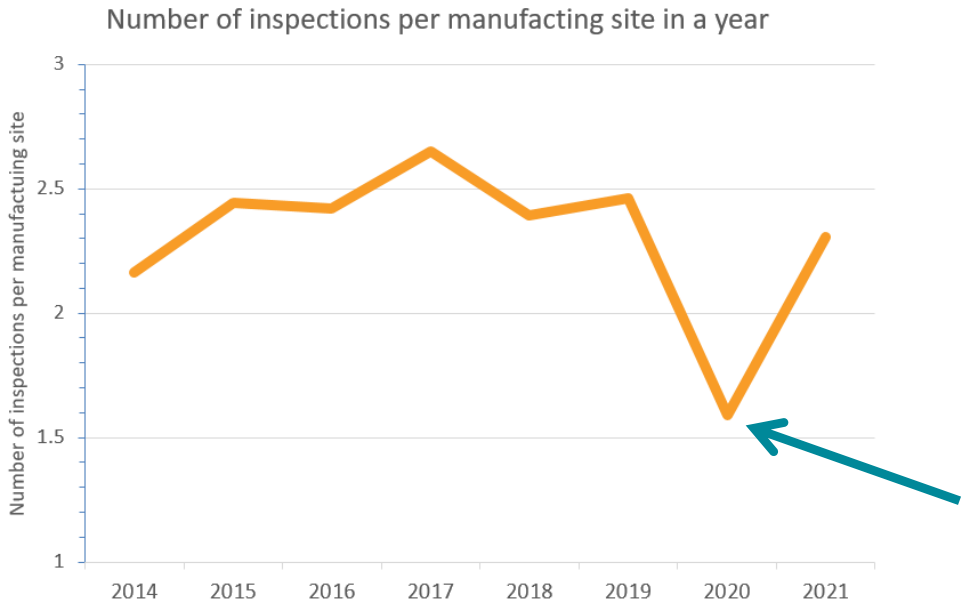
# Trends Induced by the Pandemic Continue

- Number of inspections - domestic: increasing; foreign: constantly low
- All inspection types performed (PAI, routine, for cause etc.)
- Extended use of the different inspection tools
- Domestic inspections: On-site inspections resumed sometimes in combination with virtual elements
- Foreign inspections: Number of countries* performing foreign inspection decreased: 42 in 2018 → 23 in 2021




*EU-Member States = one country

# The Number of Inspections at Manufacturing Sites in 2021 is Similar to Number Before the Pandemic




**However, the backlog due to the pandemic is remaining**

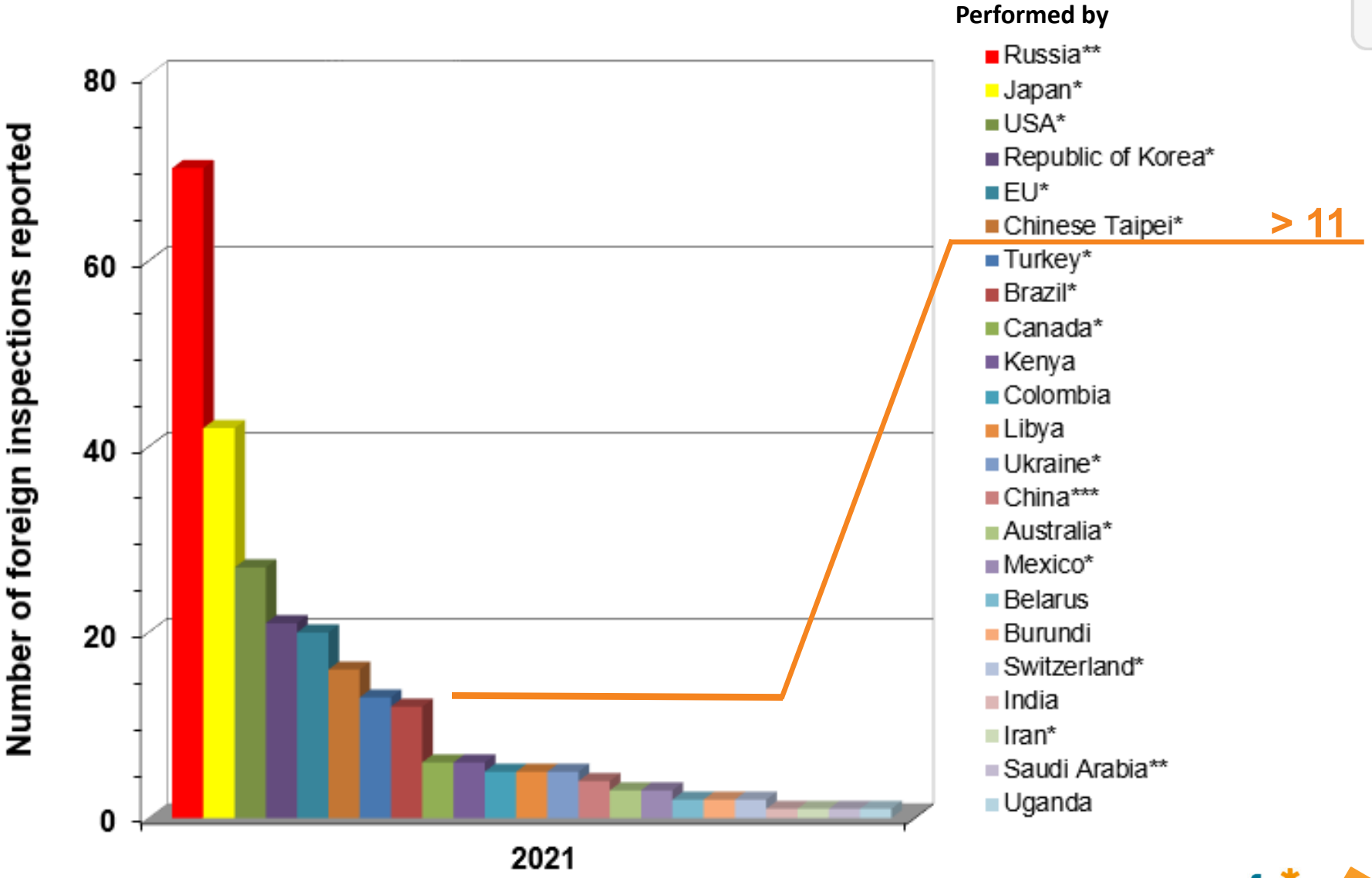
- **Suggestions for managing expiring GMP/GDP/ISO-certificates include e.g.,***
  - Pursue the current approach to prolong validity by an additional year
    Caution: the acceptance may change, when GMP-certificates are older than 5 years
  - Establish communication process between supervisory authority and companies when facing challenges with registration in a third country
  - Using the quality history of the site for planning and frequency of regulatory inspections incl. e.g., inspection history evidence of self-inspection, global audit/quality system programs



*suggestions from the answers on the questions in the survey

# Number of Foreign Inspections at Manufacturing Sites

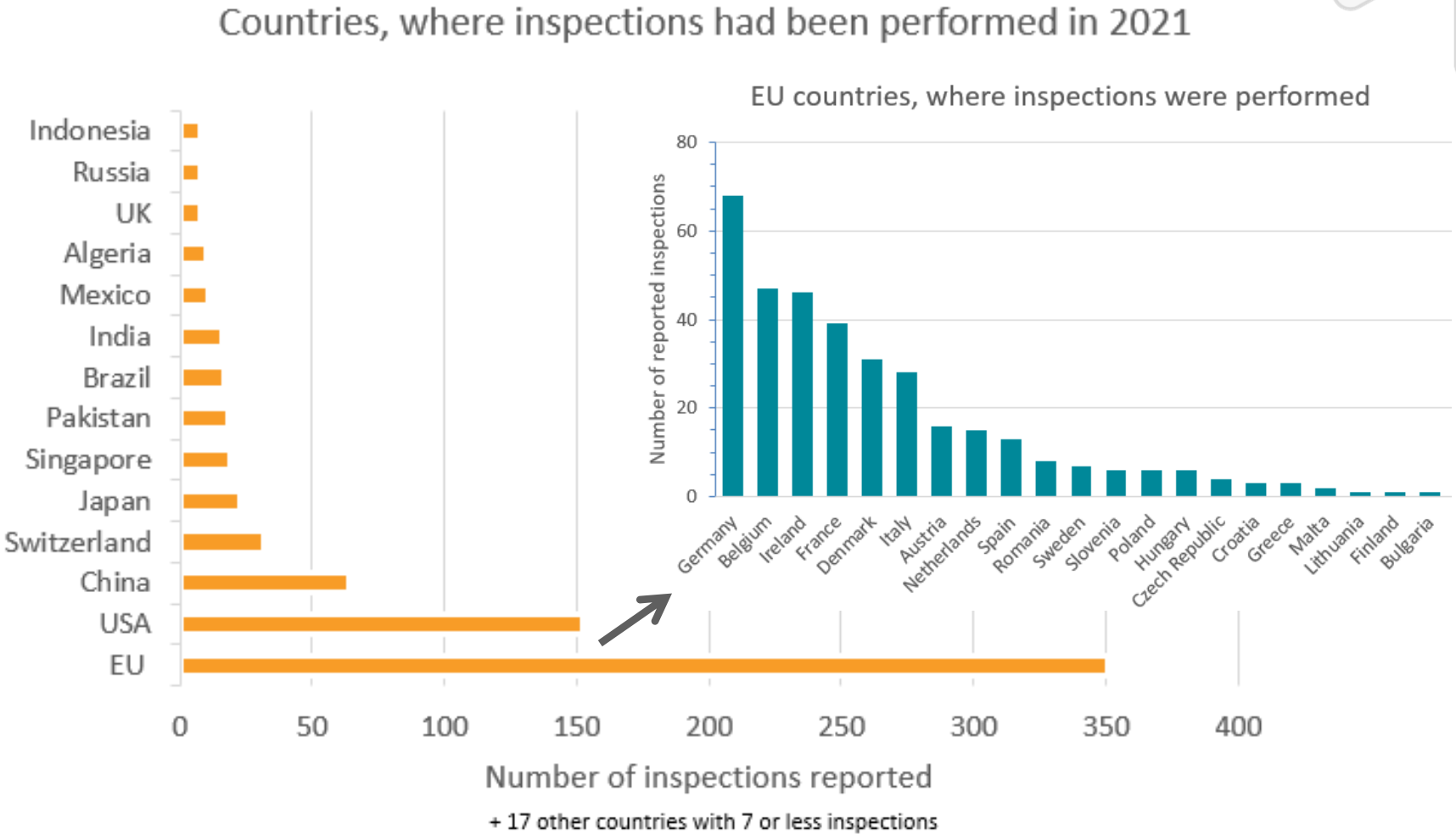
## ordered by country (EU as one entity; all inspection types and tools)




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

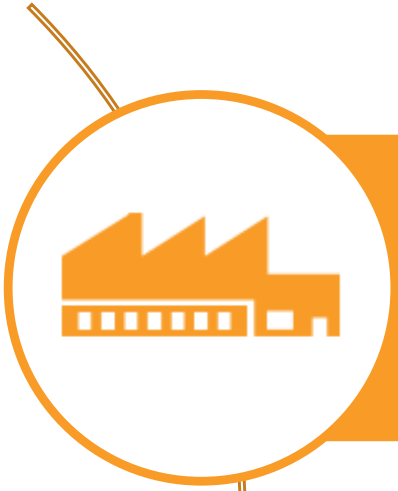
Reported foreign inspections on all countries listed

# Locations of Manufacturing Facilities Hosting Inspections




- **This data demonstrates where manufacturing sites are located for research-based pharmaceutical industry**

# Outcome of the Data



## At Manufacturing sites

- The percentage of sites with no inspection remains stable for 6 years
- Opportunities for a better risk-based approach on inspections*
- There is 3 times more focus on GDP than the years before

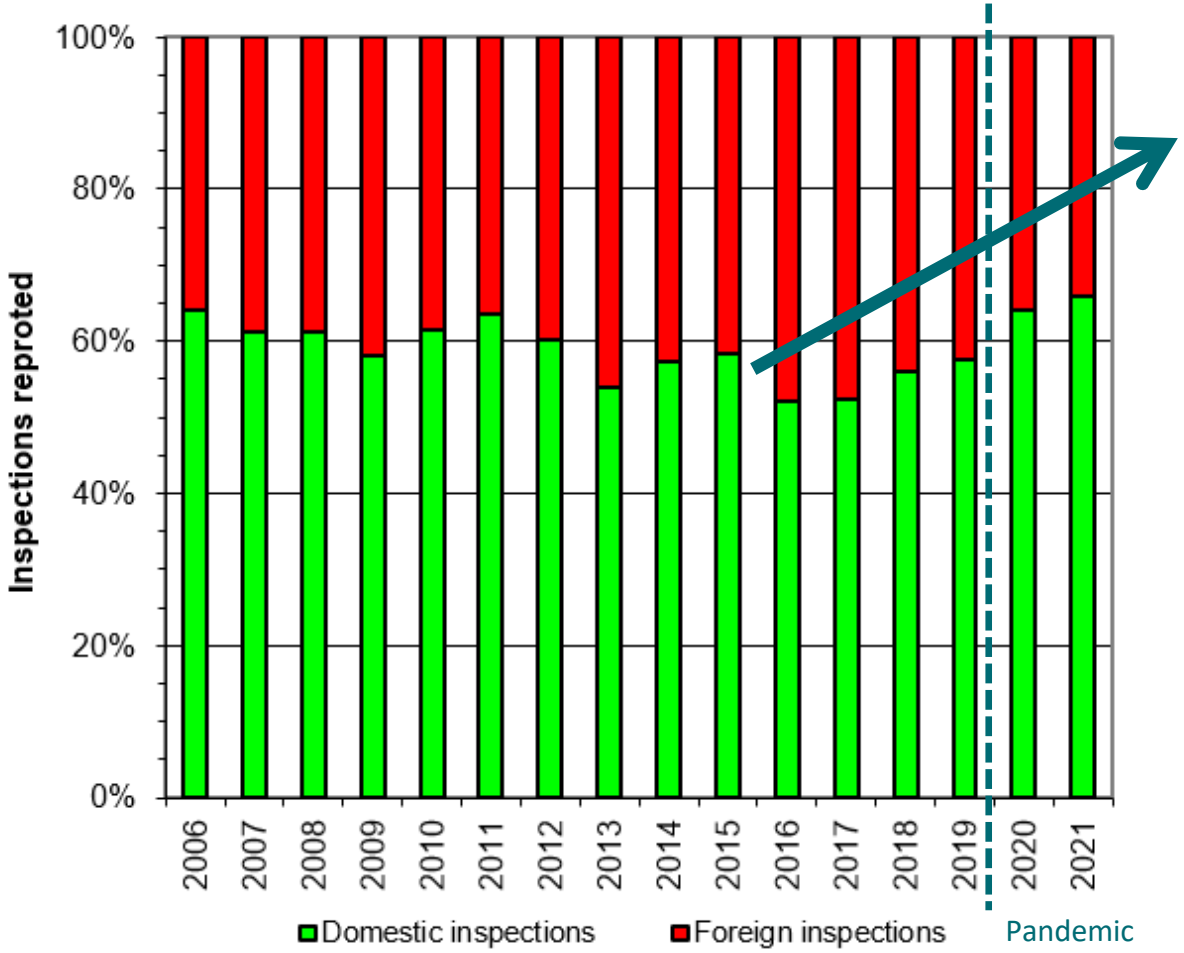
Data source:
22 Global research-based pharmaceutical companies (EFPIA member) + one NTA

## At Affiliates - worldwide

- Very limited impact by the pandemic on the number of inspections
- 25% of the affiliates having an inspection
- Scheduling and outcome is back to the level of 2019

*Countries may include Chinese Taipei, Japan, Korea, Russia, Turkey, US
NTA: National Trade Association

