European Federation of Pharmaceutical Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2019 Data

Author: MQEG Inspection team

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Version: 1






Public 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)

EFPIA'S ANNUAL INSPECTION SURVEY

Striving for Reliance: The Same Product Manufactured Going to Patients All Over the World Independent of the GMDP -Standard

> 100 strong
Regulatory Systems

n Standards

1 Manufacturing

1 Product

n Patient

520 Foreign Inspections in 2019

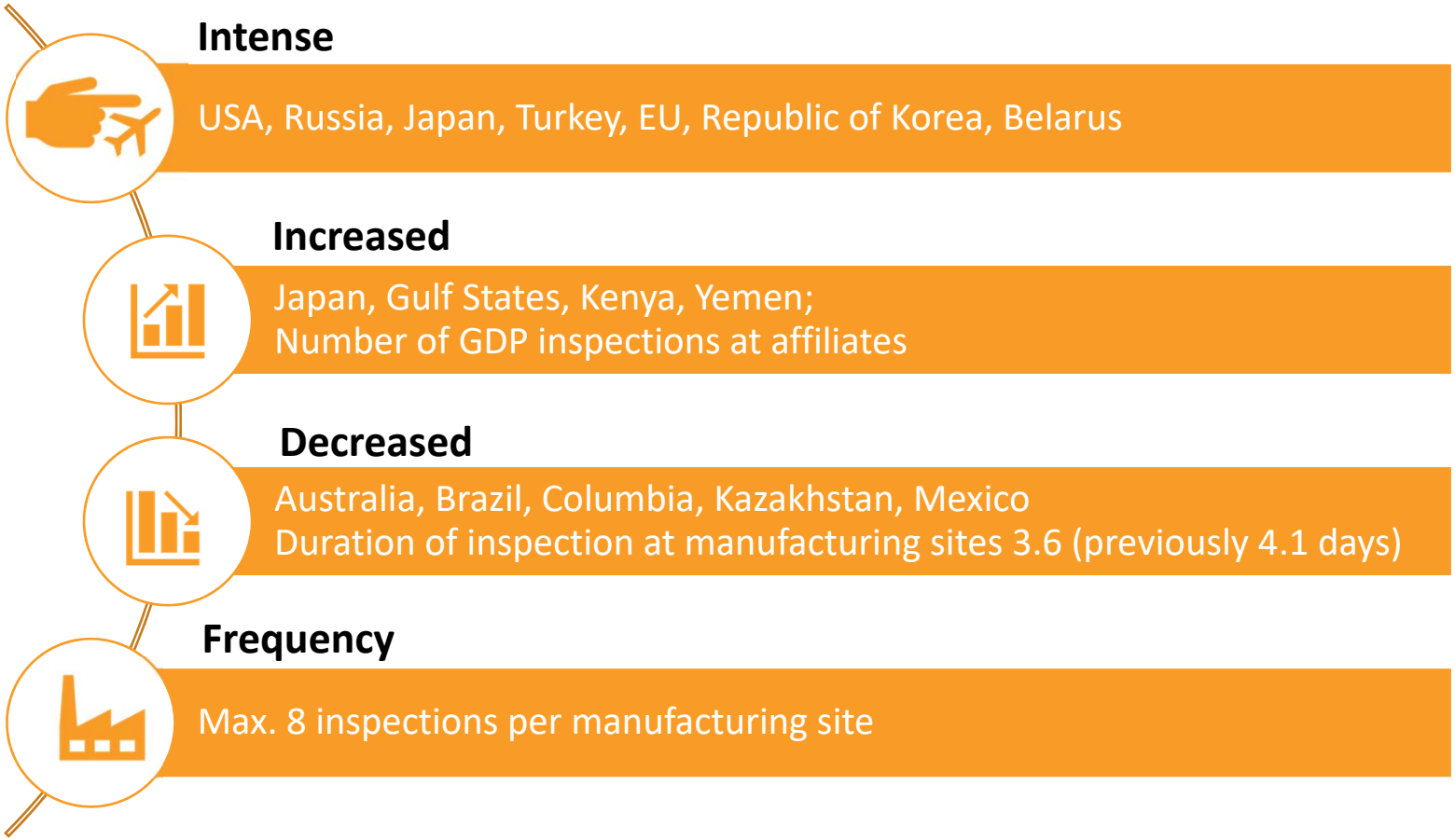
> **85 000h** invested by Regulators

> **700 000h** invested by Industry

EFPIA'S ANNUAL INSPECTION SURVEY

The Situation was Dynamic in 2019

Facts on Inspections



Based on data from 26 research-based pharmaceutical companies

We received additional feedback facilitated by the NTA from local companies in APIFARMA, Portugal (3) and Farmindustria, Italy (7)

Lessons Learned from the 2019 Data Collaboration

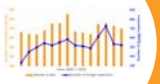
Cooperation

282 out of 520 foreign inspections (54%) are performed by a PIC/S inspectorate in a country, where the inspectorate is also a PIC/S member

Recognition

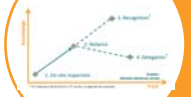
MRAs start showing benefits e.g. EU-US, but not EU-Japan

Sharing



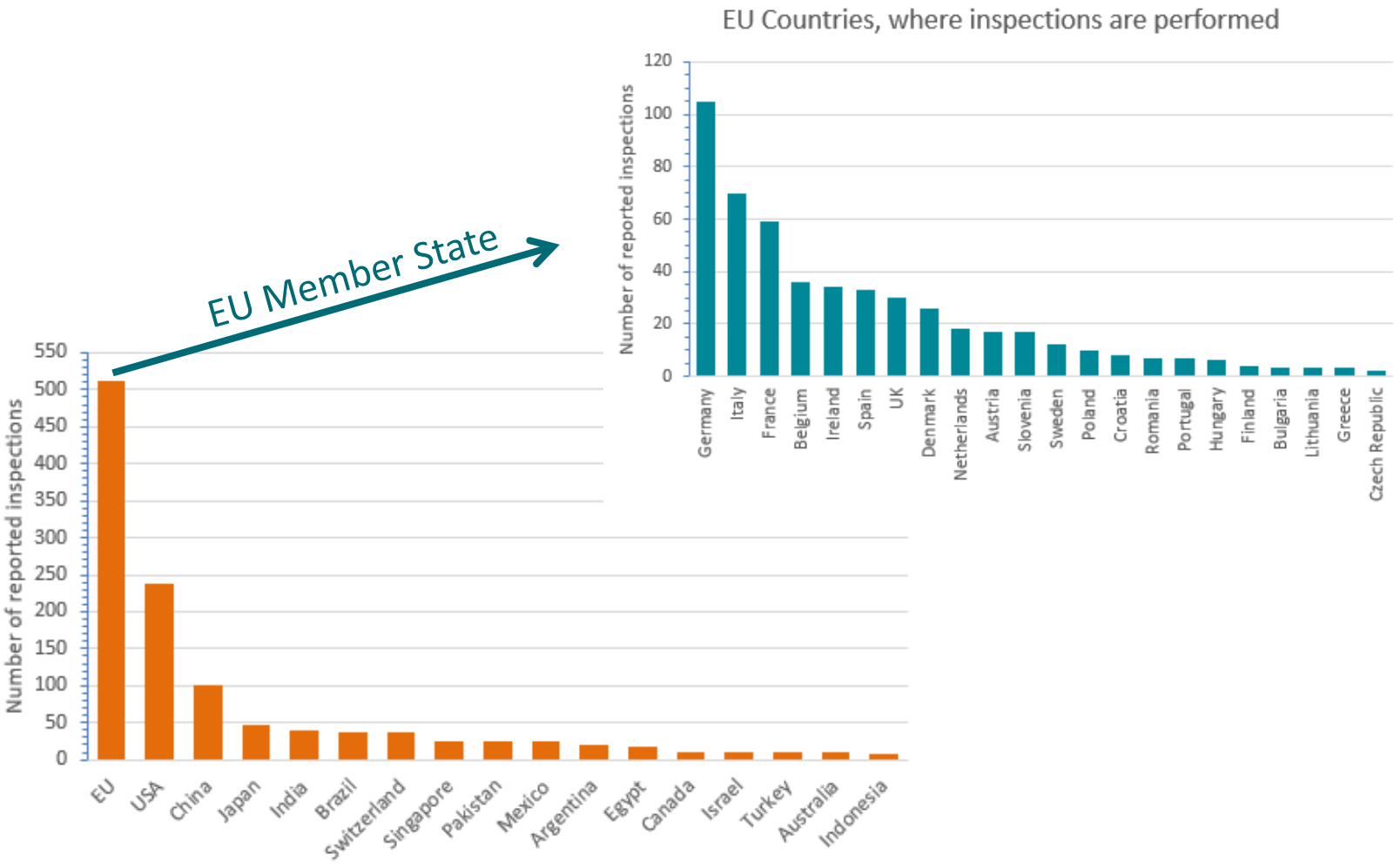
Informal collaborations e.g., joint inspection pilots

