European Federation of Pharmaceutical Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2016 Data

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Management Summary

EFPIA Inspection Survey 2016 data*

- **Intention**
  - Demonstrate opportunities for mutual reliance, collaboration and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections
  - Show benefits of PIC/S membership in optimising use of inspection resources while maintaining patient safety
- **Scope**
  - Regulatory GMP/GDP inspections & related ISO-certifications for regulatory purpose
  - Manufacturing sites and affiliates
  - Inspections inside and outside the Regulatory Authority's own borders

* Research-based industry

Survey Outcomes 2016

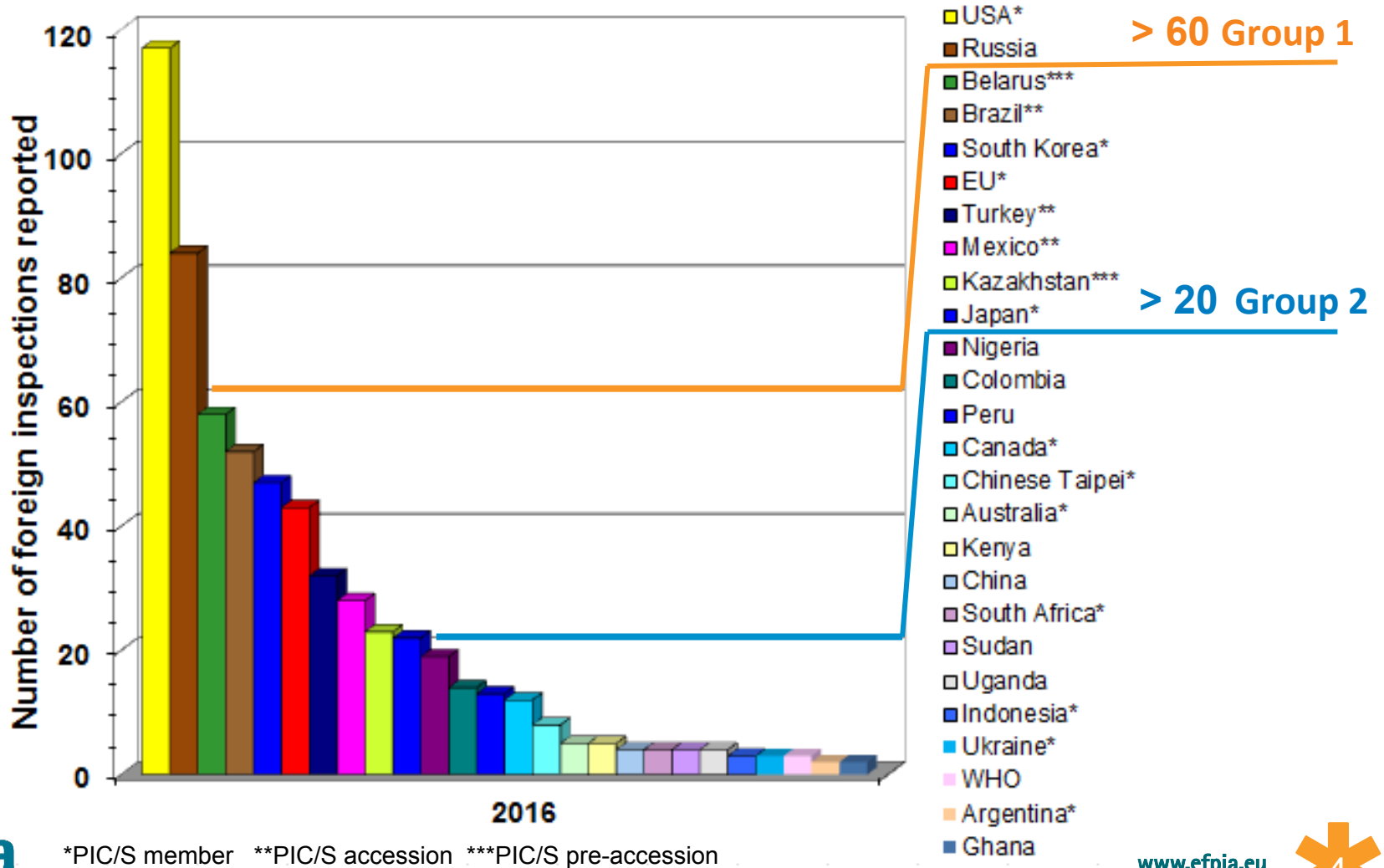
- **Number of foreign inspections* has remained consistent over several years**
  - **Based on data from 23 research-based pharmaceutical companies**
- **Most active inspectorates from 2016 survey**
  - **US, Russia followed by Belarus, Brazil, South Korea, EU**
- **Notable changes**
  - **Increase**
    - **Inspections by Russia, Belarus, Kazakhstan, Nigeria, Peru**
    - **Domestic inspections noted for China**
  - **Decrease**
    - **Foreign inspections by China, EU, Kenya, Uganda**
    - **Inspections of a facility in one PIC/S member state by another PIC/S member (exception - US)**