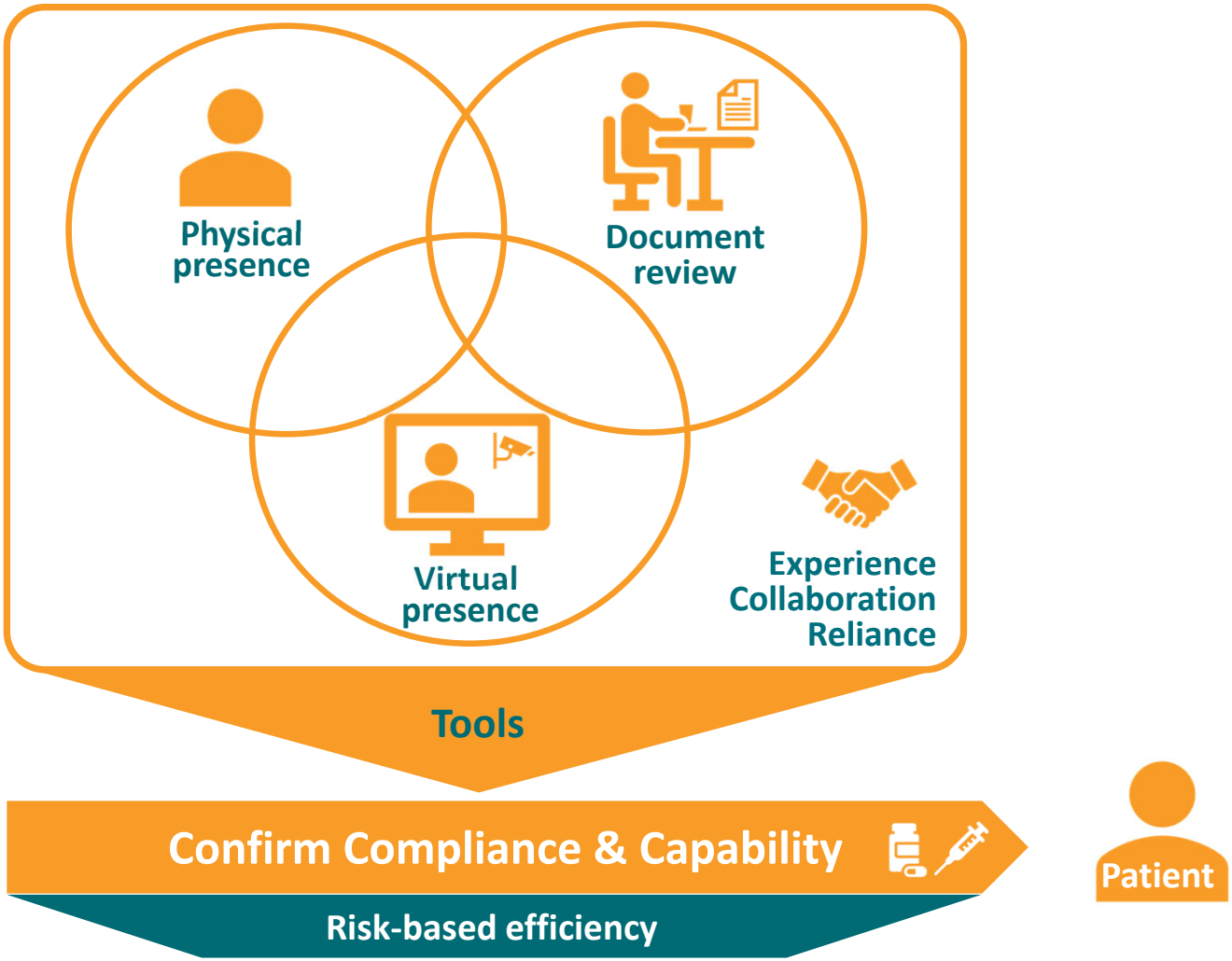
# The Ratio of Foreign to Domestic Inspection Seems not to be Influenced by the Pandemic




- Since 2016 there is a stable trend to conduct more domestic than foreign inspections

## CONSIDERATION ON INSPECTIONS TOOLS

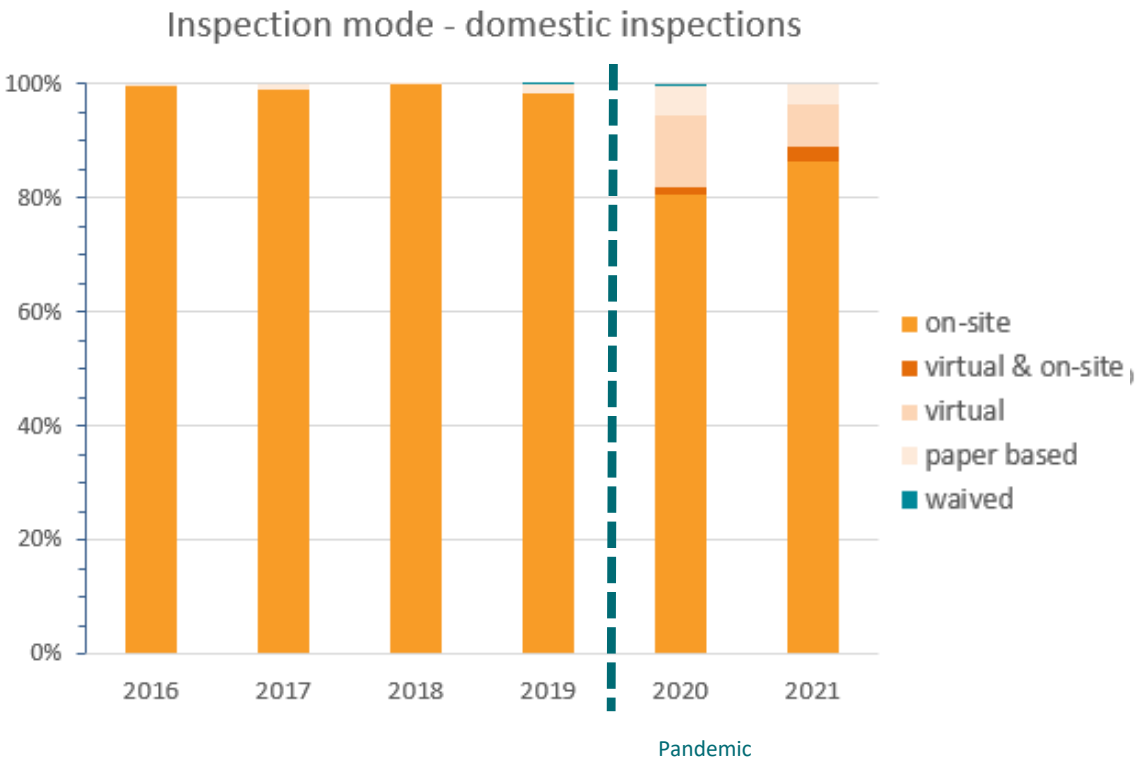
# Inspection Tools and Combinations are Not Equivalent - Each has Pros and Cons

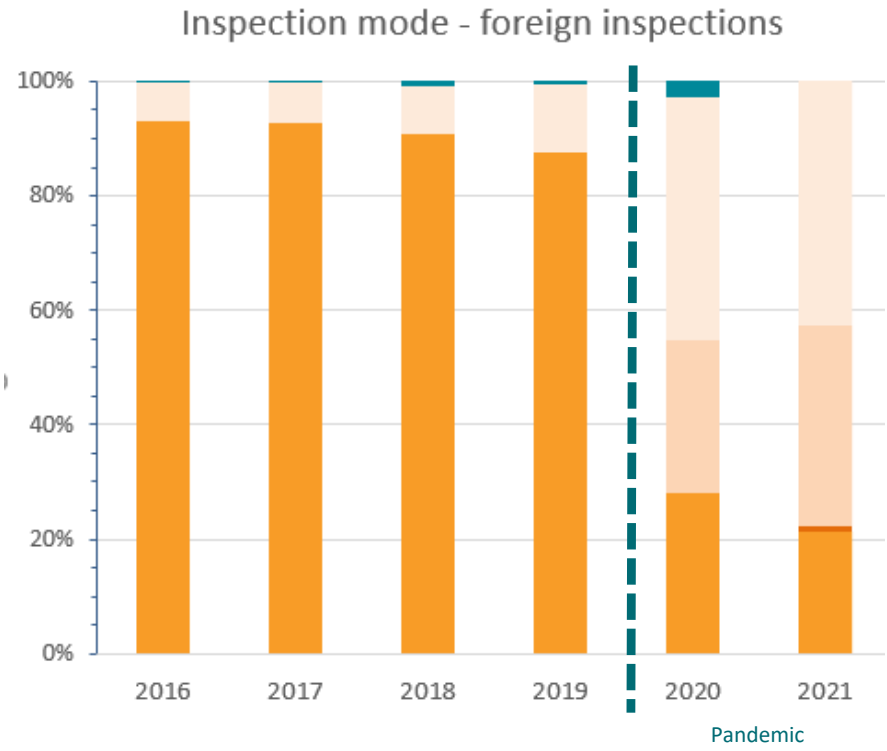



**Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic.** ICMRA, 26 November 2021. - Collaborative inspections: Inspections involving two or more regulatory authorities
Note: ICMRA defines 'hybrid' inspection as inspections where several inspectorates are participating eighth on-site or virtual.

## USE OF INSPECTION TOOLS - DATA

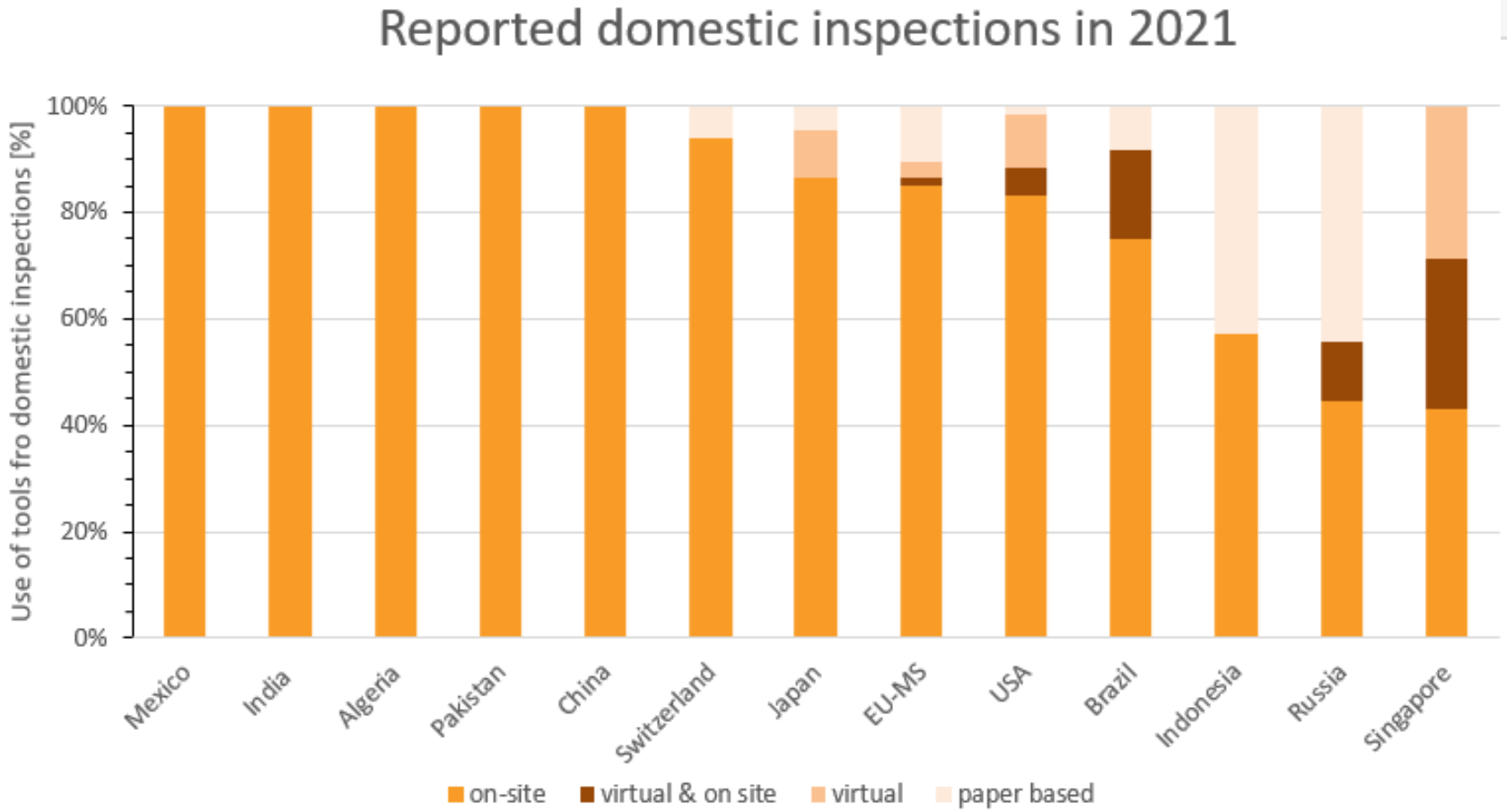
# The Use of Inspection Tools has Changed since 2020




- About 90% of the domestic inspections have had at least a partial on-site presence
- About 20% of the foreign inspections have been conducted with on-site presence

# Inspection Tools Used in Domestic Inspections



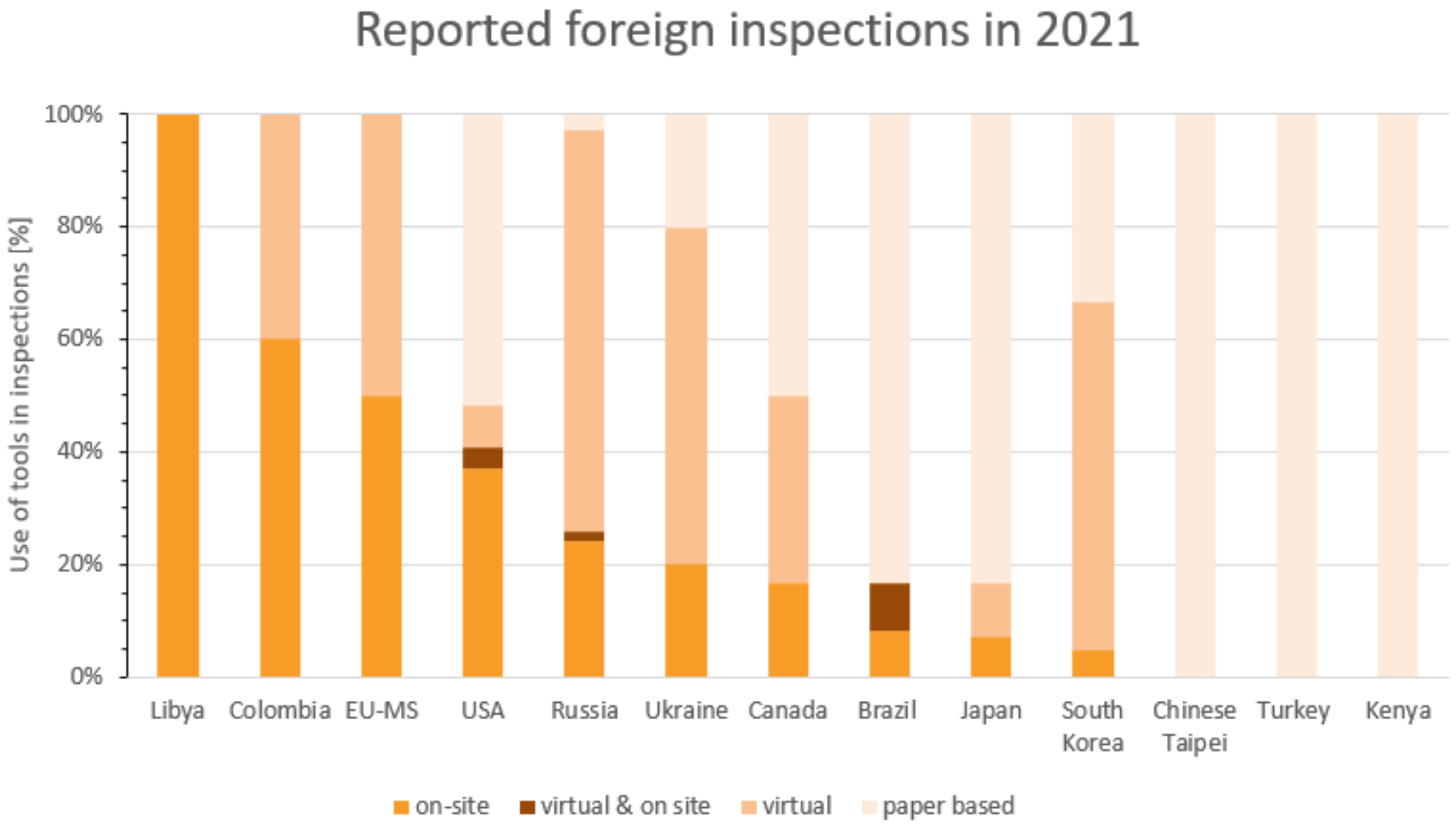

* Experience with implementing the virtual inspection tool is reported for EU-MS by
  * Denmark
  * Finland
  * Germany
  * Ireland
  * Italy
  * Poland
  * Sweden