Reliance



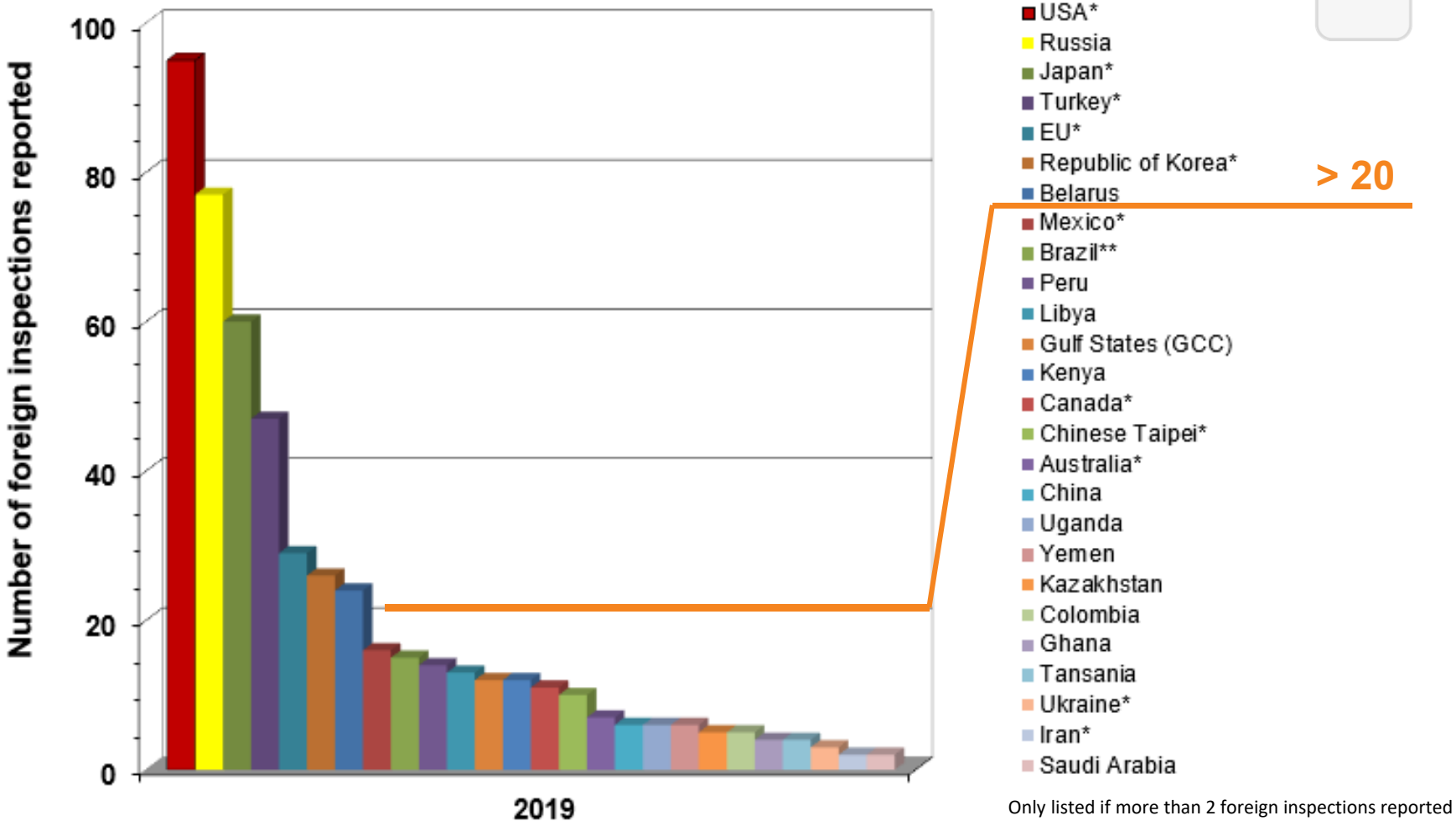
Lessons learned: Reliance is possible e.g., n-Nitrosamine, BREXIT, COVID-19

Locations of Manufacturing Facilities Included in the Survey



Number of Foreign Inspections at Manufacturing Sites

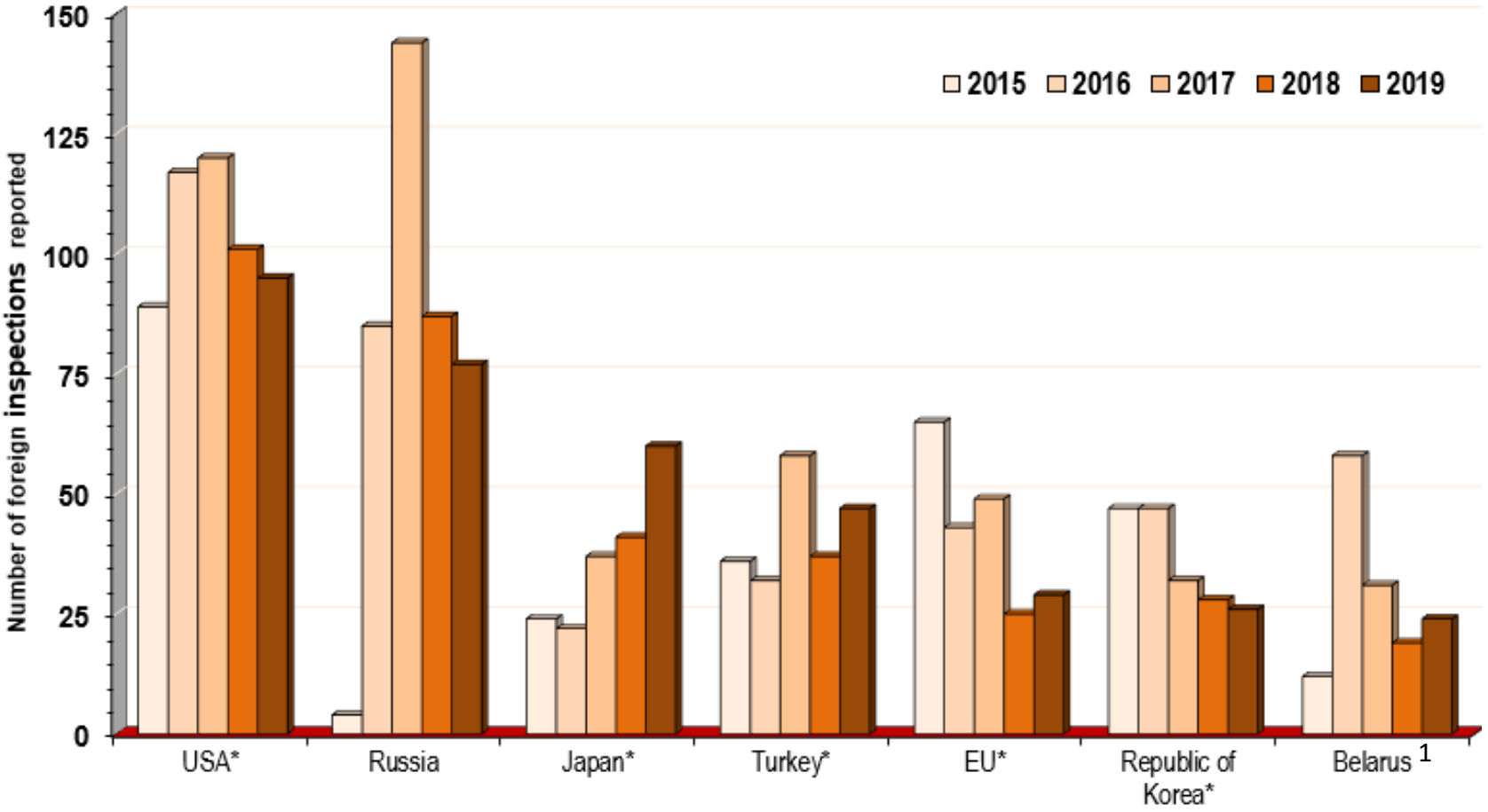
ordered by country (>1 inspections; EU as one entity)