efpia

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

Number of Foreign Inspections in 2016

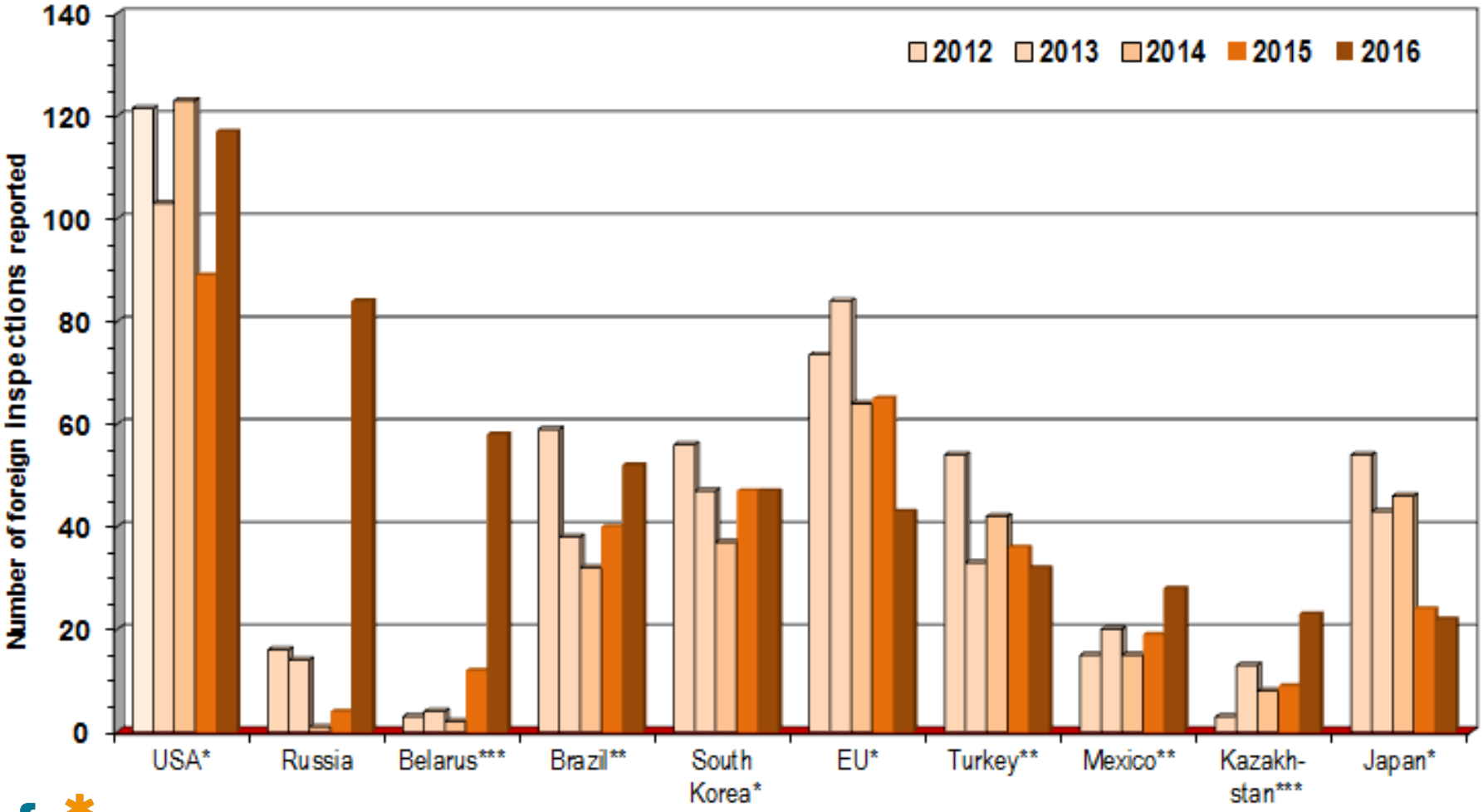
ordered by country (>1 inspections; EU as one entity)