The graphic show only inspectorates performing more than six domestic inspections

## USE OF INSPECTION TOOLS - DATA

# Inspection Tools Used in Foreign Inspections



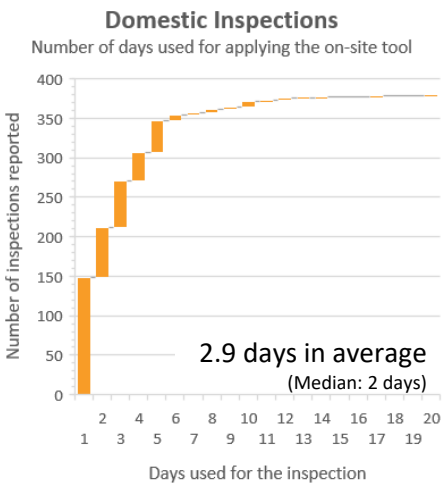

**Note: no agency is reported to use a hybrid approach (more than one inspectorate)**

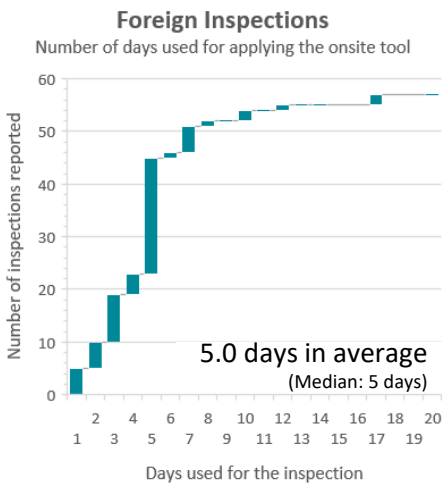


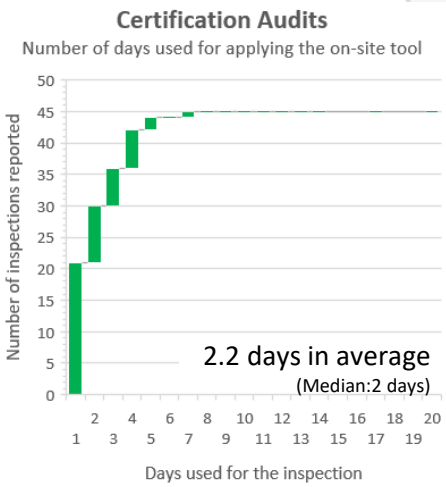
The graphic show only inspectorates performing more than four foreign inspections

# Average Inspection Duration for Applying Different Inspection Tools

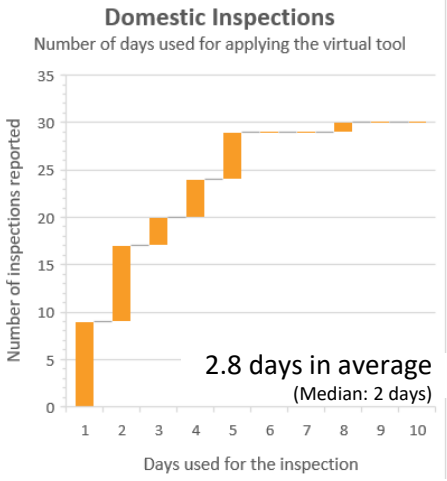
**Physical presence**

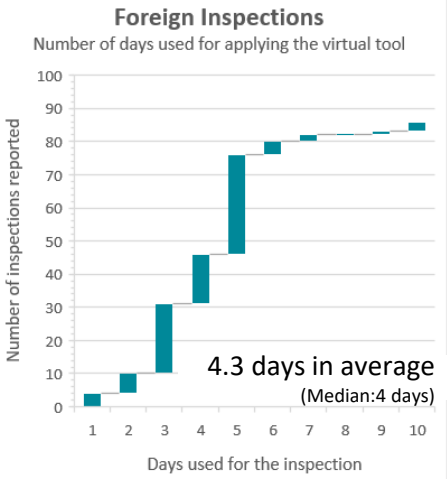


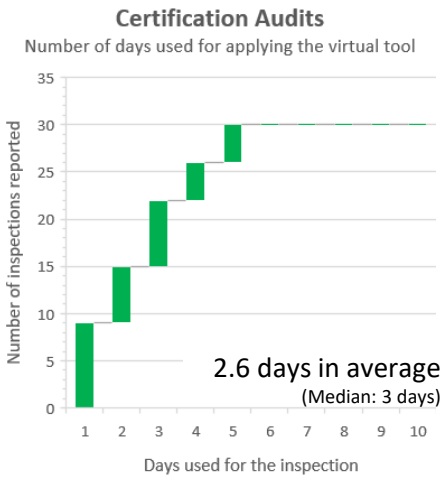




**Virtual presence**

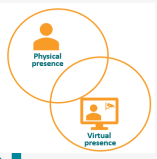



**From an industry perspective, inspections using the virtual tool take about the same time as being on-site**

Data bases: 250 data sets with inspection times < 14 days
Note: a) Travel time to site in 3rd countries is not included; b) Median count only full days ; c) certification audits are for ISO 13485




# Comparison of Efforts using the On-site or Virtual Tool for Inspections - *Still on a learning curve and improving*

| Area | Being on-site | Using virtual tools |
|---|---|---|
| Behavioral aspect | Established process | Alternative process giving more flexibility |
| Perception by the parties | Experienced for most; feels good; more flexibility | Mixed sensations<br>- Stressful for some (the day feels longer; less flexible);<br>- Welcomed by others (the more you do, the easiest it feels) |
| Opportunities | Organised agenda of the inspection | - Most efficient when performed in real-time as it would be on-site |
| Way of working | 8-10h/day – dedicated;<br>Concentrate on the inspection only | - 4-6h/day<br>- More flexibility with scheduling because you don't have to address travel;<br>- More time to prepare for next day;<br>- Opportunity to perform some day-to-day business |
| Communication | Enhanced non-verbal communications | - Alternative communication style; seems less 'natural' currently<br>- More focused communication (e.g., less distractions from people in the room) |
| Prework | Travel planning, flights, visa, hotel | - Less costly;<br>- Preparation meeting for connectivity test;<br>- More efficient and more inclusive e.g., ability to have SMEs participate that might not be in the same geographic location |
| Request documents prior to the inspection | Less | - More, currently* |
| Performing the inspection | Change between sitting and walking | - Opportunities for stretching exercise |
| Average duration (EFPIA survey data) | Domestic 2.9d<br>Foreign 5.0d | - Slightly shorter |

*More documents need more time for preparation; is this really an opportunity to have them available faster during the call(?)

# Inspection Practice


**Time for virtual presence**
slightly shorter than on-site presence

- Facts contradict the feedback from industry and regulators perceptions - *Is this a subjective feeling as of more days used overall?*

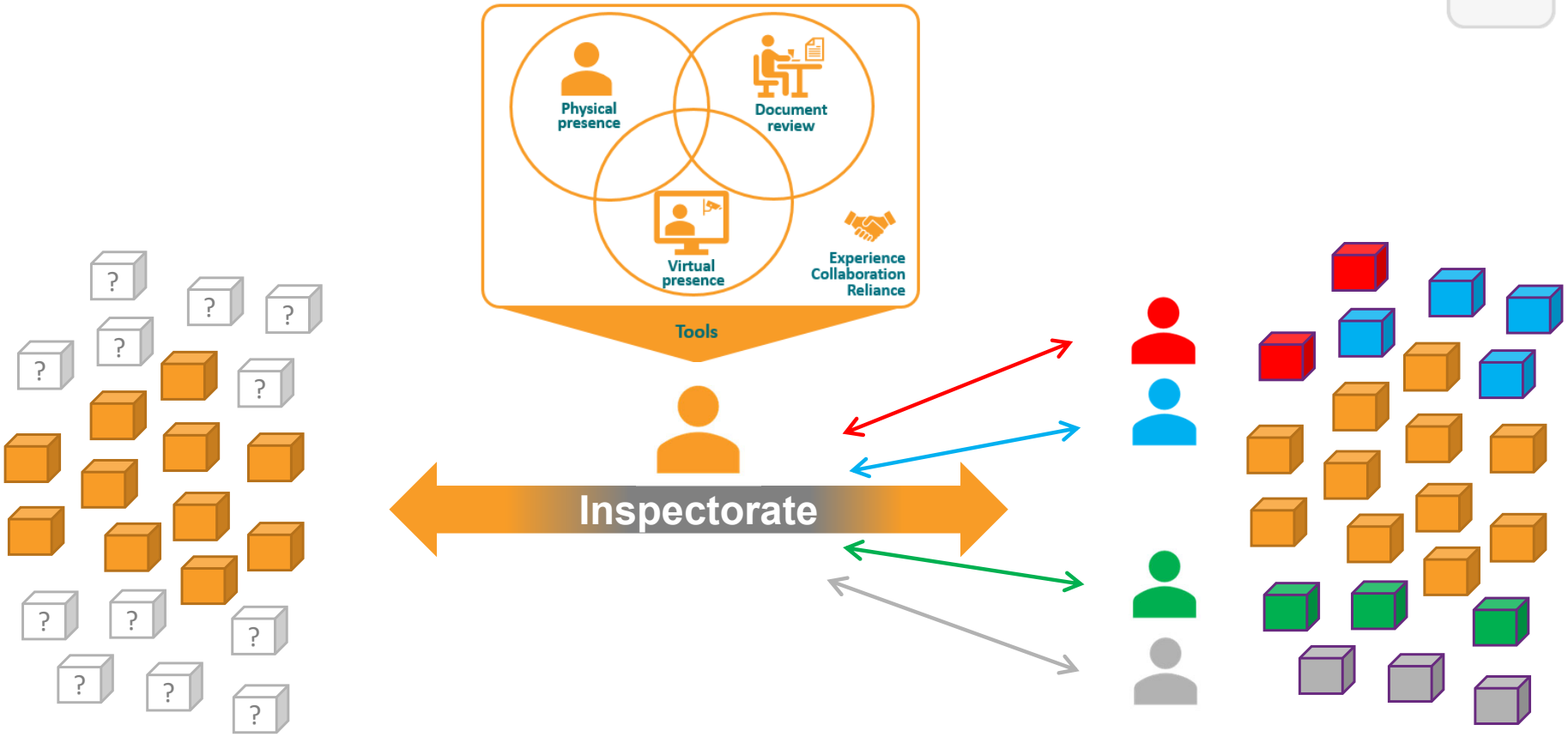
**Inspector days**
varies from 1 to 24

- Increased number of inspectors at foreign inspection
- Switzerland performed foreign inspections again, but only invested one inspector day - *appear to focus?*

**Opportunities for effectiveness**
with reliance

- ~35% of all are foreign inspections
- ~70% saving in the MRA US/EU

# Well Founded Reliance Results in More Knowledge and Improves Decision Making




**Limited knowledge when self dependent**

**Collaboration leads to more knowledge**

= Symbol for 1 inspection = symbol for an inspectorate; Colors represents inspections performed by a specific inspectorate

# Enabling Reliance on Inspections and its Processes – Opportunities

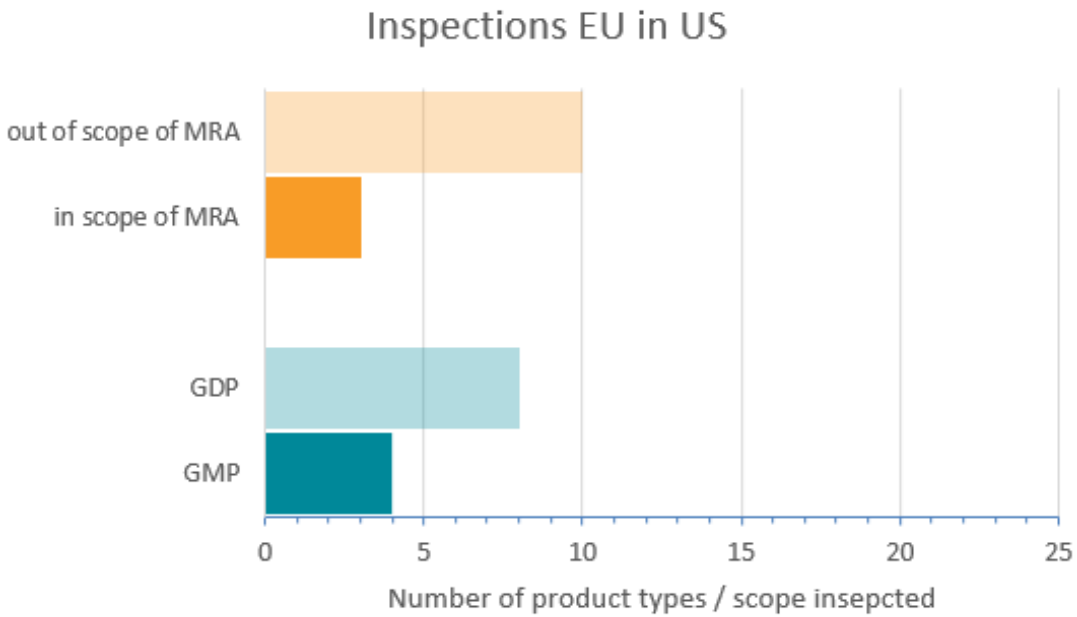
The preferred model is the virtual tool combined with on-site presence

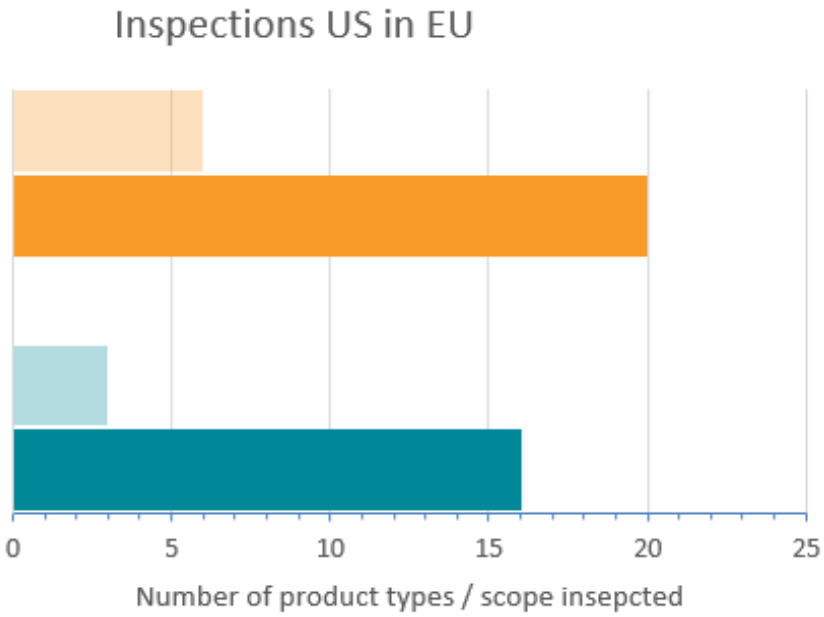
Risk-based approach for the inspection frequency (1-5 years)