Only listed if more than 2 foreign inspections reported

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

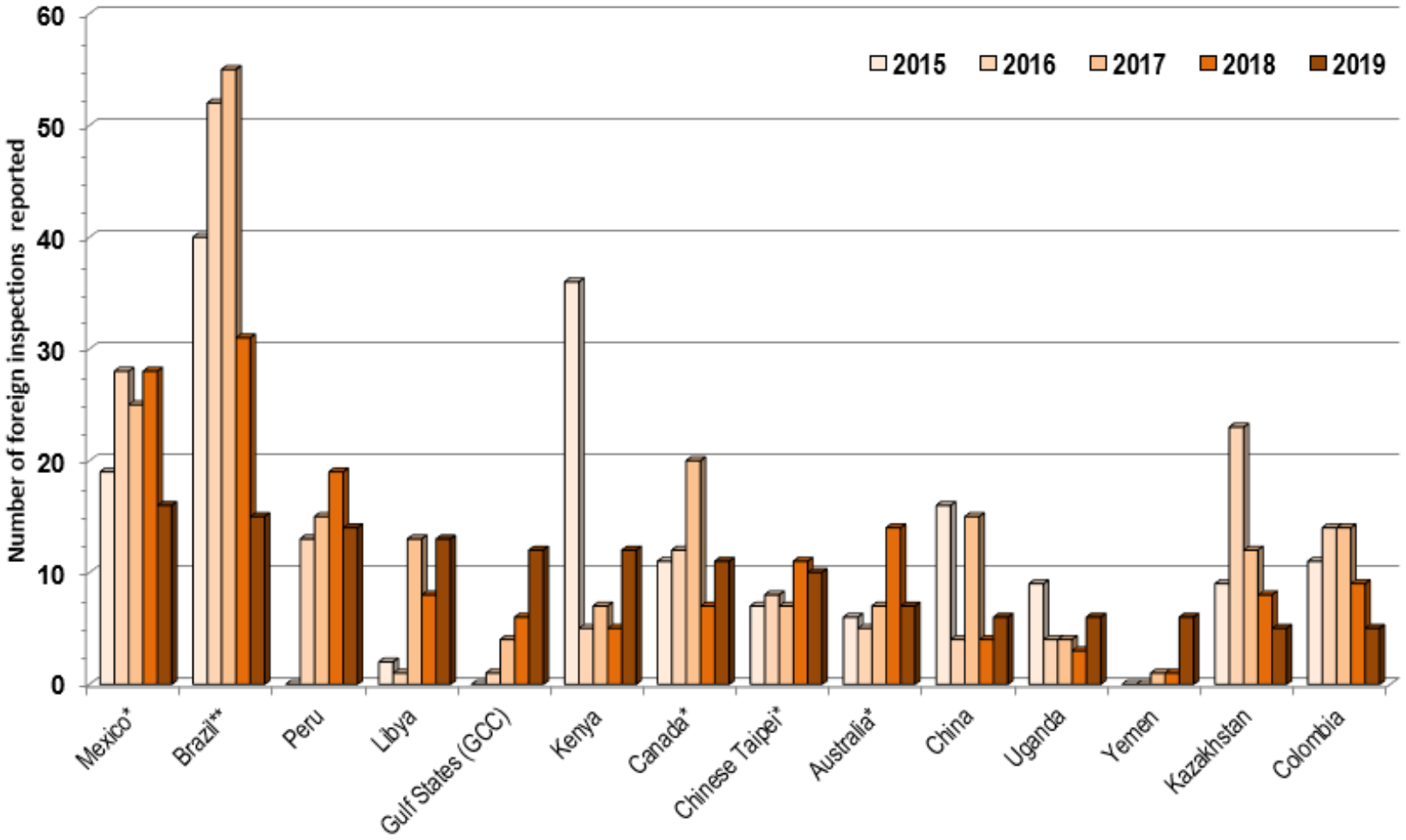
Number of Foreign Inspections by Country



*Inspectorate is a PIC/S member **PIC/S Applicant ***PIC/S Pre-Applicant [1]issuing also EEU certificates (4)

EFPIA'S ANNUAL INSPECTION SURVEY

Number of Foreign Inspections by Country



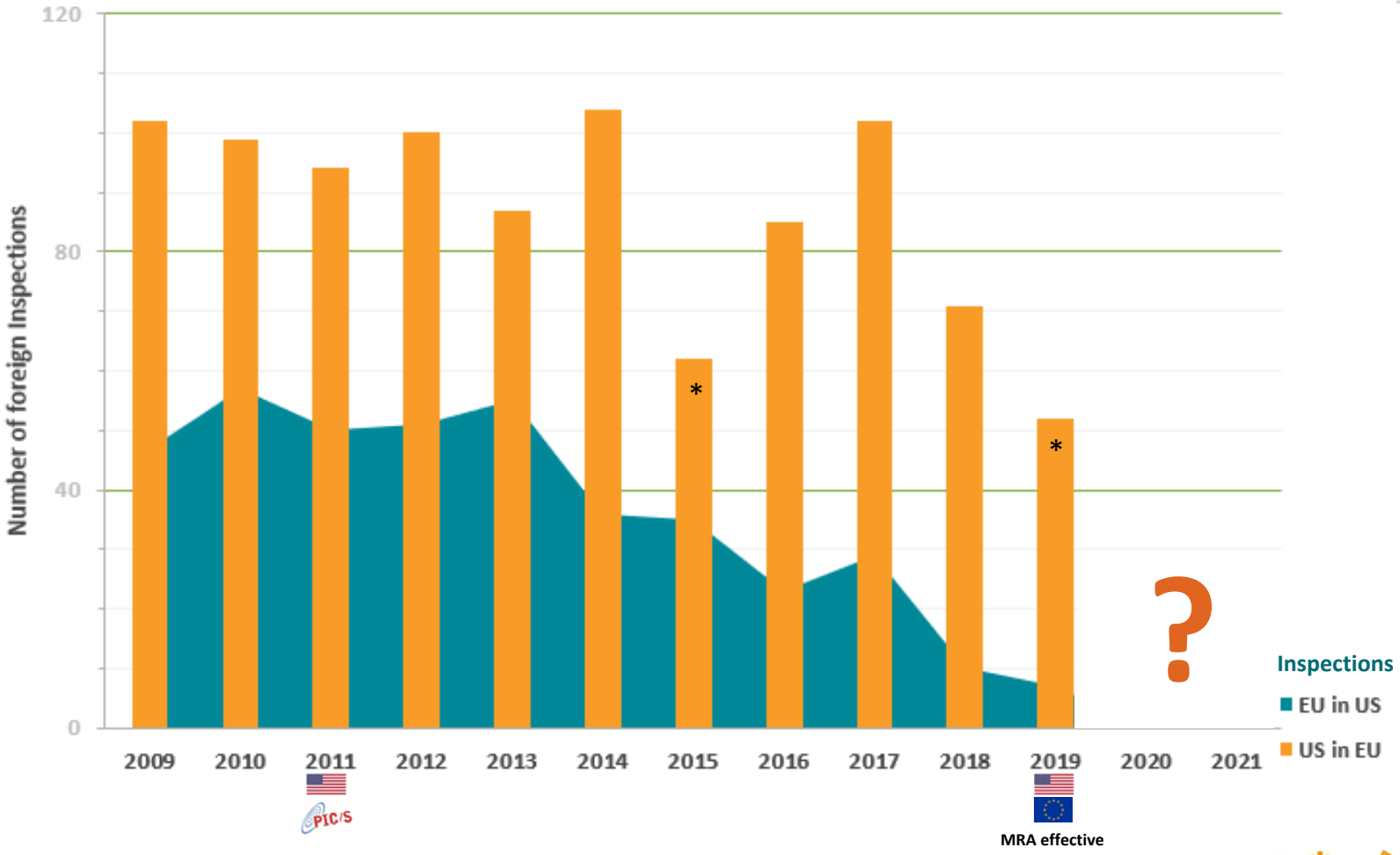
*Inspectorate is a PIC/S member **PIC/S Applicant ***PIC/S Pre-Applicant

Examples of Inspection at one Manufacturing Site of Different Companies

Site in country	Domestic inspections	Foreign inspections	Sum	Foreign inspectorates
Germany	1	**7**	8	Russia (2), US (2), Iran, Libya, Canada
Italy	1	**6**	7	Belarus, Russia, Kazakhstan, Belarus (for EEU), Turkey, China
US	1	**6**	7	Japan (2), Canada, South Korea (3)
US	1	**6**	7	Brazil, Chinese Taipei, South Korea, Japan (3p)
Ireland	0	**6**	6	Kazakhstan, Libya, Japan (2p), GCC, Belarus
Netherlands	2	**4**	6	Libya, US (2), Russia
Germany	1	**4**	5	GCC, Yemen, Ivory Coast, Ukraine
US	5	**3**	8	EMA, Canada, Australia
Belgium	5	**3**	8	US(2), Kenya