*PIC/S member **PIC/S accession ***PIC/S pre-accession

Number of Inspections by Countries

Performing foreign inspections 2012 - 2016



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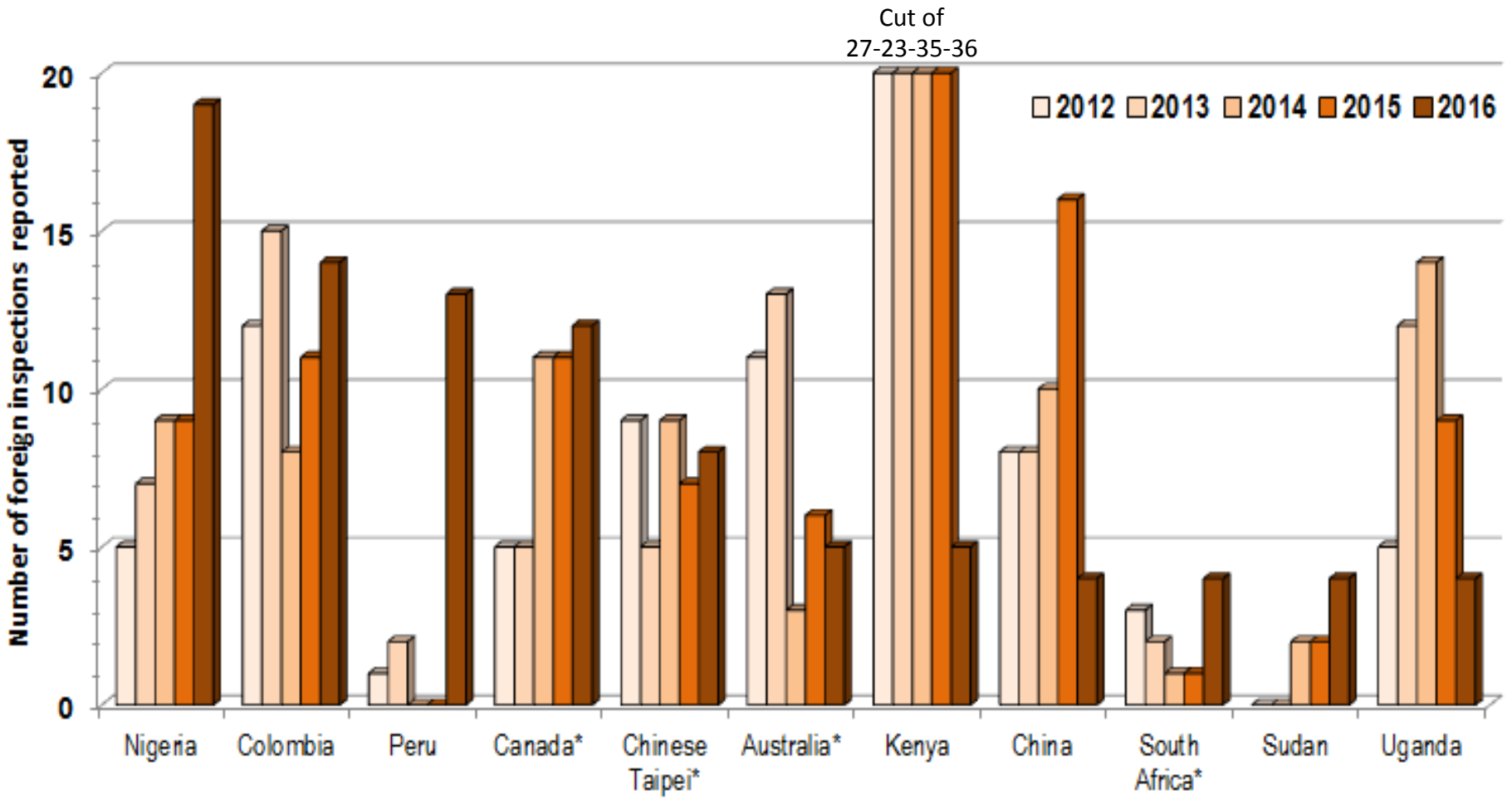

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Foreign Inspections at Manufacturing Sites