Focus on inspections by the domestic authorities and on reliance

1. **Implementing MRAs** is in general beneficial for inspectorates and companies to prevent duplication of efforts in e.g., a) inspections incl. inspections in 3rd countries and from foreign inspections (e.g., when performing and accompanying) and b) additional batch testing upon importation
2. **Harmonise the scope of and update** existing MRAs (e.g., Switzerland)
3. **Additional MRAs:** Consider establishing between the EU and PIC/S participating authorities e.g., Argentina, Brazil, South Korea, Turkey, UK
4. **Update of the EU legislation:** Consider leveraging the concept of listed 3rd countries as applied for the importation of active substances as per Falsified Medicines Directive (FMD) to allow listing of specific 3rd countries (e.g., PIC/S participating authorities) without an MRA

# Full EU / US MRA Implementation Could Leverage Further Benefit - Details 2021




In scope of the MRA – 43 inspections

Out of Scope of the MRA – 27 Inspections

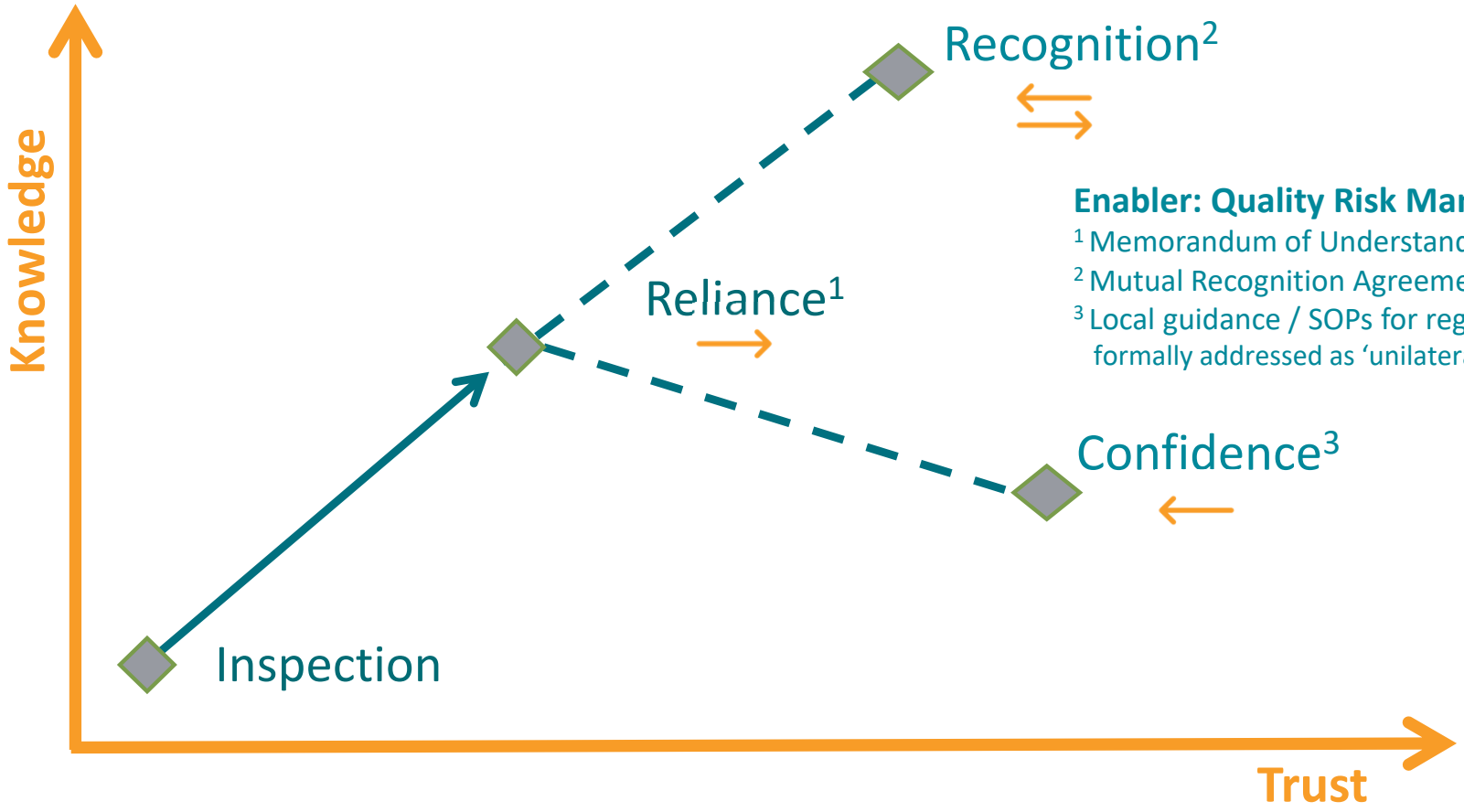
Potential saving: about 70%

- Vaccines
- ATMP
- Medical Device
- Combination Product
- GDP focus

# 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%)
*3 8 out of 12 inspection from the EU in US had been reported to be for GDP purpose – no GMP

# Pandemic Showcases Demonstrate Opportunities Towards an Ideal State




**Enabler: Quality Risk Management**

[1] Memorandum of Understanding (MoU) – 'may'
[2] Mutual Recognition Agreements (MRA) – 'must'
[3] Local guidance / SOPs for regulatory – 'can' formally addressed as 'unilateral waiver'

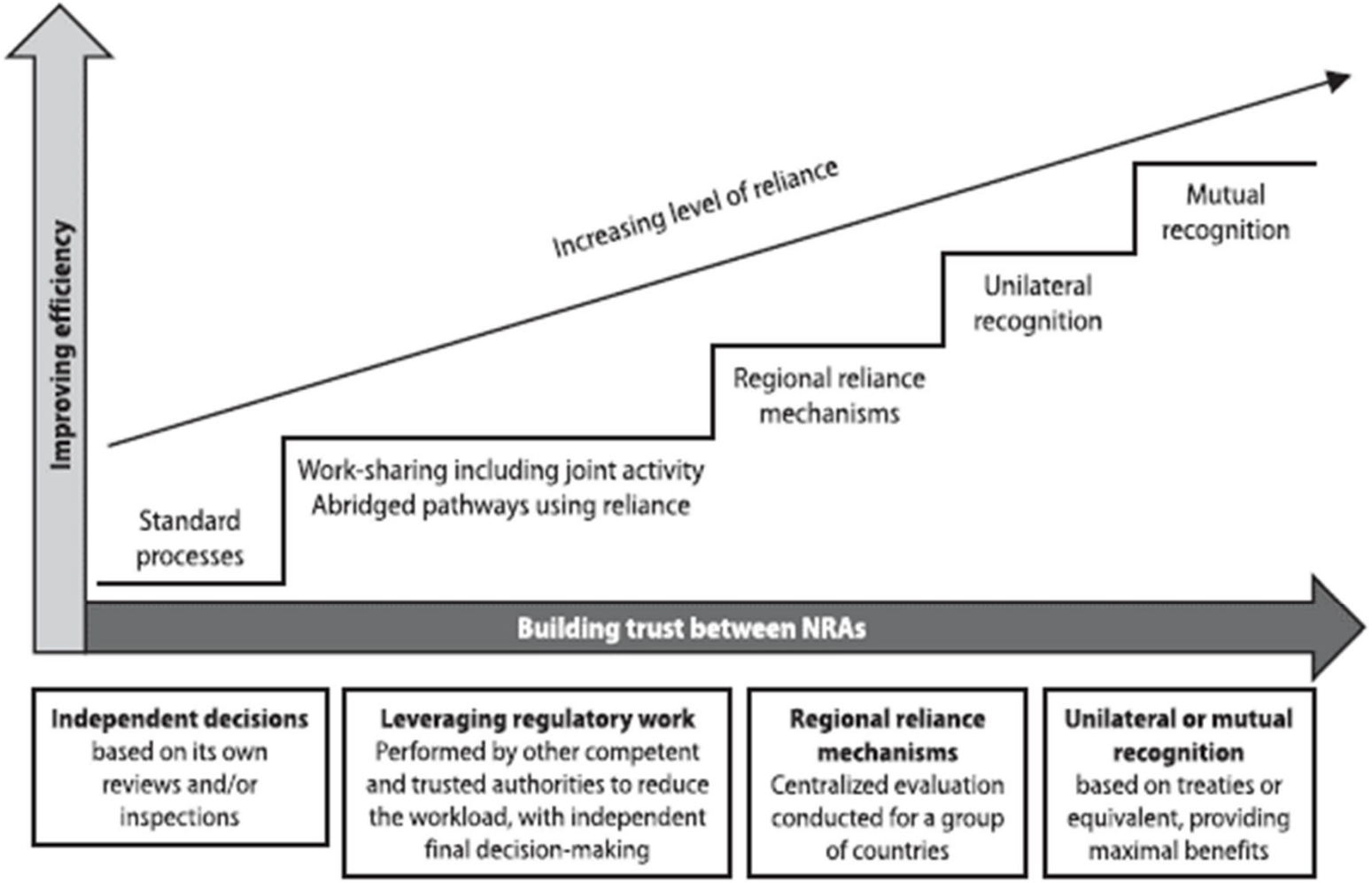
**Good reliance practices in the regulation of medical products: high level principles and considerations,** WHO, *TRS 1033, Annex 10,* **2021,** 237-267.
**Report on the review of regulatory flexibilities/agilities as implemented by National Regulatory Authorities during Covid-19 pandemic** – WHO & ICDRA, published December 2021

- **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

# 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

# Industry Supports PIC/S Membership

## PIC/S Participation Authorities performed at research-based manufacturers…

…in contrast to non-PIC/S member inspectorates…


*82% for Pre-Approval Inspections (PAI); 55% for non PAI

# Consideration on the Inspection Activities by PIC/S Participating Authorities

**8%** **More domestic inspections**
vs. in 3rd countries performed by PIC/S participating authorities (65% vs. 57% by non-PIC/S)

**8%** **More follow up actions**
after inspections by PIC/S participating authorities (17% vs. 9% by non-PIC/S)

**13%** **Virtual inspections**
by PIC/S Participating Authorities (28% by non-PIC/S)

**24%** **Paper-based inspections**
by PIC/S Participating Authorities (7% by non-PIC/S)

**61%** **Onsite inspection**
by PIC/S Participating Authorities (64% by non-PIC/S)

**60%** **Of reported foreign inspections** had been performed by a PIC/S participating authority **in a country where the inspectorate is also a PIC/S participating authority** (170 of 282)

## FOR FURTHER READING

# Explaining Reliance in the Inspection Landscape

- **Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency**, EFPIA position paper, 19. May 2014.
- **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.
- Alternative GMP/GDP Inspection **Practices in a Pandemic Situation** (COVID-19) and Beyond EFPIA position paper, 28 May 2020.
- **Opportunities for Optimising the GMP Inspection Process post pandemic,** in publication based on 'Request for Optimising the **GMP paper-based Inspection Process** by Regulatory Authorities', EFPIA position paper, 26 June 2019.
- Proposals for Quality and GMDP aspects: **Regulatory response to Covid 19 crisis**, 30. Mar. 2021
- **Opportunities and Challenges with MRAs on GMP,** EFPIA Reflection Paper, 21. December 2021
- EFPIA: Annual Regulatory GMP/GDP Inspection Survey's

efpia

- Guidance on good practices for **desk assessment**… for medical products regulatory decisions, WHO, TRS 1010 (2018), Annex 9.
- **Good reliance practices** in the regulation of medical products: high level principles and considerations, WHO, TRS 1033, Annex 10, 2021, 237-267.
- International regulators recommend use of remote inspections as complementary tool beyond pandemic, EMA-News, 13. Dec 2021.
- Guidance related to GMP/GDP and PMF: **distant assessments**. EMA/335293/2020, 15. Oct. 2020
- **Remote Interactive Evaluations** of Drug…, FDA , Guidance for Industry, FDA-2020-D-1136, April 2021
- Joint Audit Programme for EEA GMP inspectorates - JAP Procedure (Rev.3)
- **Report on the review of regulatory flexibilities/agilities as implemented by National Regulatory Authorities during Covid-19 pandemic - December 2020,** WHO & ICDRA, published November 2021
- **Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic.** ICMRA, 26 November 2021.

- **Considerations for effective regulatory reliance,** 21. June 2019
- **Convergence of Good Manufacturing Practice (GMP) standards and Related Inspections**, IFPMA Position paper, v2, January 2020.
- **Points to Consider for Virtual GMP Inspections – an Industry perspective**, 5 Feb 2021, update in progress with Annexes on
  - 'best practices' and
  - 'IT considerations'
- Inspections **Infographic**
- Related: import testing

IFPMA

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

PIC/S

- 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.
- 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.
- 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; **Part II: Considerations and Opportunities**, *Pharm. Tech. Europe*, February, 2017, 5-9.
- S. Rönninger, P. Gough, V. Davoust, **Opportunities for Saving Resources in the Regulatory Inspection Process: 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.
- S. Rönninger, A. Kurz, and F. Raya, **GMP/GDP Inspections: Challenges and Opportunities from COVID-19**, Pharmaceutical Technology Europe, *33 (11) 2021,* 36-39; print version; full version

## ACKNOWLEDGEMENT

# Contributors to the EFPIA Inspections Survey 2021

- AbbVie
- Almirall
- Amgen
- Astra Zeneca
- Bayer
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- Eli Lilly and Company
- Grünenthal GmbH
- GlaxoSmithKline
- Johnson & Johnson
- Lundbeck
- Merck
- MSD
- Novartis
- Novo Nordisk
- Pfizer
- Roche
- Sanofi
- Servier
- Teva
- UCB

### National Trade Associations

- LEEM (France)

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European Federation of Pharmaceutical Industries and Associations