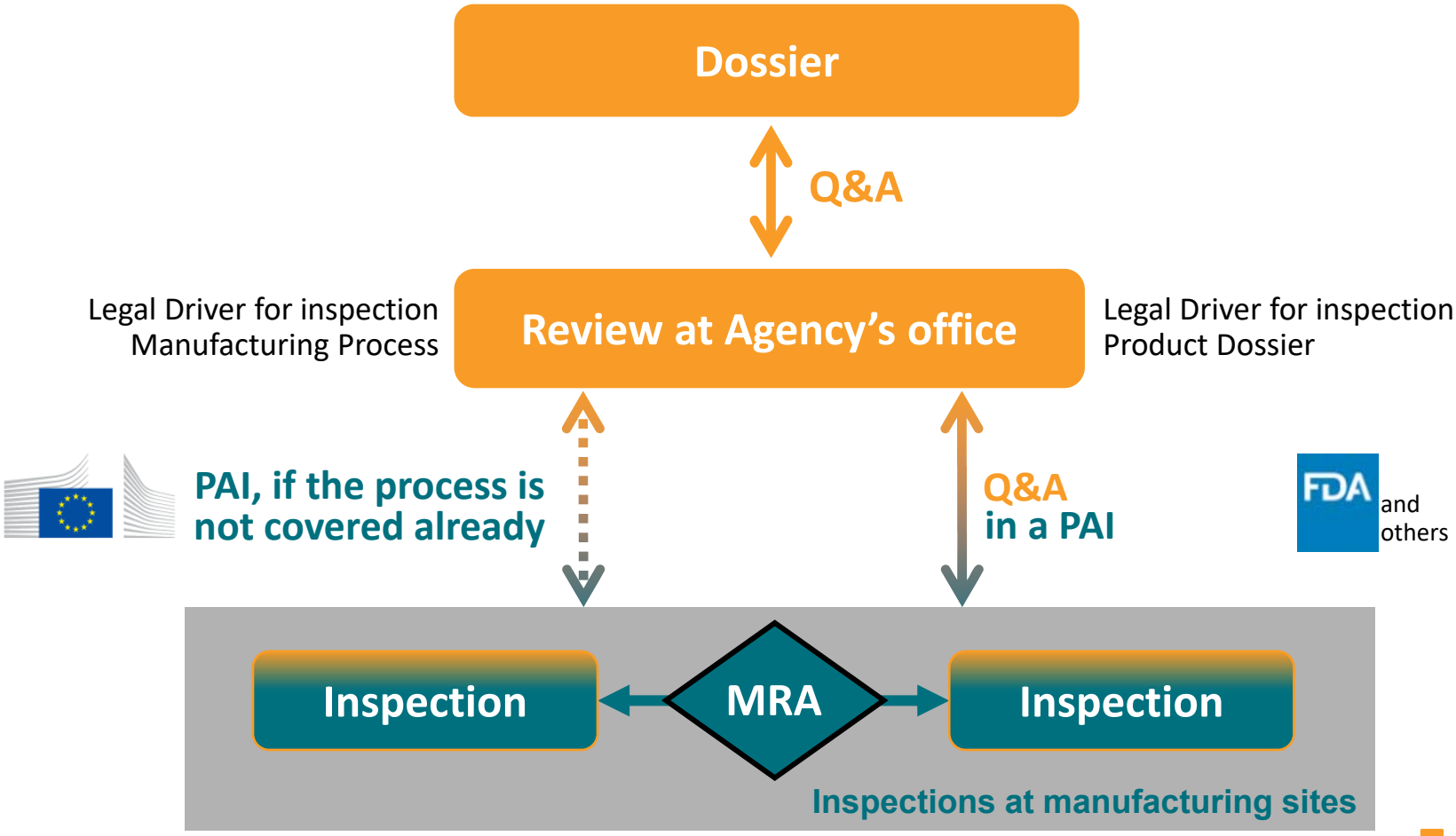
Top 5 and more inspections at one site if reported by the companies

Opportunities: Efficient MRA Implementation can Drive Further Reduction of Inspections



*Government shut down in US >20 days

Pre-Approval Inspections (PAIs) can be Focused on Dossier Review and Relying on Previous Inspections

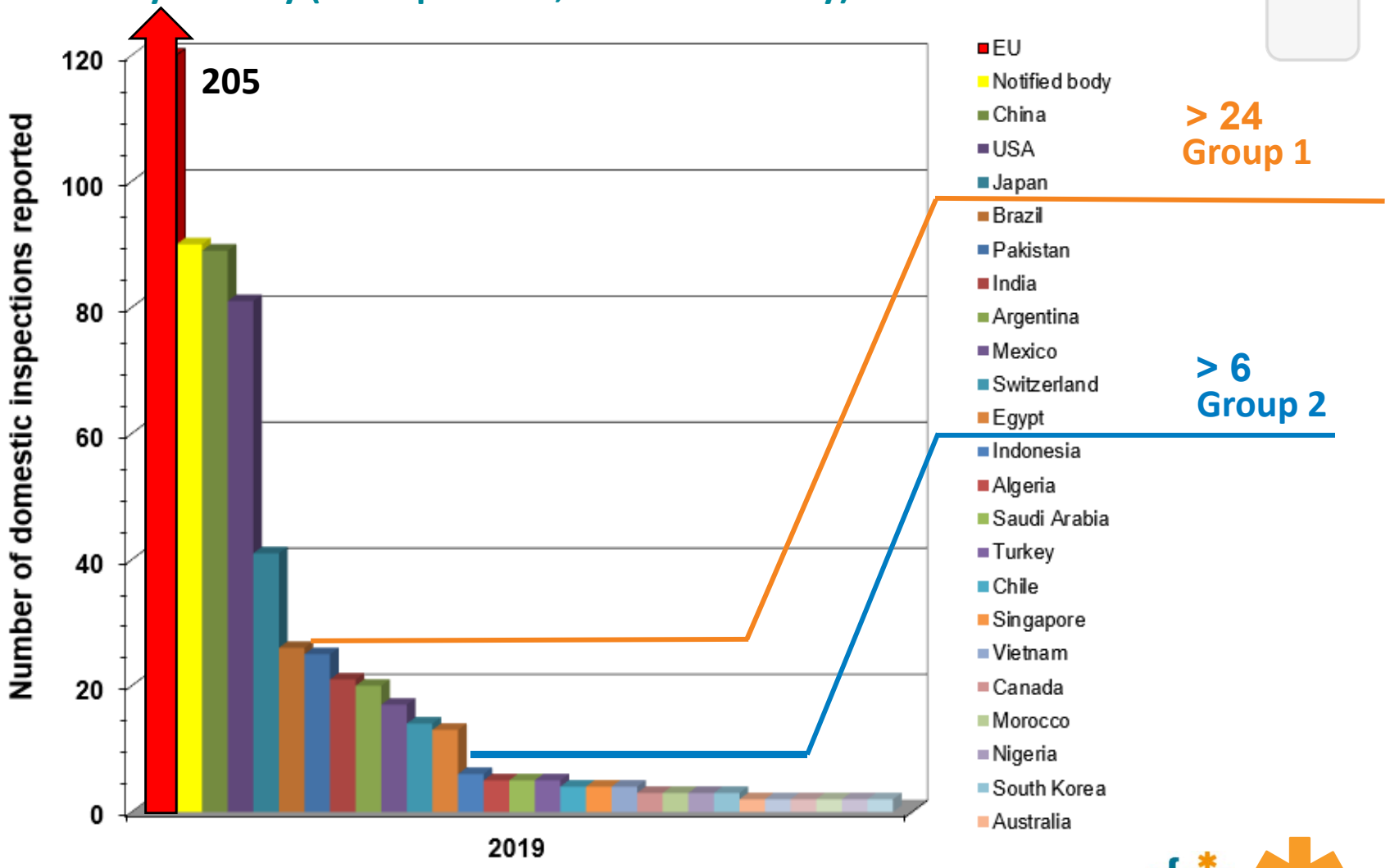


EU-US MRA
Situation on Pre-Approval Inspections

- **Legal situation**
  - The MRA allows recognition of inspections prior approval
- **Results of the Data Assessment**
  - There is no evidence that EU inspections are generally recognized under the Pre-approval inspection paradigm of US-FDA
- **Opportunities for focused PAIs**
  - The duration of a PAI could be reduced to e.g., 1 day focusing on the clarification of the content of the dossier by referencing the results from routine GMP inspections

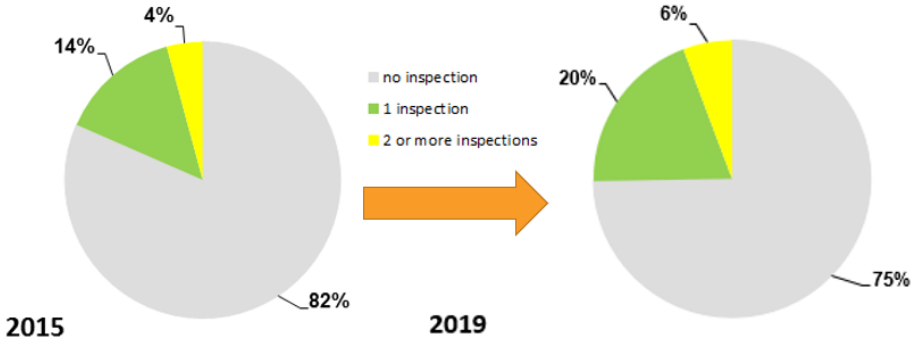
Number of Domestic Inspections Reported

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

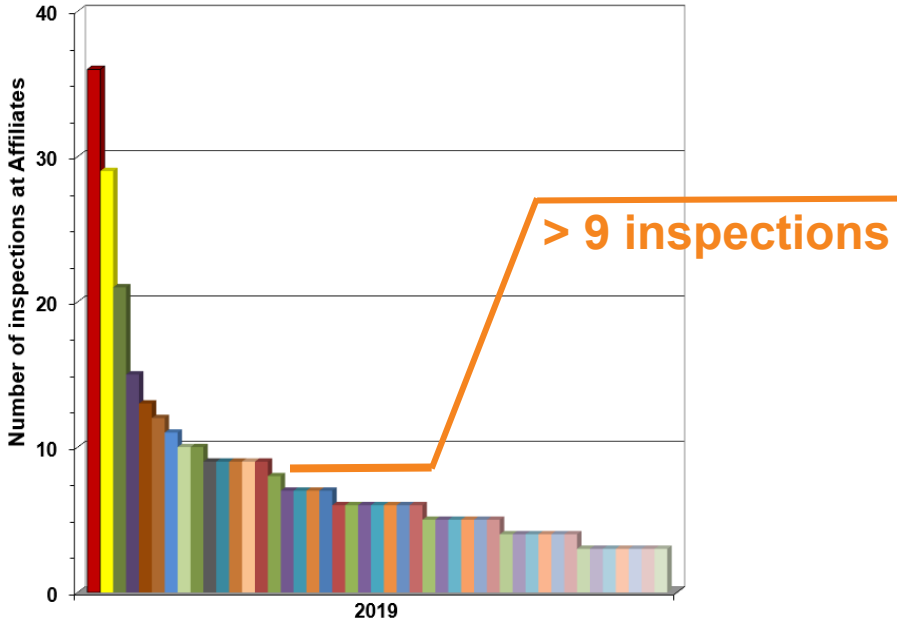


Only listed if more than 1 domestic inspection; Certification audits not included