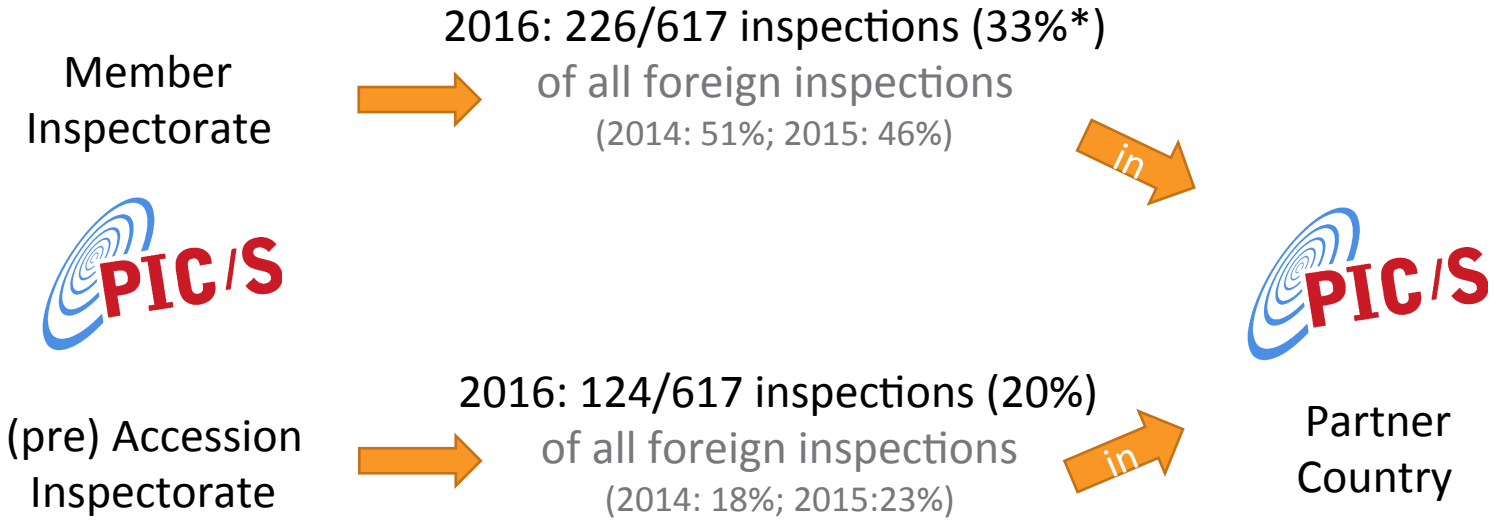
2016 data

- **48 Countries inspecting**
- **99.7% Positive outcomes***
- **33 % Between PIC/S members****

* a) no disruption to product supply or approval of new applications and b) no changes; consistent over the last several years

** Inspectorates from PIC/S members inspecting in territory where the inspectorate is also a PIC/S member

PIC/S Facilitating Cooperation



Assessment of the data

- PIC/S members inspect less in other member inspectorates' territory

* Without US (112 foreign inspection sin PIC/S member inspectorate) the number would be 18%