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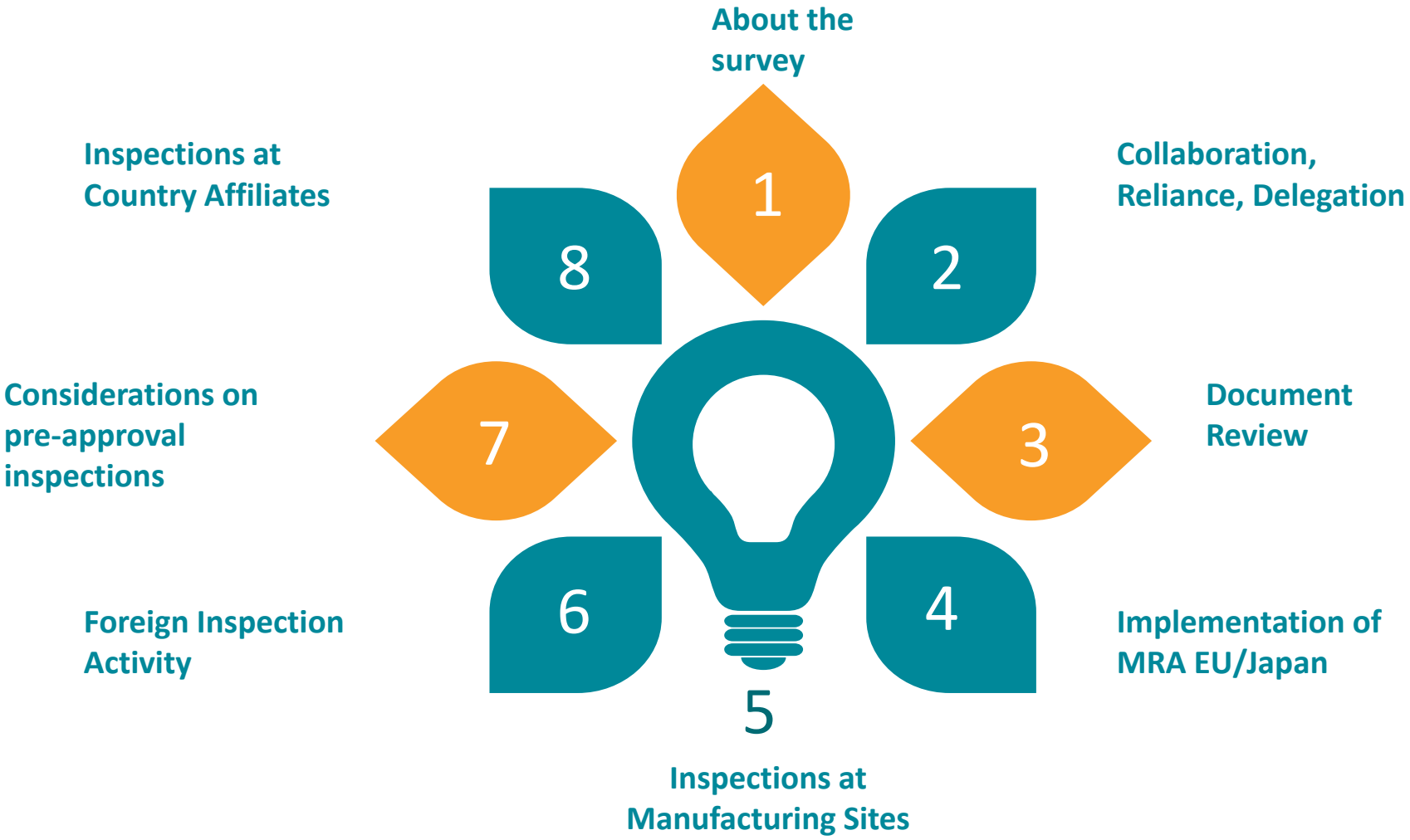
# Further Data and Thoughts



# Limitation on the Data Assessment

- **Out of scope**
  - Sponsored inspections at CMOs are not in scope because of the risk of double counting
- **Excluded from the assessment**
  - If a company named more than 10 days for a virtual inspection, we set the value to 10 as we assume that this had not been full days where the inspection was performed
  - All inspections referencing only to
    - 'other GxP' only (e.g., R&D facilities for GCP/GLP)
    - 'other' products as there was no GMP/GDP inspection relevant activity (e.g., OTC, cosmetics)
    - ISO 9000 certifications, because they are no required by regulatory statutes (even marked as 'GMP')
  - Mock inspections = for profit organisation preparing for FDA inspections (e.g., arca, spcm, dsp, Presafe)
- **Consideration**
  - We consider not having the full overview on inspections with document review only (paper-based)
  - Companies may have reported the first and last day of an inspections with document review even if there had been days with no inspection in between. This the inspector days had been set to 'n.a.'
  - Duration of inspections with document review was not accounted
  - Duration of inspection using the virtual tools may not reflect the actual inspection time
  - Inspections at affiliates are domestic, if the country is supported e.g., Czech Republic in Slovakia
- **Note**
  - Insufficient data (e.g., no product category named) -> added GMP for manufacturing sites and GDP for affiliates
  - All local inspectorates are listed under the name of the state inspectorate

## 2. COLLABORATION, RELIANCE, DELEGATION

# A Simple and Qualitative Tool for Inspection Planning

### Elements

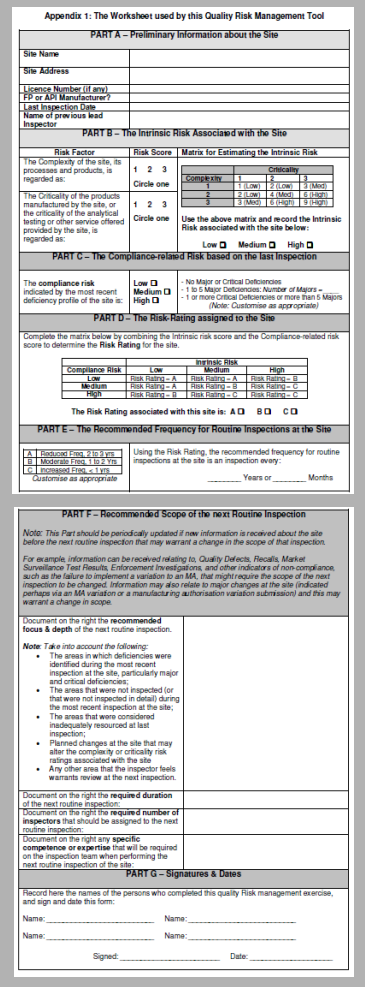
- Knowledge of the GMP compliance history of the site
- Footprint of history of critical and major deficiencies
- Type of inspection i.e., routine, for cause, pre-approval

### 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<br>Circle one | Criticality: 1 / 2 / 3 — Complexity: 1: 1 (Low) / 2 (Low) / 3 (Med); 2: 2 (Low) / 4 (Med) / 6 (High); 3: 3 (Med) / 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<br>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 ☐<br>Medium ☐<br>High ☐ | - No Major or Critical Deficiencies<br>- 1 to 5 Major Deficiencies; *Number of Majors – ____*<br>- 1 or more Critical Deficiencies or more than 5 Majors<br>*(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 | Using the Risk Rating, the recommended frequency for routine inspections at the site is an inspection every: |
| B | Moderate Freq. 1 to 2 Yrs | |
| C | Increased Freq. < 1 Yr | _____ Years or _____ Months |

*Customise as appropriate*

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.<br>***Note:** Take into account the following:*<br>• The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies;<br>• The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site;<br>• The areas that were considered inadequately resourced at last inspection;<br>• Planned changes at the site that may alter the complexity or criticality risk ratings associated with the site<br>• 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

32

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

**Regulatory Decision**

**Assessment of the outcome and rationale**

## 2. COLLABORATION, RELIANCE, DELEGATION

# Inspections by a Local Inspectorate are 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 / environmentally 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

* The 2021 date demonstrated that domestic inspection have more follow up actions

PIC/S **GMP-INSPECTION RELIANCE**, PIC/S GUIDELINE PI 048-1, 01 JUNE 2018, CHAPTER 5.2 – as basis

## 3. DOCUMENT REVIEW - MESSAGE FROM EFPIA

Documents

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

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

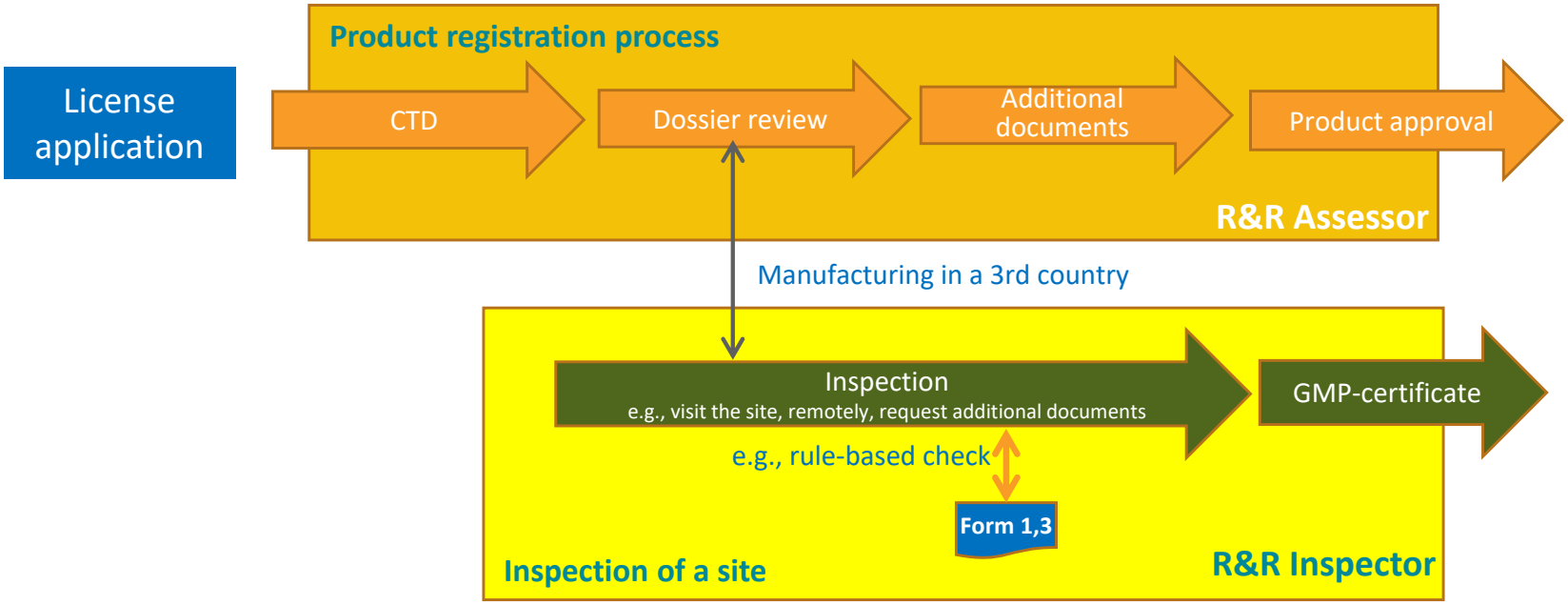
For further reading

- GMP/GDP Inspection Efficiency, EFPIA position paper 19. May 2014. www.efpia.eu/media/25712/position-paper-on-enhanced-good-manufacturing-and-good-distribution-practices-gmp-gdp-inspection-efficiency-2014.pdf
- Optimising the GMP paper-based Inspection Process EFPIA, Position Paper 26. June 2019. www.efpia.eu/media/413129/request-for-optimising-the-gmp-paper-based-inspection-process-by-regulatory-authorities.pdf

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

# Understanding of the role of form 1 & 3 in Japan

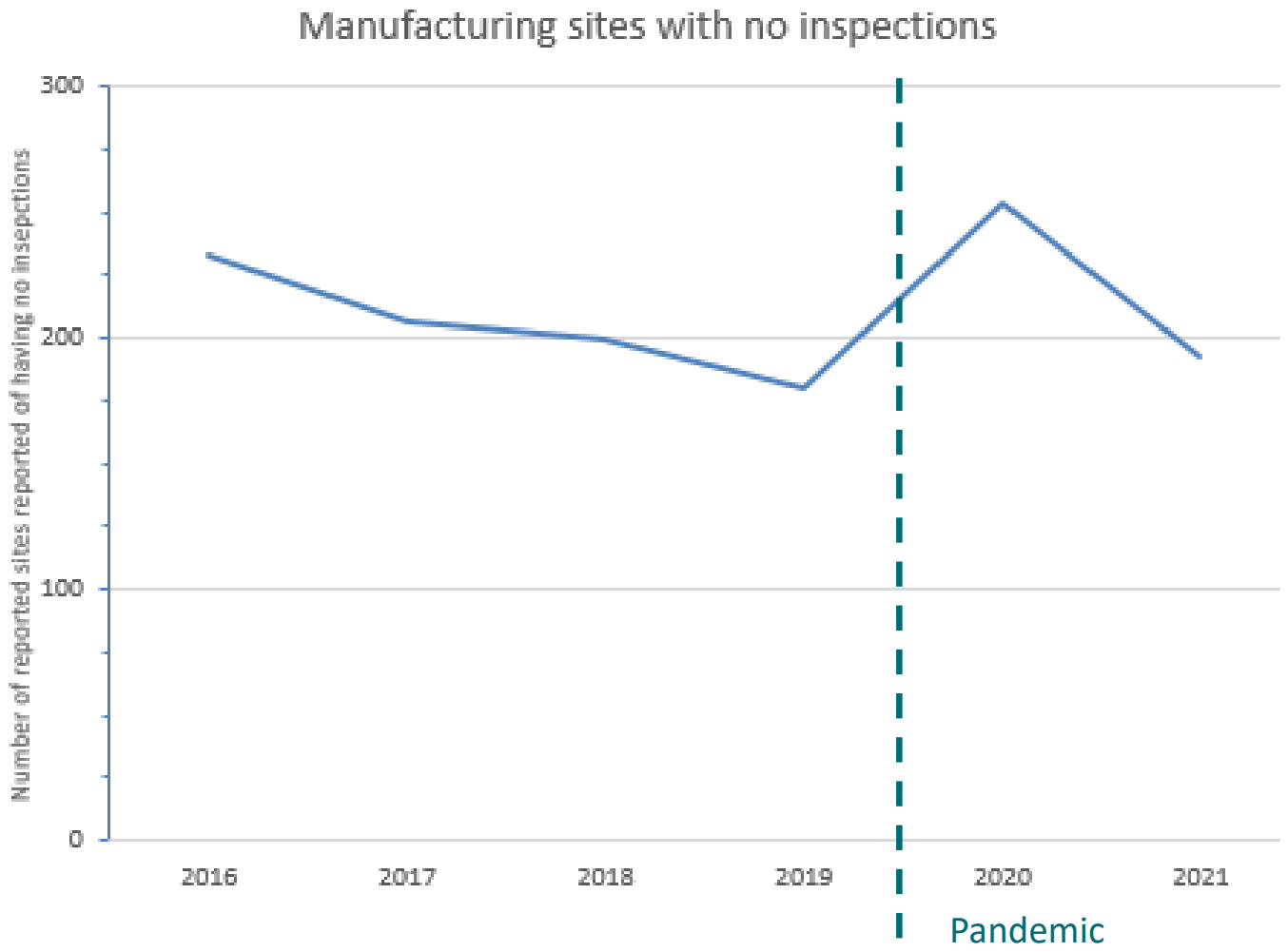
Documents




* **The forms 1 & 3 in Japan are checked by inspector as part of the licensing process on a role-bases and therefore not waived by the MRA**

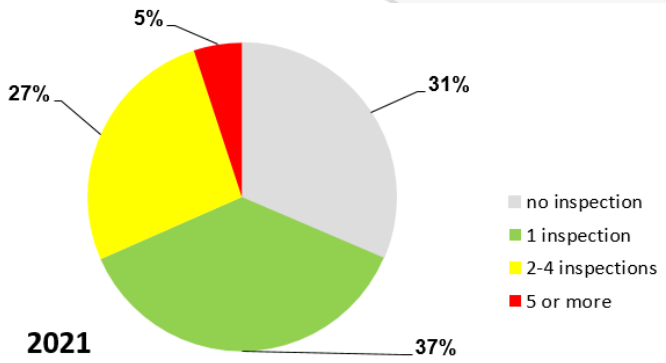
## 5. INSPECTIONS AT MANUFACTURING SITES