The Numbers of Reported Good Distribution Practice (GDP) Inspection at Local Affiliates Have Increased



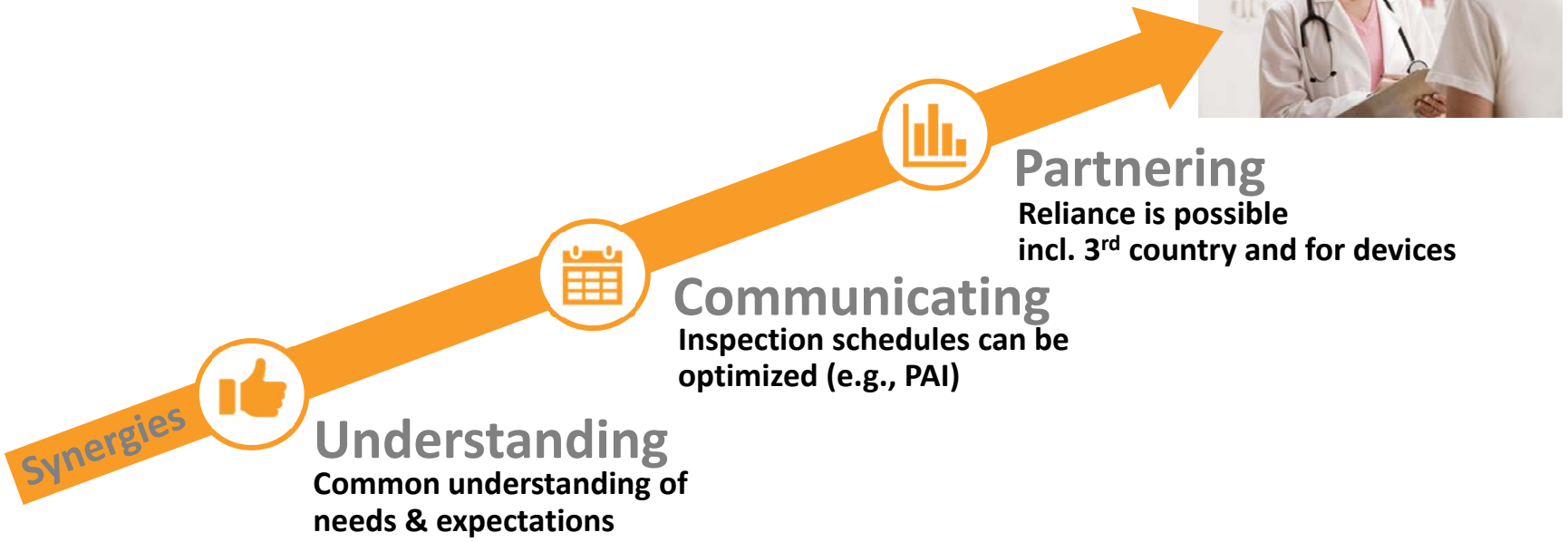
More GDP inspections
No trend by region



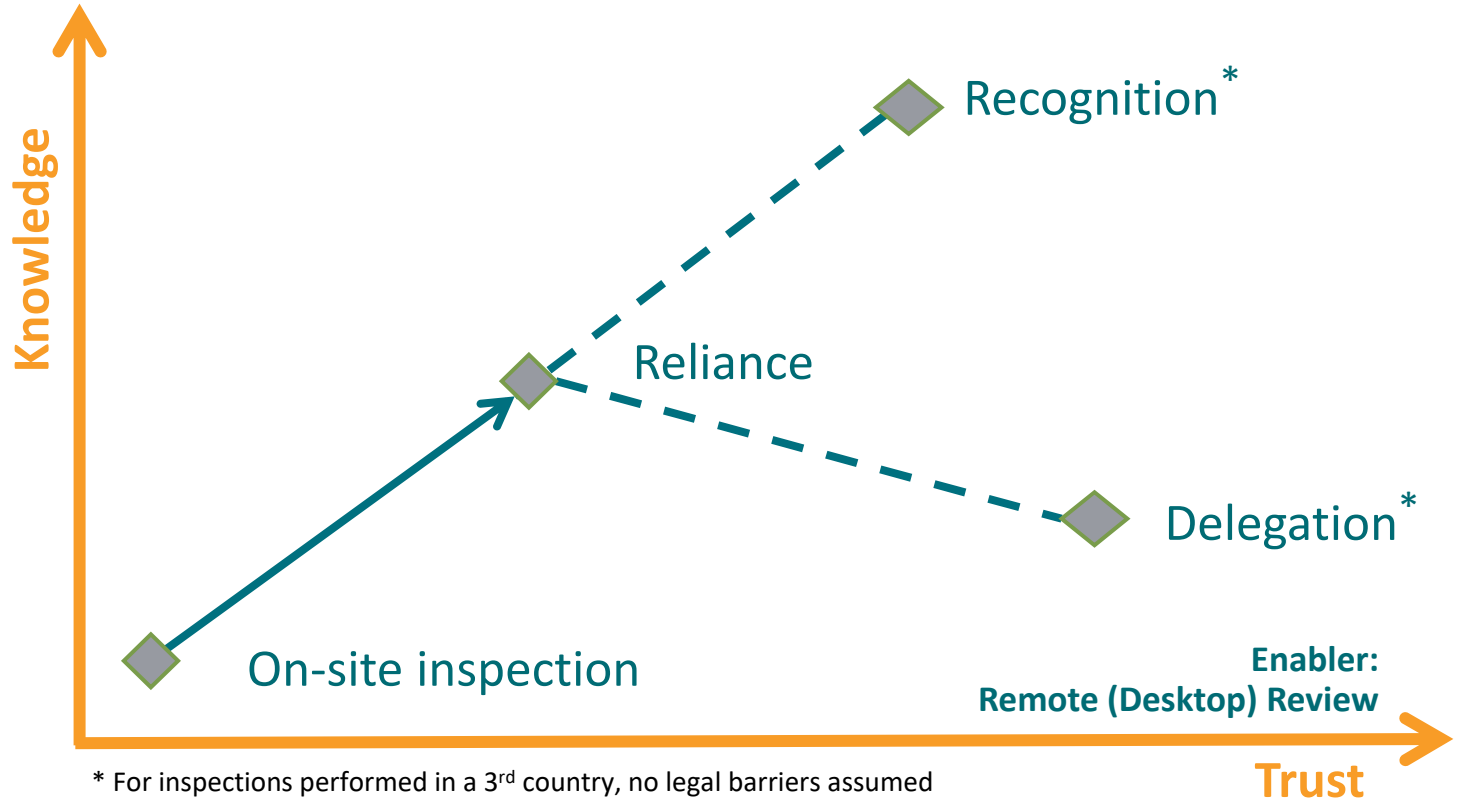
- Ecuador / ARCSA
- Czech Republic / SUKL
- Japan / PMDA
- Chile / ISP
- Denmark / DKMA
- Poland / CPI
- South Africa / SAHPRA
- Belgium / AFMPS
- Canada / HPFBI
- Peru / DIGEMID
- Philippines / FDA
- Bulgaria / BDA
- Hungary / OGYEI
- Argentina / ANMAT
- Indonesia / NADFC
- Colombia / INVIMA
- Slovakia / SIDC
- Honduras / ARSA
- Latvia / SAM
- Hong Kong China / MoH
- Algeria / LNCPP
- UK / MHRA
- Spain / AEMPS
- Notified Body
- Netherlands / IGJ
- China / NMPA
- Germany / RP
- Romania / NMA
- Brazil / ANVISA
- Switzerland / Swissmedic
- France / ANSM
- Malaysia / NPCB
- Saudi Arabia / SFDA
- South Korea / MFDS
- Austria / AGES
- USA / FDA
- Ireland / HPRA
- Portugal / INFARMED
- Singapore / HSA
- Sweden / MPA
- Ukraine / MoH
- Lithuania / SMCA
- Finland / FIMEA
- Greece / NOM
- Costa Rica / MoH