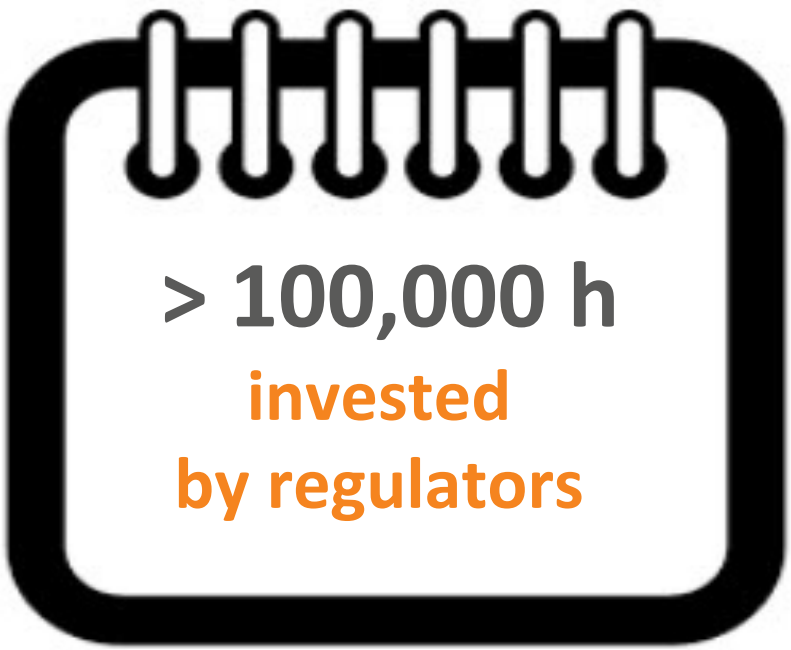
Call for Action to PIC/S members

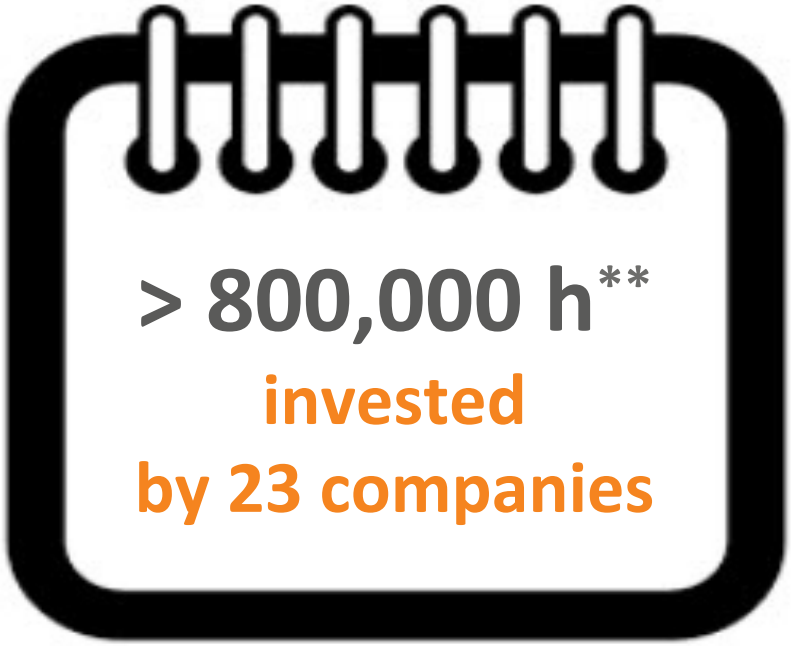
- **PIC/S member inspectorates should continue working towards mutual reliance**
  - **Industry and regulators have not yet fully realised the benefit of mutual reliance on inspections**
  - **Mutual reliance between PIC/S member inspectorates appears to be increasing; however 112 out of 119 inspections by US-FDA were in a PIC/S member country**
- **Industry and inspectorates would benefit from harmonised inspection guidance e.g.**
  - **Classification of inspection observations**
  - **Alignment on documentation requirements prior to an on-site inspection and/ or for a paper based/desk-top inspection**
  - **Incorporating opportunities for mutual reliance on inspections within local statutes**

PIC/S member inspectorates could use comparable inspection processes to facilitate reduction in need for foreign inspections

Assessment of Foreign Inspections

Estimated resources used in 2016*





* Estimation includes preparation + on-site + post-inspection activities

** Manufacturing sites only; domestic and paper based inspections excluded

Estimated Resources Required

per foreign on-site Inspection

Resources	Inspector	Industry
Preparation *for specific requirements by individual inspectorates*	4 person days (experience from industry audits)	90 person days
On site	8 person days (on average 2 inspectors 4 days)	55 person days
Post-inspection	4 person days (experience from industry audits)	15 person days
Sum	16 person days	160 person days
Travel / Fee	+4 person days (2 inspectors 2 days)	Approx. 30'000 EUR

- **Key Points**
  - **Inspected companies need 10 times more resources than regulators for inspection preparation and conduct**
  - **The preparation effort is driven by specific requirements from individual inspectorates**