# There is no trend (i.e., no impact by the pandemic) in the number of sites with no inspection in the last 6 years



## 5. INSPECTIONS AT MANUFACTURING SITES

# Examples of Inspection at one Manufacturing Site of Different Companies



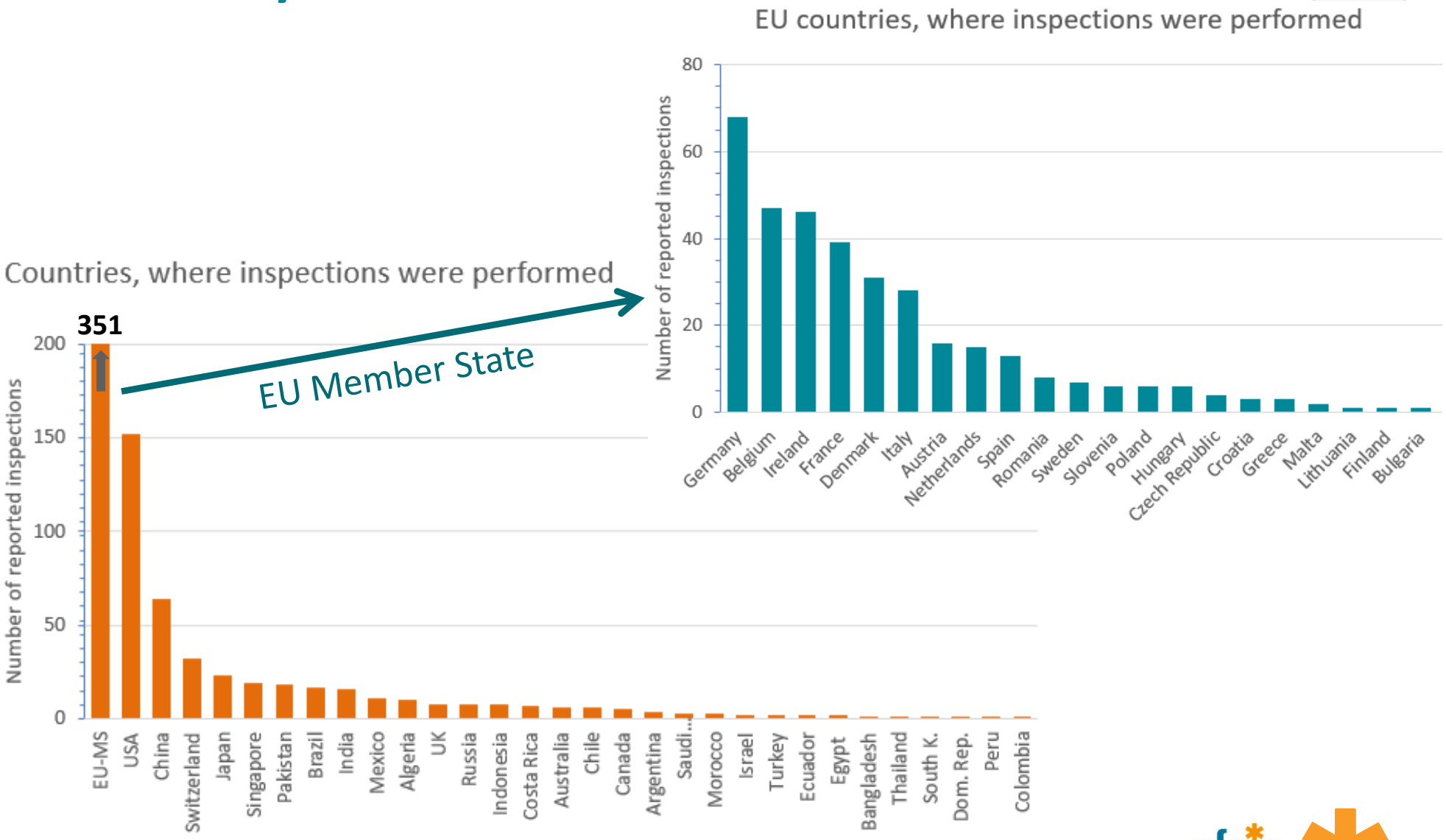

| Site in country | Domestic inspections | Foreign inspections | Sum | Foreign inspectorates |
|---|---|---|---|---|
| Belgium | 1 | **15*** | 16 | Japan / PMDA (7), Chinese Taipei / TFDA (3), Iraq / MoH (1), Kenya / PPB (1), Saudi Arabia / SFDA (1), Switzerland / SwissMedic (1), Turkey / TMMDA (1) |
| Ireland | 0 | **7** | 7 | Japan / PMDA (3), Russia / MoIT-SID&GP (1), Turkey / TMMDA (1), Chinese Taipei / TFDA (1), USA / FDA (1) |
| Switzerland | 1 | **6** | 7 | Japan / PMDA (3), USA / FDA (1), Turkey / TMMDA (1), Russia / MoIT-SID&GP (1) |
| Denmark | 2 | **5** | 7 | Turkey / TMMDA (2), South Korea / MFDS (2), Russia / MoIT-SID&GP (1) |
| Denmark | 1 | **5** | 6 | Chinese Taipei / TFDA (2), Brazil / ANVISA (2), Russia / MoIT-SID&GP (1) |

- **Countries with opportunities for a better risk-based approach include**
  - Chinese Taipei
  - Japan
  - Russia
  - Turkey

***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*
***Note:*** *Not all companies are sharing details on specific manufacturing sites in a country*

*The spike may relate to vaccine manufacturing

# Locations of Manufacturing Facilities Included in the Survey

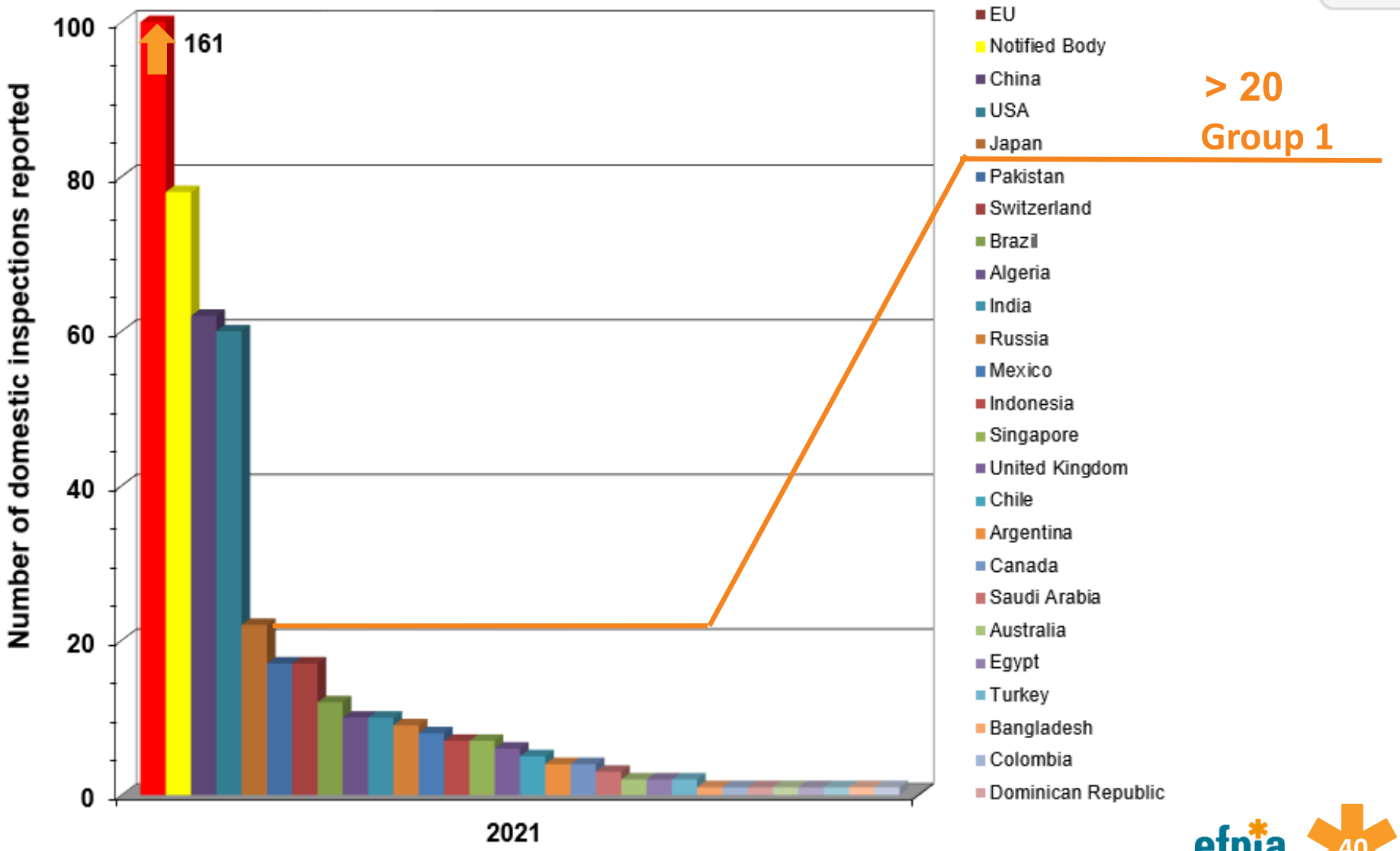



Countries listed with sites having > 4 inspections

## 5. INSPECTIONS AT MANUFACTURING SITES

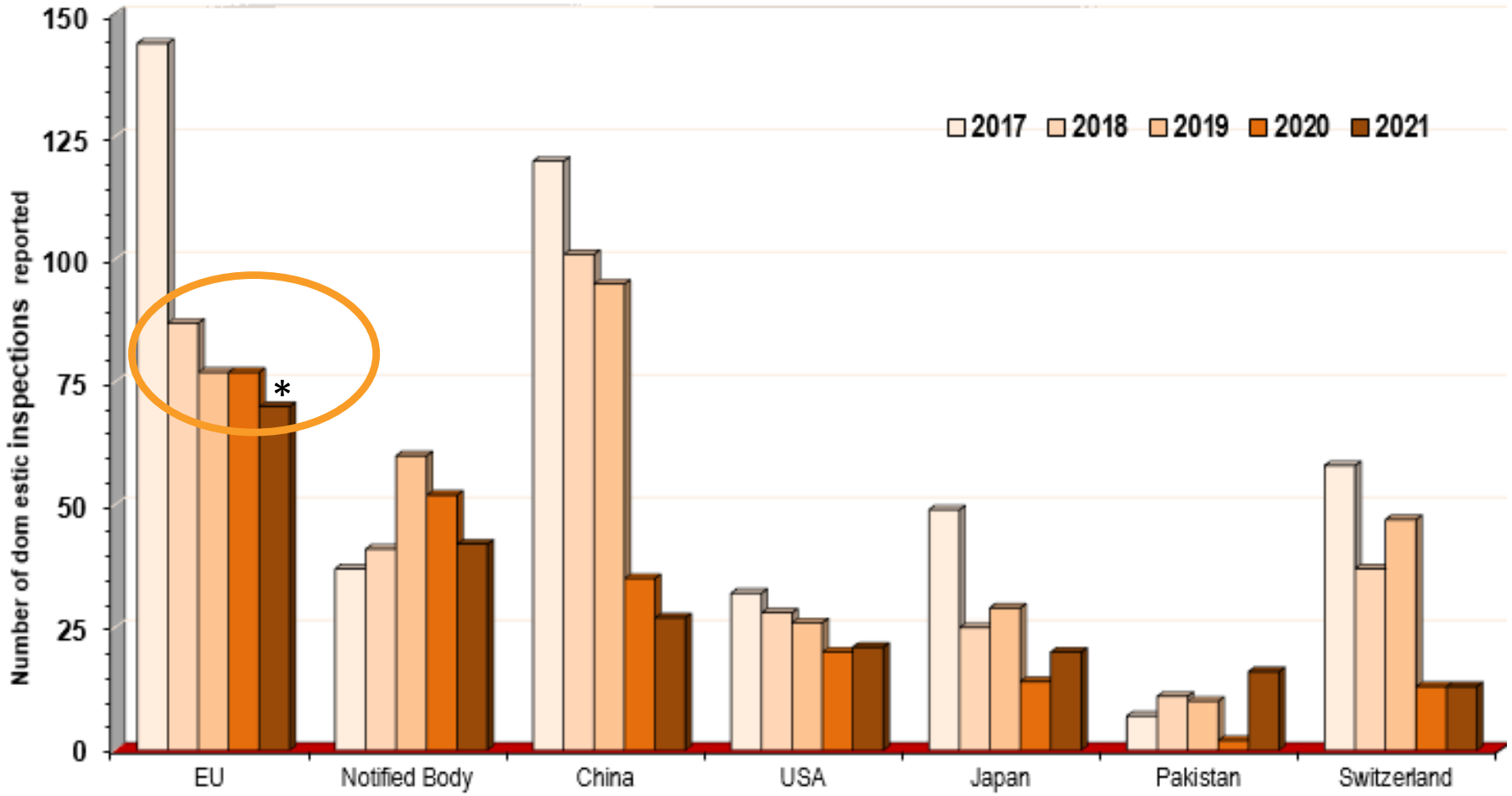
# Number of Domestic Inspections

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



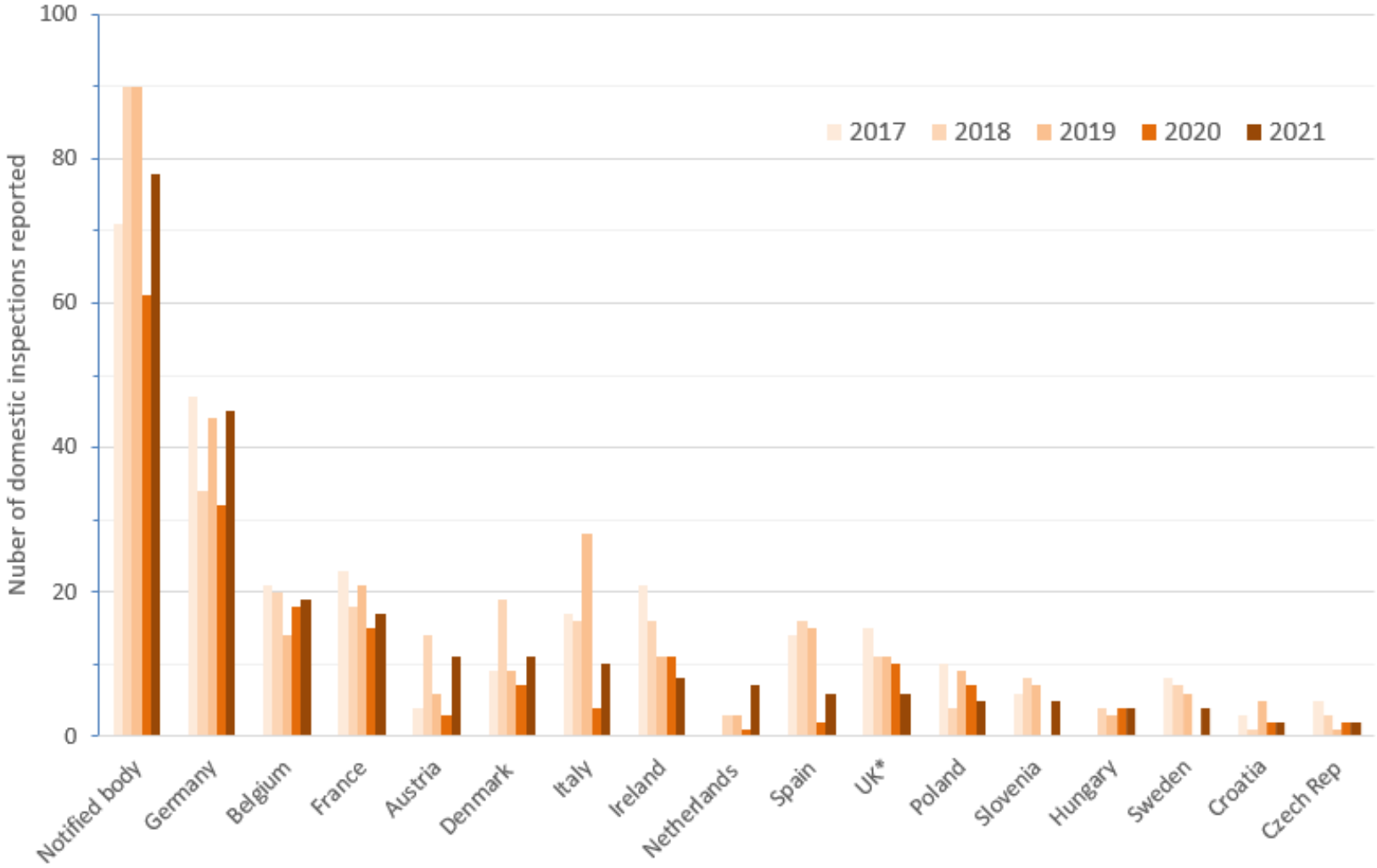
## 5. INSPECTIONS AT MANUFACTURING SITES