Only listed if more than 2 inspections

Resources Can be Saved for Better Use



An Approach Towards the Ideal State



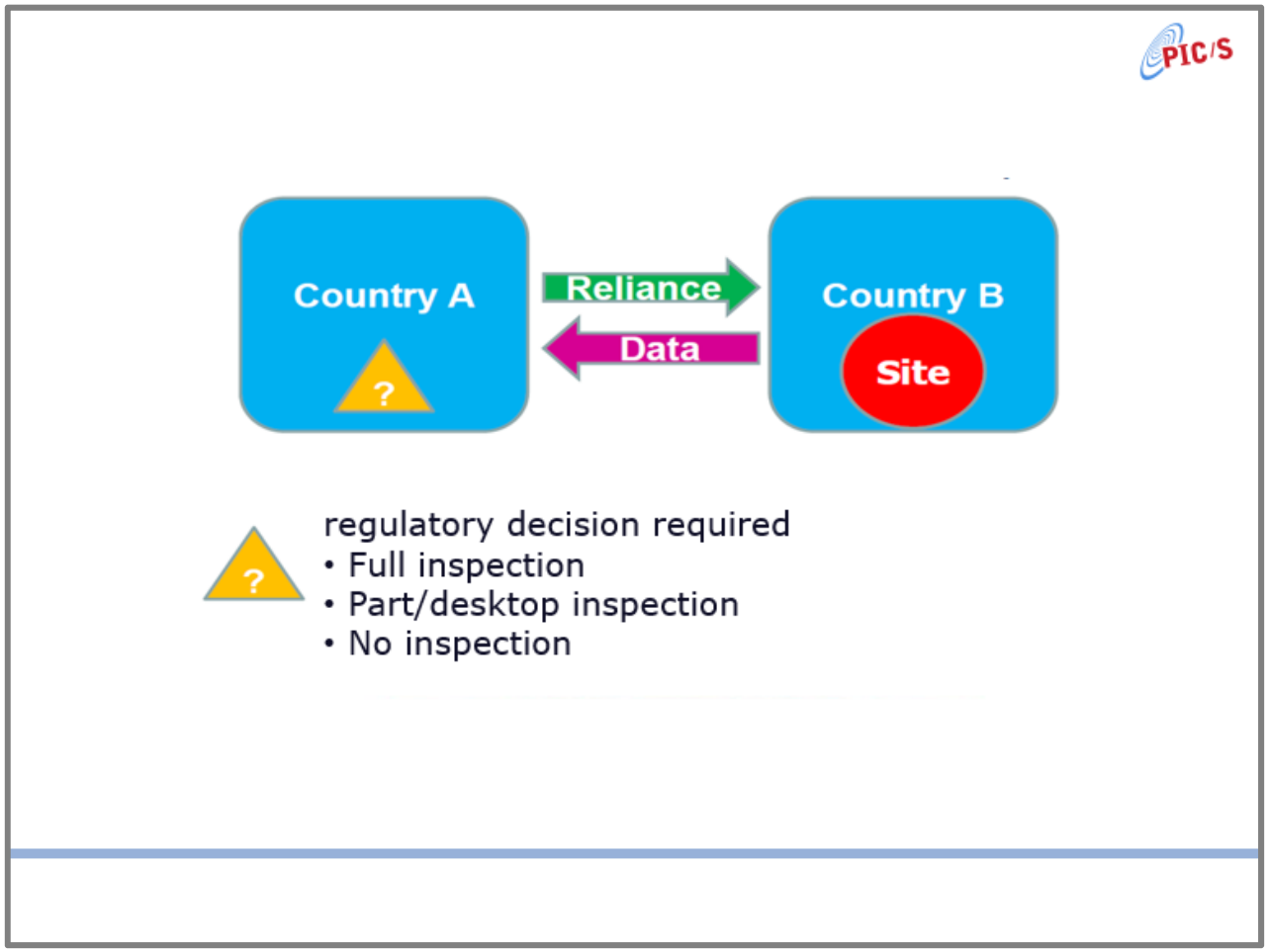
* For inspections performed in a 3rd country, no legal barriers assumed

- **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.

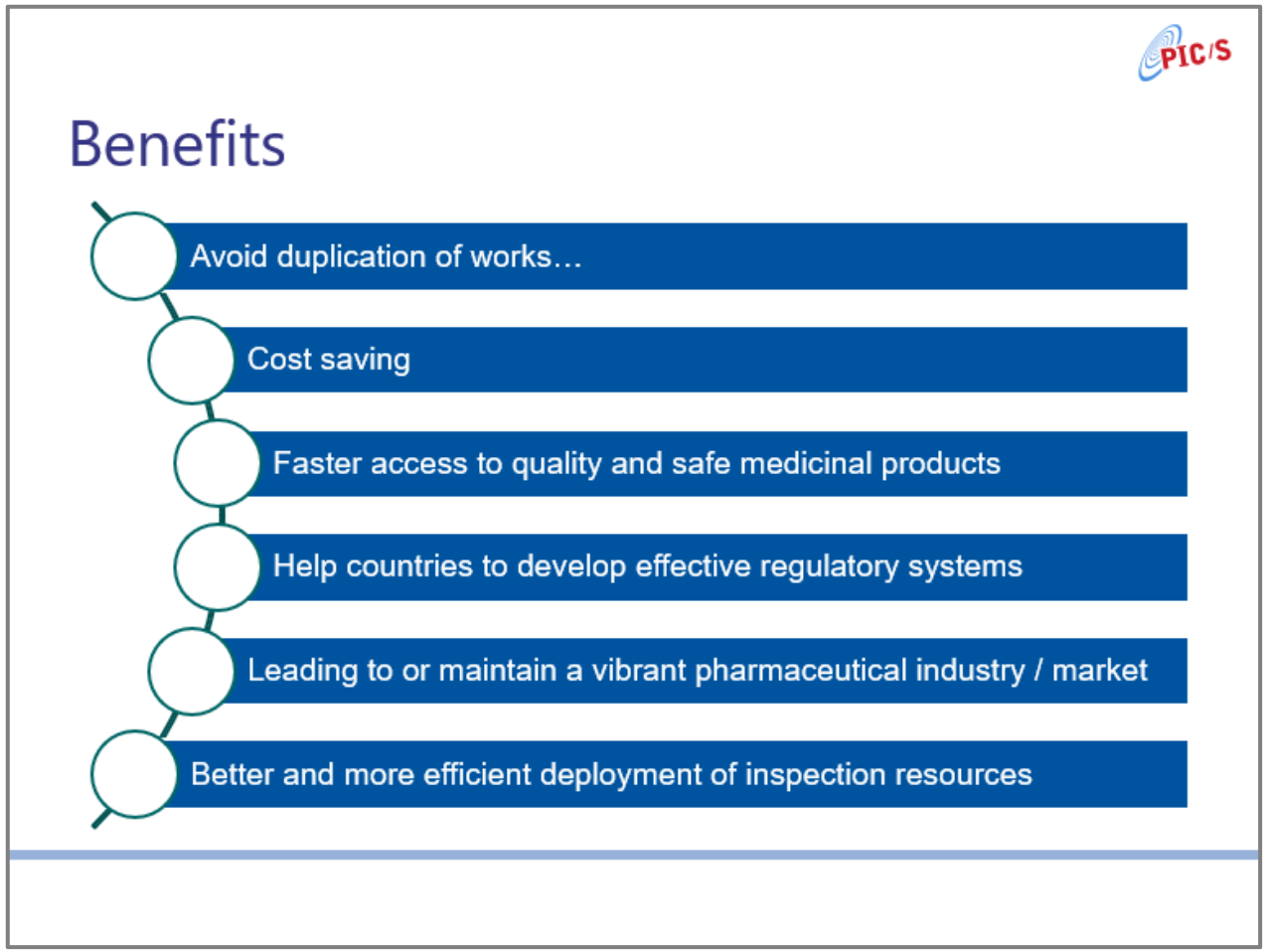
PIC/S Promotes Reliance by Exchanging Data and Facilitate Different Options for Regulatory Decision



Credit to the PIC/S secretariat for using the slide, 23. April 2020

GMP-Inspection reliance, PIC/S guideline PI 048-1, 1 June 2018

PIC/S Highlights Benefits Inspectorates can Achieve Implementing Reliance

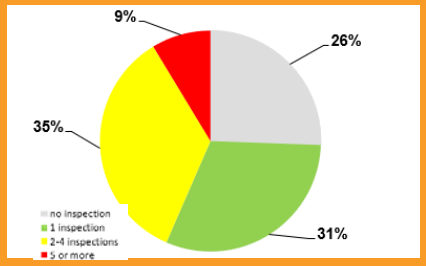


Credit to the PIC/S secretariat for using the slide, 23. April 2020

GMP-Inspection reliance, PIC/S guideline PI 048-1, 1 June 2018

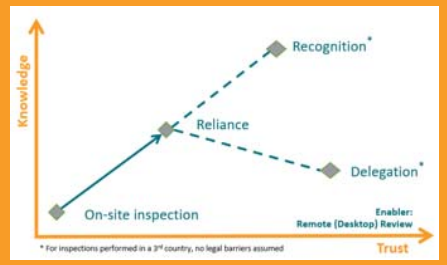
The 2019 Data Demonstrates Reliance can Replace Redundant Inspections

Redundant inspections at one site



Health authorities are more efficient locally

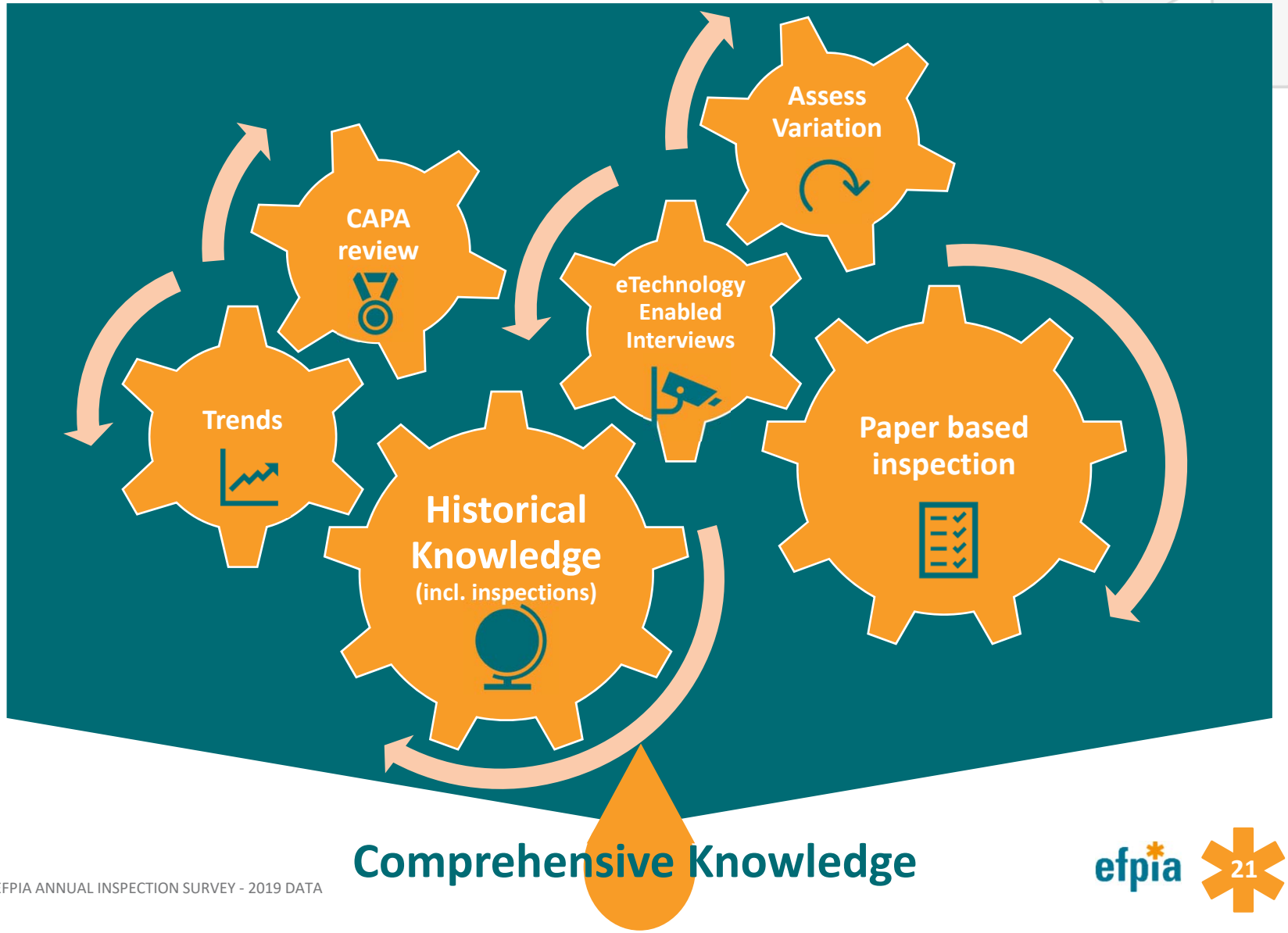
Remote Desktop Review* can be an alternative



*GMP-Inspection reliance**, PIC/S guideline PI 048-1, 1 June 2018

REMOTE DESKTOP REVIEW

Comprehensive Knowledge can be Gained from Available Information



STEP 1: INSPECTION PLANNING

A Simple and Qualitative Quality Risk Management Tool for Inspection Planning is Available by PIC/S

Elements

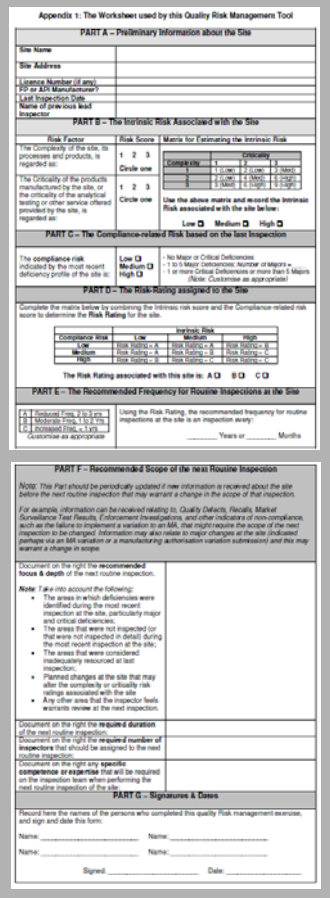
- Knowledge of the GMP compliance status of the site
- Footprint of critical and major deficiencies
- Type of inspection i.e., routine, for cause, pre-approval

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)
PIP 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	Complexity × Criticality
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: _____

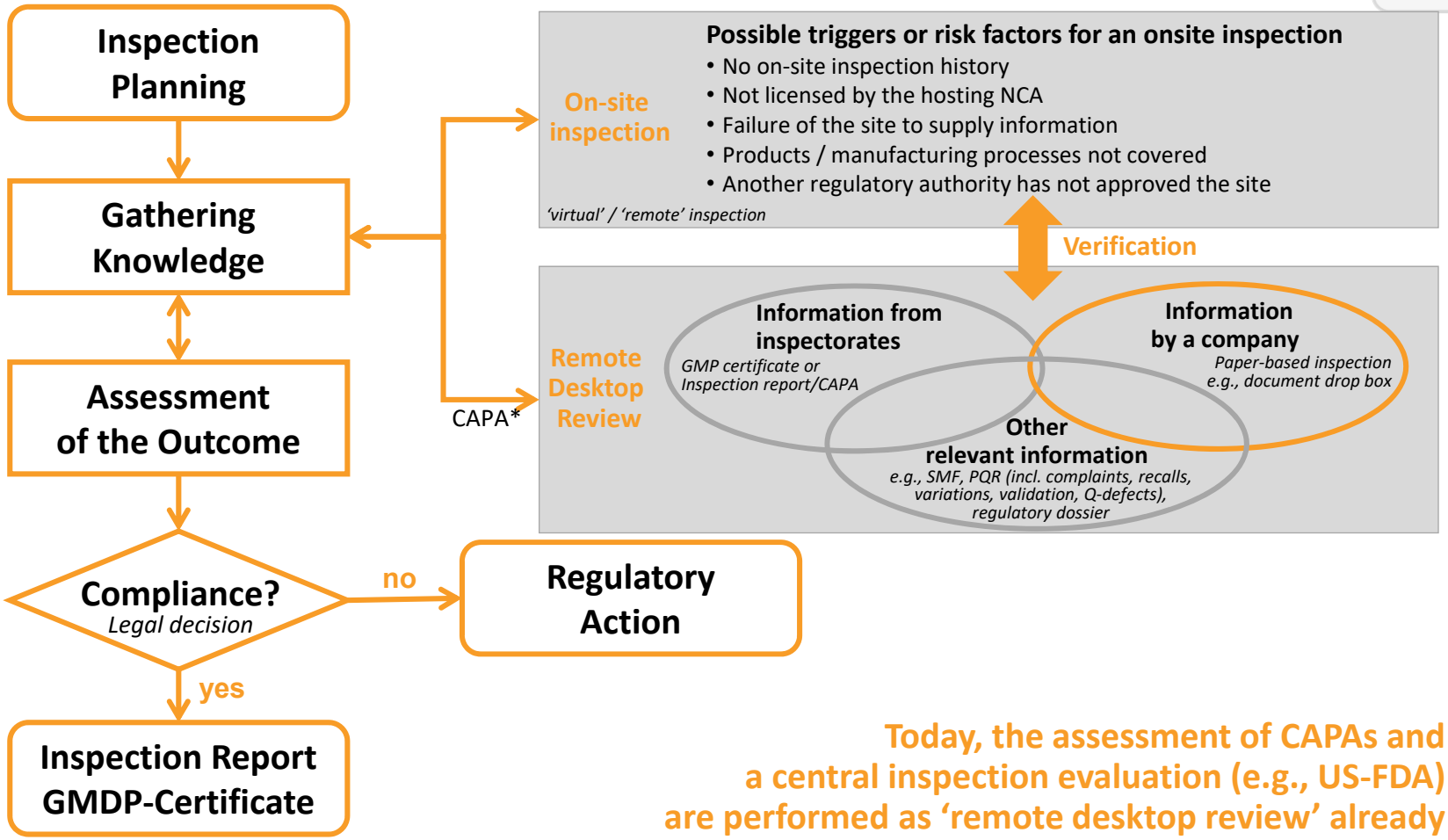
Name: _____ Name: _____

Signed: _____ Date: _____

Fulfill the Legal Requirement for ‘Inspection’