# Number of reported Domestic Inspections




*Note: in 2021 the UK does not count for the EU-MS any more

# Number of reported Domestic Inspections by Authorities in EU Member States*



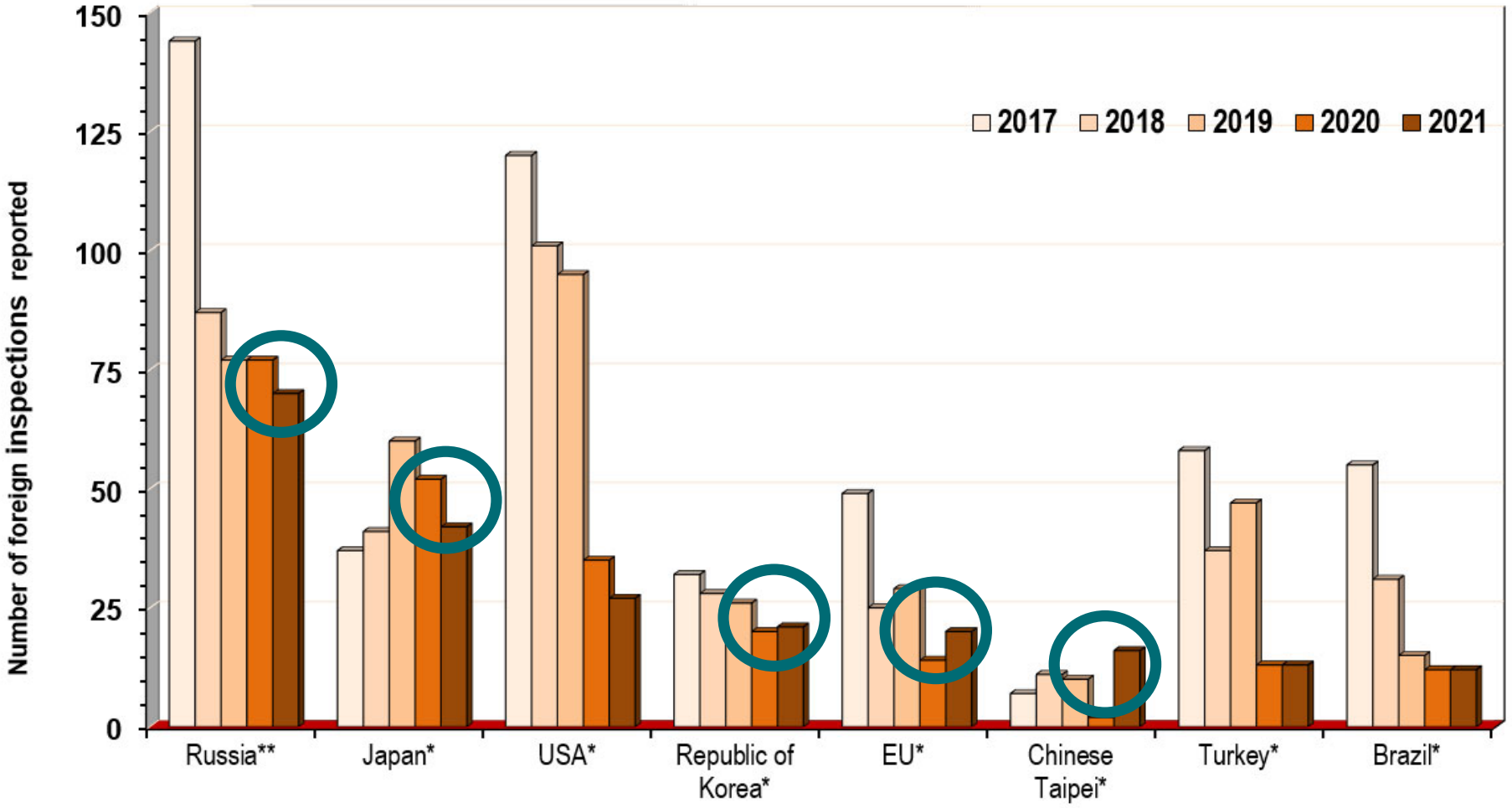



*Note: in 2021 the UK is listed for continuity

# Countries Performing Foreign Inspections

# Number of Foreign Inspections by Country 1/2

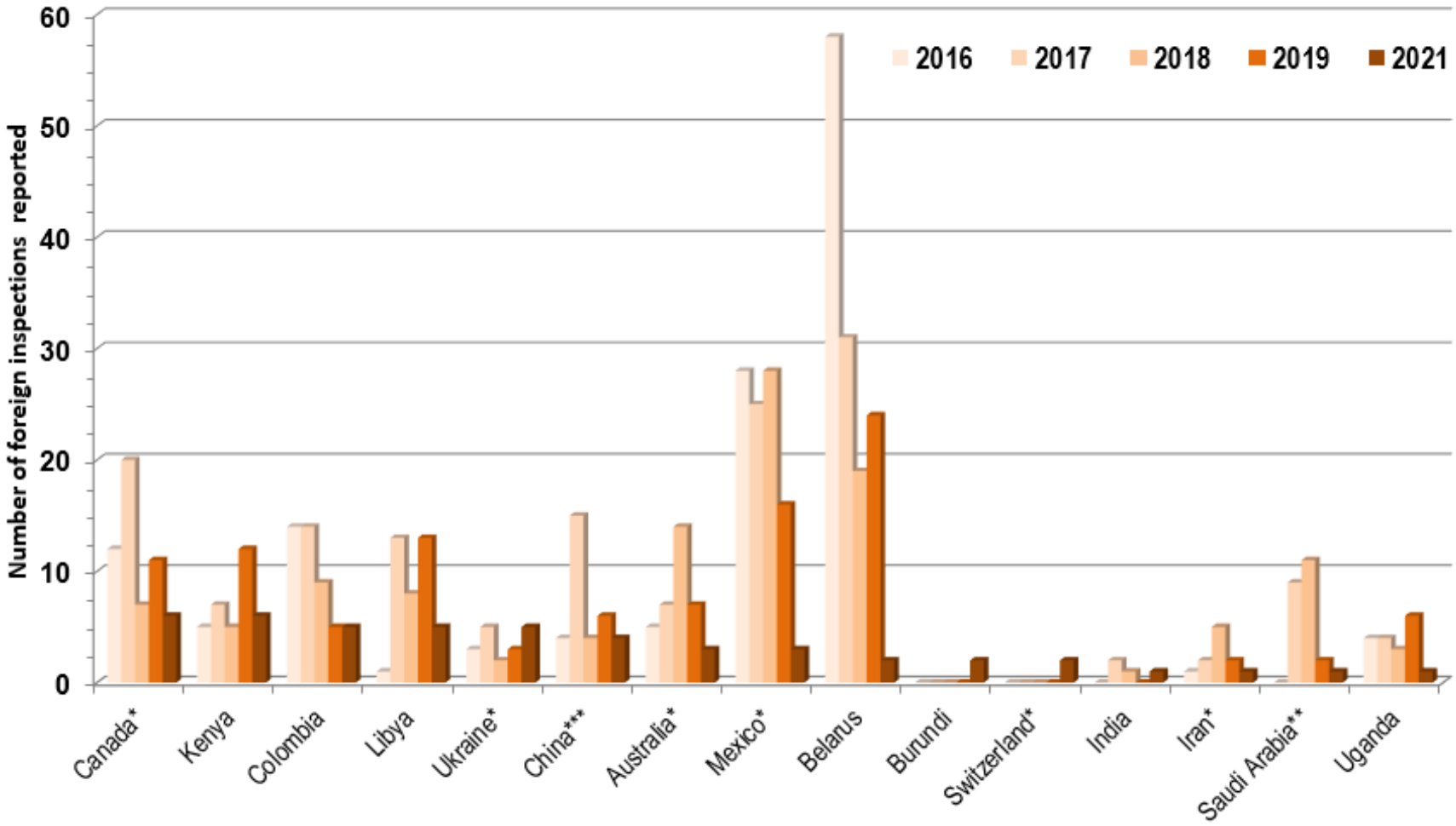
## Some countries reduced numbers of inspection while other may have switched inspection mode 2020/2021




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

## 6. FOREIGN INSPECTION ACTIVITY

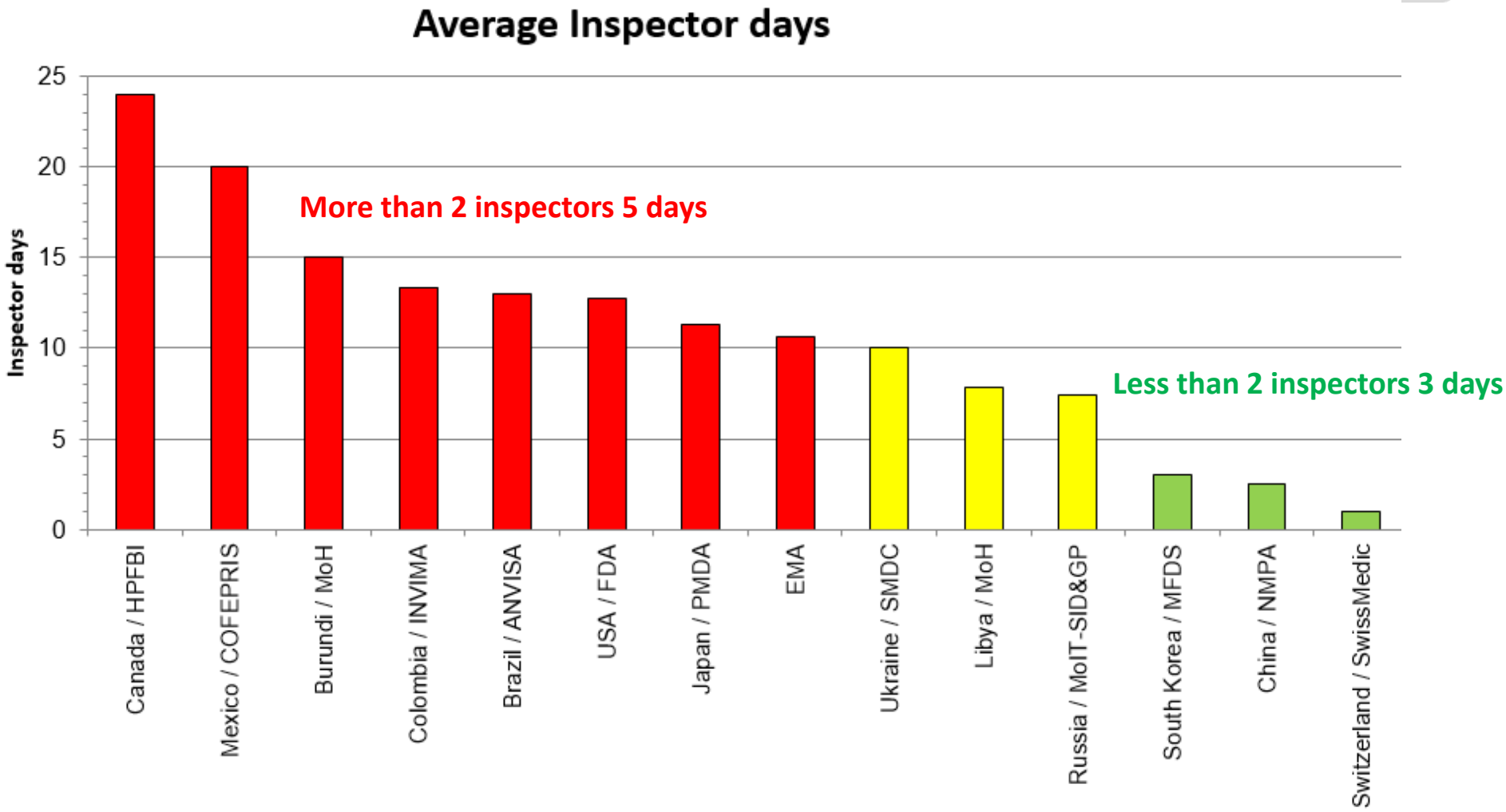
# Number of Foreign Inspections by Country 2/2




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

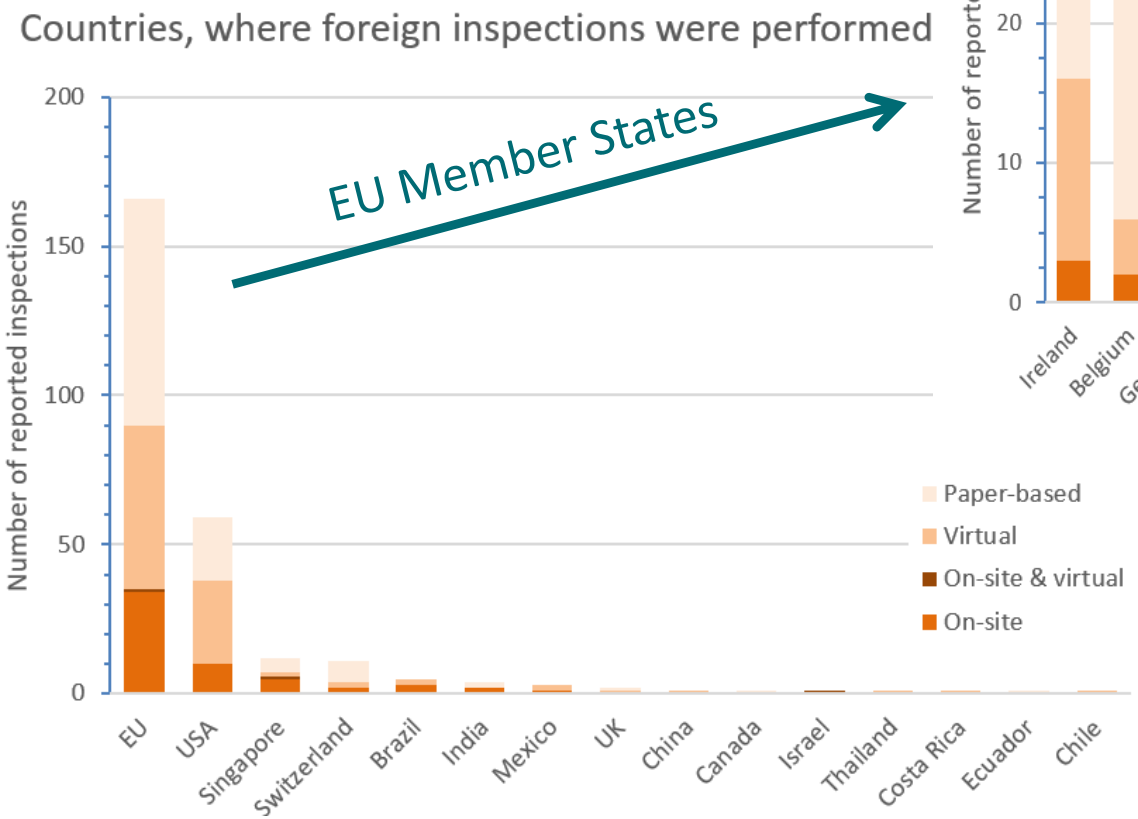
Note: No foreign inspection reported by the UK in 2021

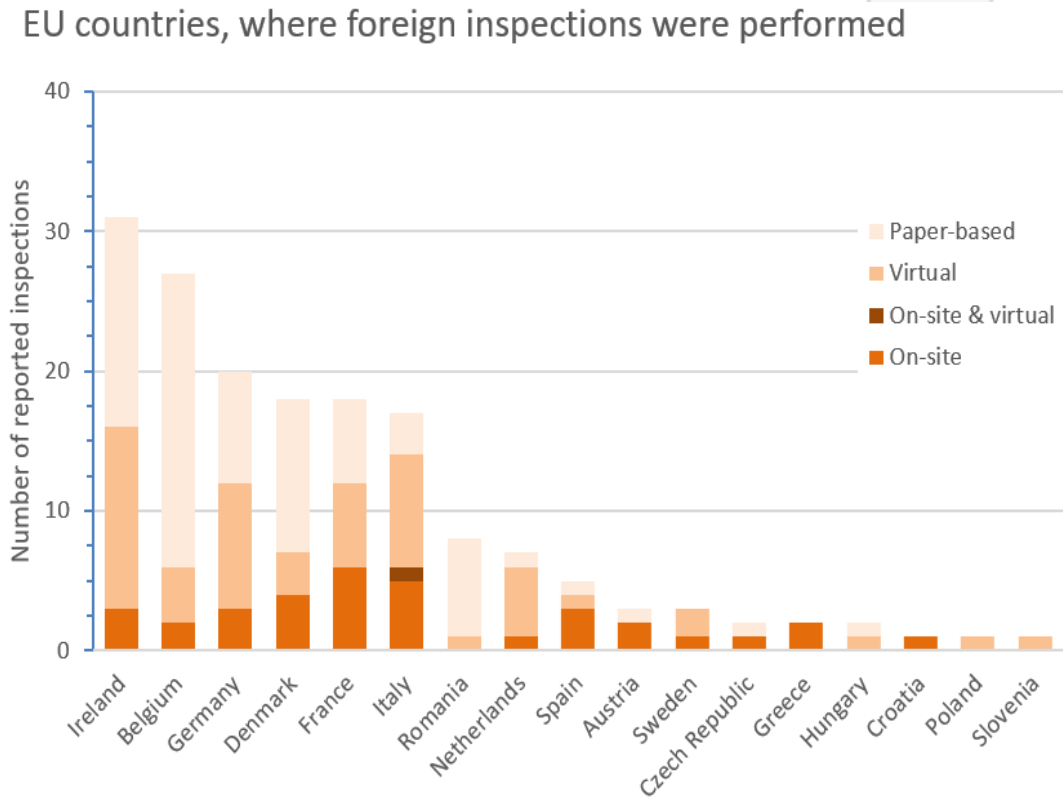
# Average Inspector Days for Foreign Inspections at a Manufacturing Site



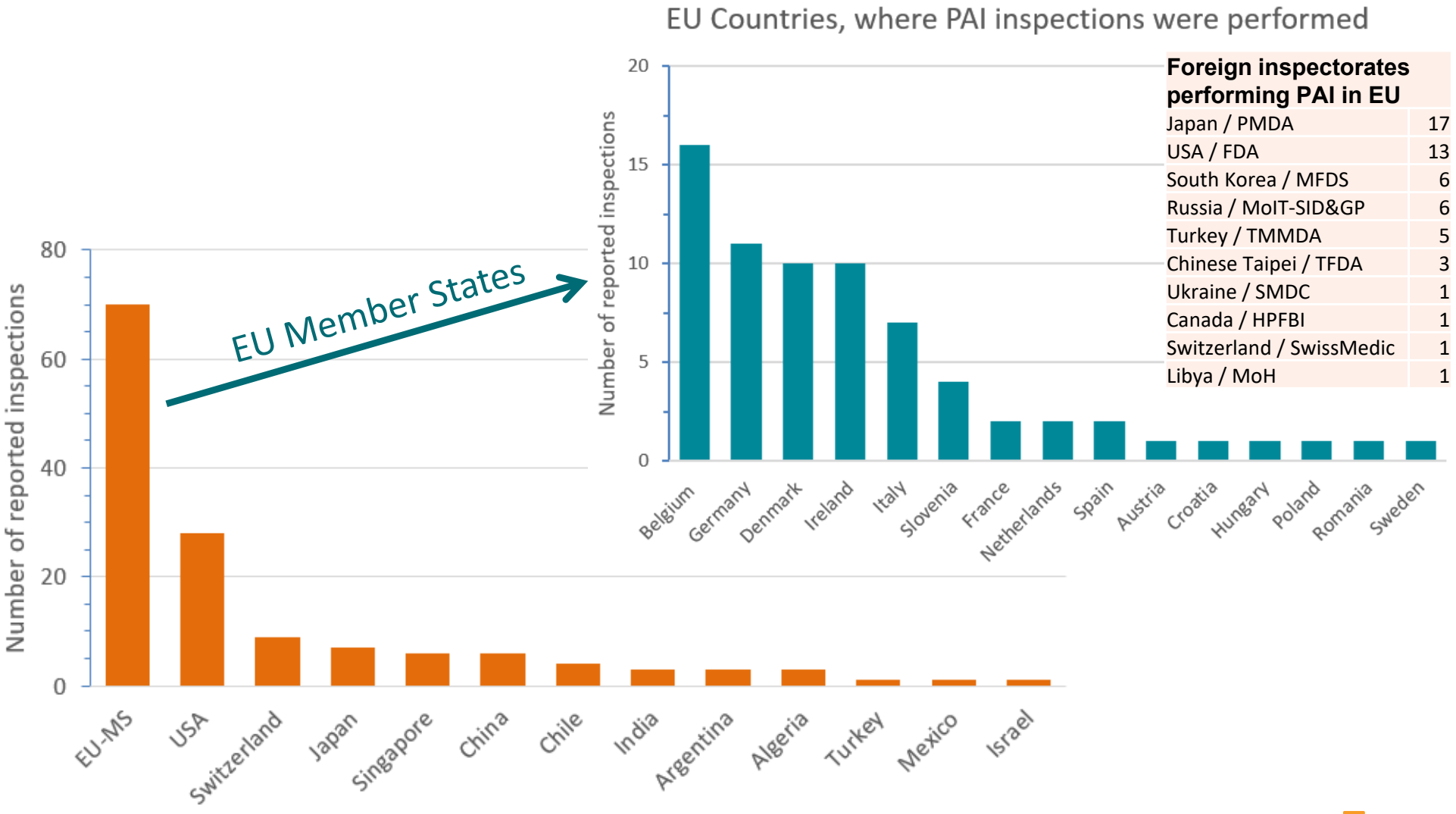
## 6. FOREIGN INSPECTION ACTIVITY

# Locations of Manufacturing Facilities Hosting Foreign Inspections



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

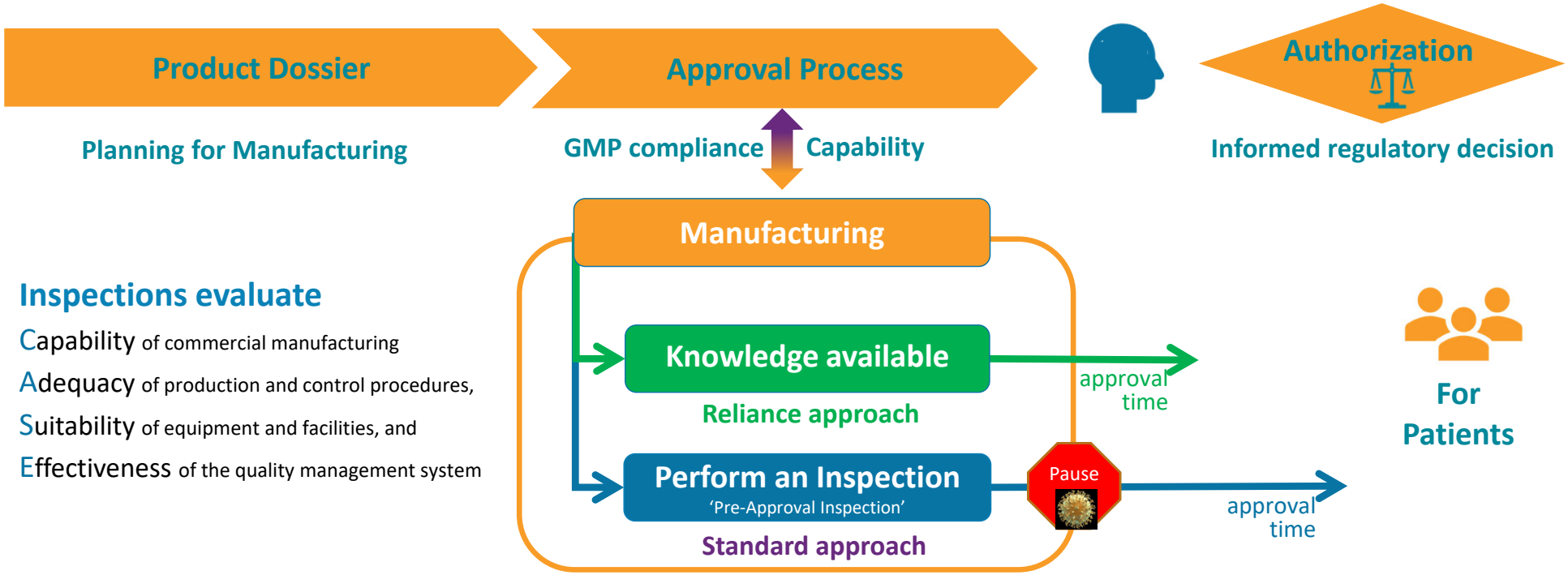



| Foreign inspectorates performing PAI in EU | |
|---|---|
| Japan / PMDA | 17 |
| USA / FDA | 13 |
| South Korea / MFDS | 6 |
| Russia / MoIT-SID&GP | 6 |
| Turkey / TMMDA | 5 |
| Chinese Taipei / TFDA | 3 |
| Ukraine / SMDC | 1 |
| Canada / HPFBI | 1 |
| Switzerland / SwissMedic | 1 |
| Libya / MoH | 1 |



PAI: Pre-Approval Inspections

# Regulators Have Different Pathways to Determine Approval of a Registration Application and for a Manufacturing Site




**Inspections evaluate**

**C**apability of commercial manufacturing

**A**dequacy of production and control procedures,

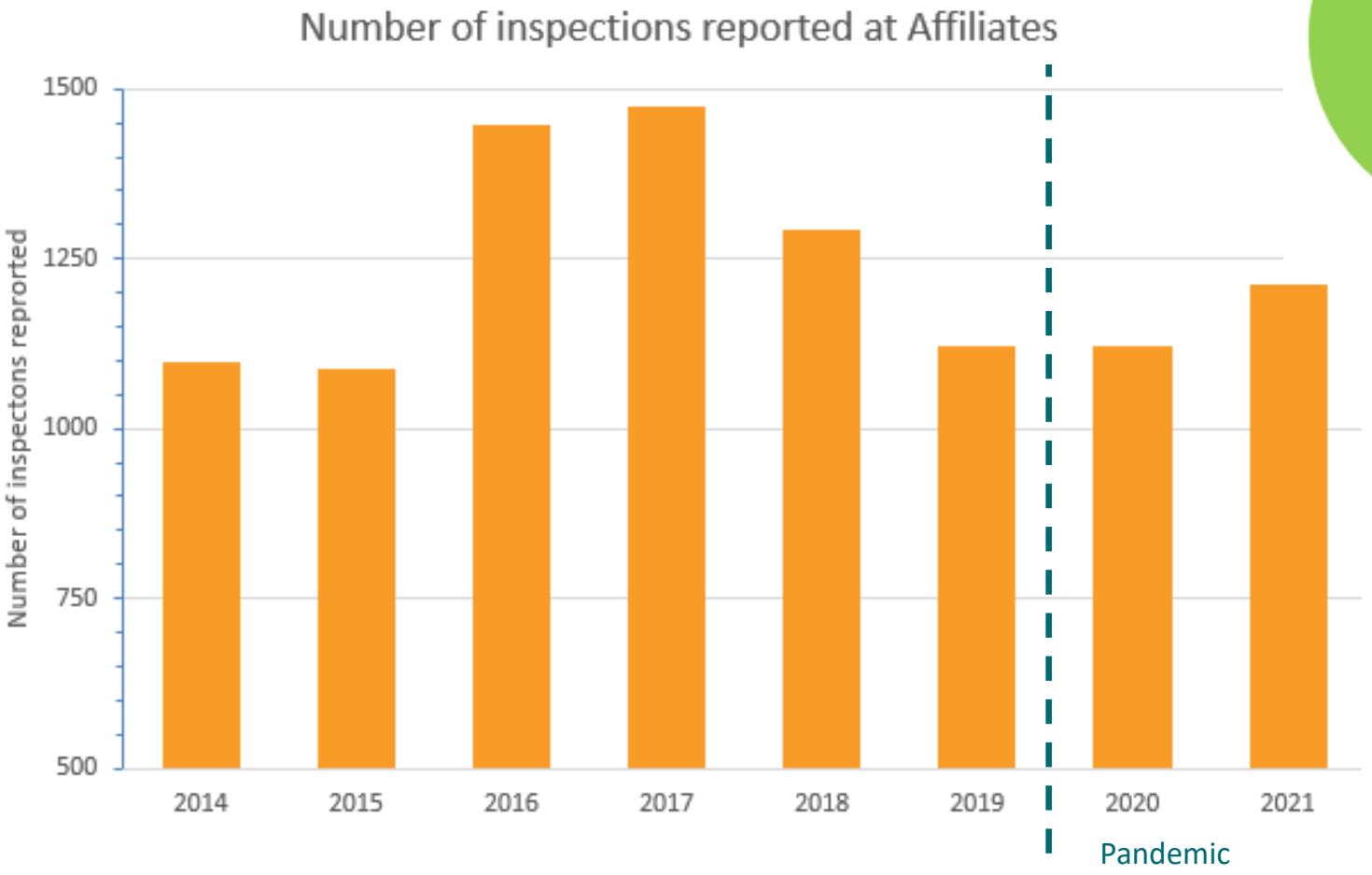
**S**uitability of equipment and facilities, and

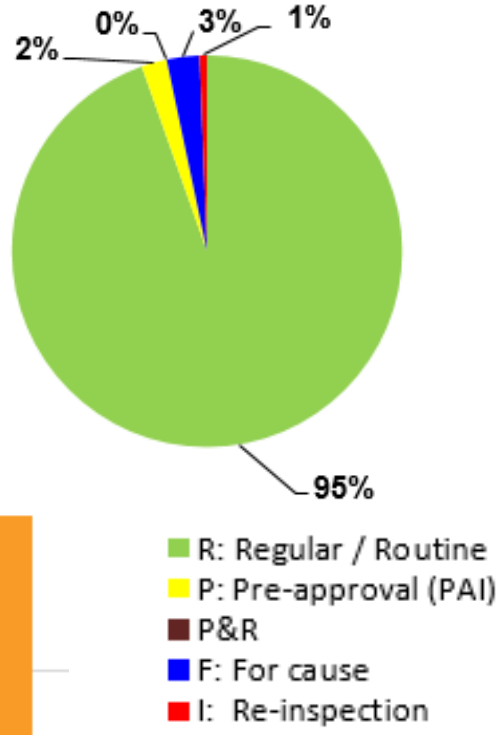
**E**ffectiveness of the quality management system

Identify the areas of the regulation that can be used to support alternative approaches, e.g., reliance

## 8. INSPECTIONS AT COUNTRY AFFILIATES

# There is a Very Limited Influence by the Pandemic on the Number of Inspection at Affiliates



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