OPTIONS FOR 'INSPECTIONS'

Processes Agencies Have Implemented to Fulfil the Legal Requirement for 'Inspection'

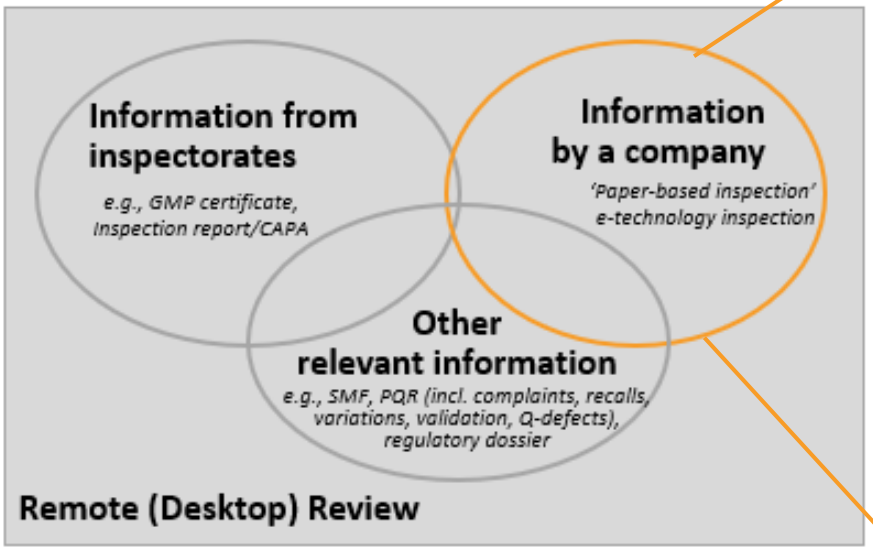


Today, the assessment of CAPAs and a central inspection evaluation (e.g., US-FDA) are performed as 'remote desktop review' already

* i.e., assessments of the responses to inspection observations e.g., from on-site inspections

PAPER - BASED INSPECTIONS IN 2019

Paper Based Inspections as Part of Remote Desktop Review in 2019 Setting the Stage for the Future



PIC/S **GMP-Inspection reliance**, PIC/S guideline PI 048-1, 1 June 2018

Inspectorate / country where paper based inspection are conducted	Numbers reported
Japan / PMDA	**53**
USA	21
Japan	9
Denmark	5
Spain	5
Belgium	4
France	4
Ireland	2
Germany	1
Singapore	1
UK	1
South Korea / MFDS	**6**
USA	5
Italy	1
Chinese Taipei / TFDA	**3**
USA	2
Croatia	1
Turkey / MoH	**2**
USA	1
Germany	1
Uganda / NDA	**2**
USA	1
Bulgaria	1

It is reported that Australia, Brazil, Kenya, Spain, Ukraine, and the UK conducted one paper-based inspection

62 foreign / domestic paper based inspections are reported

PAPER - BASED INSPECTIONS - MESSAGE FROM EFPIA

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

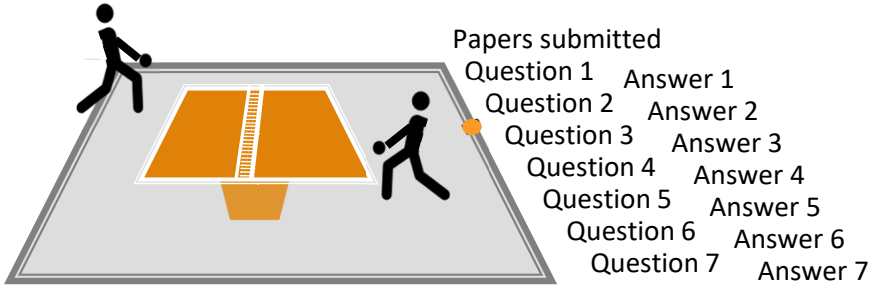
Site	• Site Master File (SMF)*
Product	• Annual Product Quality Review
Pharmaceutical Quality System	• Site Quality Manual
Additional information	• List of inspections / audits

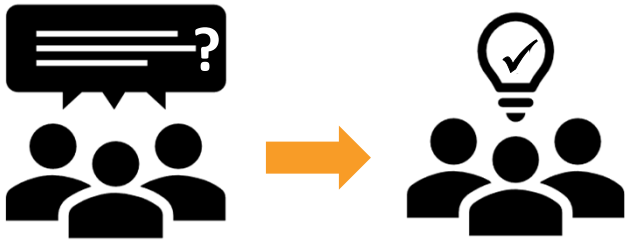
Adobe Acrobat Document — Enhanced GMP/GDP Inspection Efficiency, EFPIA, Position Paper 19. May 2014.

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

The ‘Paper Based Inspection’ Tool could be Used More Effectively





Inspector <-> Site translation enabled

Considerations for Utilizing a Video Call Technology Replacing a Physical Presence of Inspectors in a Controlled Way

Videocall technology can replace on-site inspections for discussions and interviewing staff

Similar to on-site inspections, such discussions are not recorded - notes can be taken

There might be the need for multiple videocall transmissions and translation simultaneously

There may be significant issues with privacy, security standards for software / transmission mode used and EHS

EHS: Environmental Health and Safety, e.g., explosive control zones

A secure drop box for document submissions

Industry Considerations on Joint Advantages of Inspections by Supervisory Authority

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

Inspections by a local inspectorate can be more efficient and mature than an inspection by a 3rd country

CONSIDERATIONS ON INSPECTION RELIANCE

We will Monitor if the COVID-19 Pandemic Situation Encourages Inspection Reliance


U.S. FOOD & DRUG

Coronavirus Update: FDA steps to ensure quality of foreign products


Ministry of Food and Drug Safety

Recipient Amgen Korea Ltd., Sung Kyung Noh (20th Floor Ferrum Tower, 19, Teaheran-ro, Gangnam-gu, Seoul, 06141)

Title Notification for Change of Prior GMP Assessment Method

1. Regarding your application for drug approval submitted in 2019, to prevent Corona 19 spread, manufacturing site which is scope of on-site inspection will be assessed by document review. Please refer to in to your business.

2. In addition, according to this change, it could be selected first at the subject of the

Travel is prohibited

- Agencies are forced using alternative approaches

Reliance is implemented

- GMP inspections reliance, *PIC/S guideline, PI 048-1, 1 June 2018*

Call for Action by industry and regulators

- Lessons learned: Was inspection reliance used to assure quality and compliance? If so, how?


The New York Times :trictions and Bans Globally: Updating ...

On March 15, the Kenyan government announced the **suspension** of all travelers ... has **suspended** all flights to Algeria, Belgium, China, France, **Germany**, Italy, the ... Additionally, any **foreign** traveler who has visited high-risk countries in the past 20 ... citizens — must undergo 14 days of quarantine and a health **inspection**.


GOV.UK

Coronavirus (COVID-19): what you need to do

News story

Routine Ofsted inspections suspended in response to coronavirus

Latest measures set out in the Government's coronavirus response


TGA Suspends Overseas GMP Inspections and QMS Audits Until Further Notice

(Posted Mar 19, 2020)

Consistent with the Australian Government's latest travel restrictions, the Therapeutic Goods Administration (TGA) has suspended all **overseas GMP (Good Manufacturing Practice) inspections and QMS (Quality Management System) audits until further notice**.

In addition to our commitment to ensuring that overseas manufacturers meet GMP and QMS requirements, we are also mindful of the need to provide transparent information to sponsors affected by these delays. Sponsors immediately affected by the suspension to GMP inspections have been contacted and, where applicable, advised about maintaining the validity of their existing GMP clearances.

Conclusions and Opportunities for Controlled Regulatory Flexibility

Establishing remote desktop review tools as alternative and complementary reliance concept

- Sharing experience between regulators and discuss opportunities with industry
- Enabling the compliance decision supporting local registration and licencing processes
- Developing a commonly accepted set of documents to be submitted prior to, or as alternative to, an on-site inspection would be beneficial - for example by PIC/S

Facilitating trade through aligned and reasonable regulatory expectations

- GMP/GDP at Marketing Authorisation Holders / affiliates locally
- Proportionate transparency to be provided in the drug shortages prevention

Leveraging inspection reliance as a benefit from PIC/S and MRAs

- Implement recognition of the inspection part of PAIs
- Recognise of inspections in 3rd countries
- Continue the discussion on the extension on the scope of any MRA in this regard

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

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