An Example

A new site submitted applications in several countries

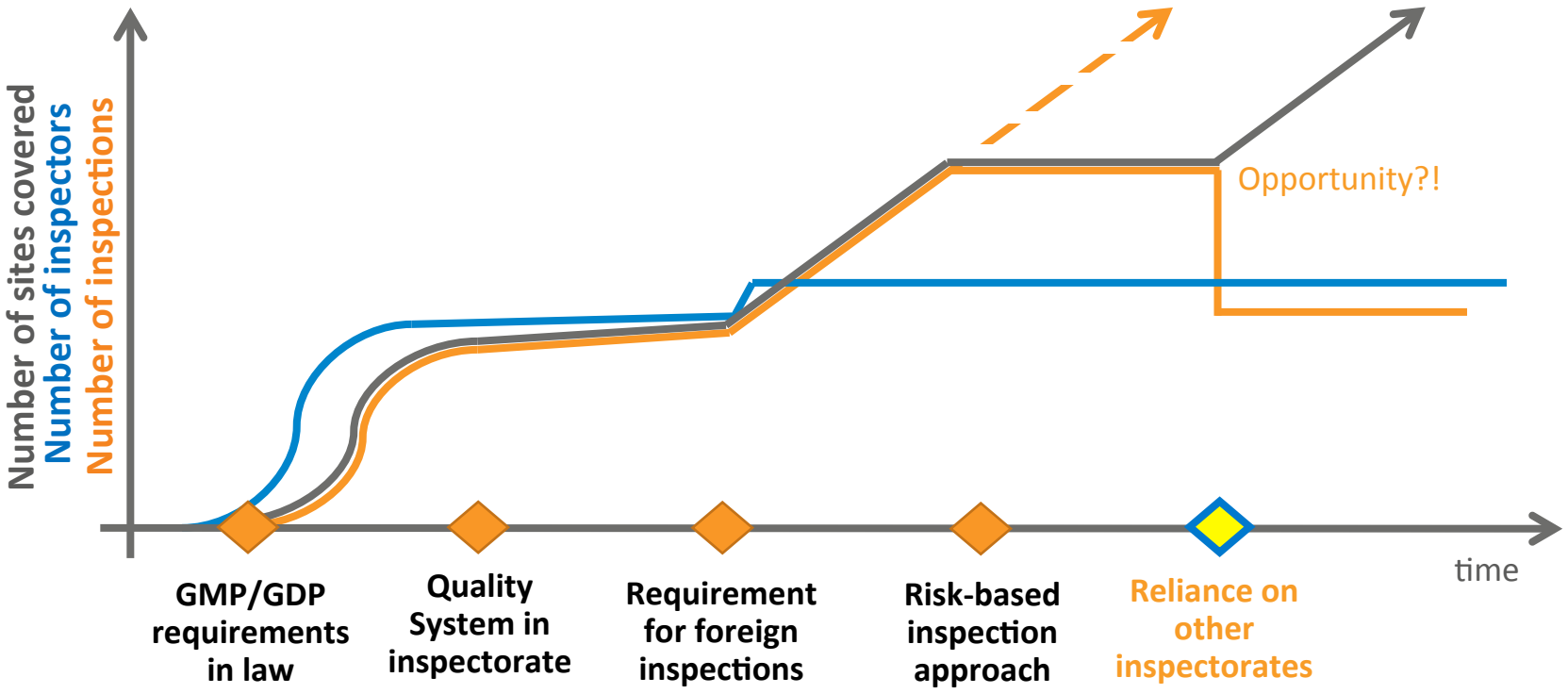
	Domestic Inspectorate	Inspectorate 2	Inspectorate 3	Inspectorate 4
When	August 2016	week 2 2017	week 3 & 4 2017	week 6 2017
Inspectors	2 inspectors 4 days	2 inspectors 3 days*	4 inspectors, 1 reviewer; 10.5 days	2 inspectors 5 days
Inspectors time	64h on site	48h on site	420h on site	80h on site
Resources at site	> 1'930 h	> 1'440 h	> 5'040h	> 2'400h
PIC/S member	yes	yes	yes	yes

Conclusion

- **3 non-value added inspections using lots of inspector and site hours, with outcomes which were effectively the same, that could have been avoided through reliance on the domestic inspection (PIC/S member)**

* Inspectors left a day earlier than scheduled
**about 40+20 experts from the site and SMEs

Prospects for a More Collaborative Approach



Reliance on other inspectorates allows knowledge of more sites with appropriate use of resources

Considerations on Paper(-based) Inspections

- **Opportunities**

  Standardised preparation documentation packages for faster provision of information, better facilitation and use of resources

  - Site related: Site Master File (SMF)
  - Product related: Annual Product / Annual Quality Reviews
  - Quality System related: Quality Manual (reflecting QMS)
  - Additional compliance information: e.g. valid GMP/GDP-certificates for the site; list of inspections, list of internal audits and number of customer / contractor audits, major changes, rejected batches, out of specifications

Based on EFPIA Position Paper, Enhancement of Good Manufacturing and Distribution Practice (GMP/GDP) Inspection Efficiency, May 2014

Standard package of documents should be agreed for both on-site and paper-based inspections

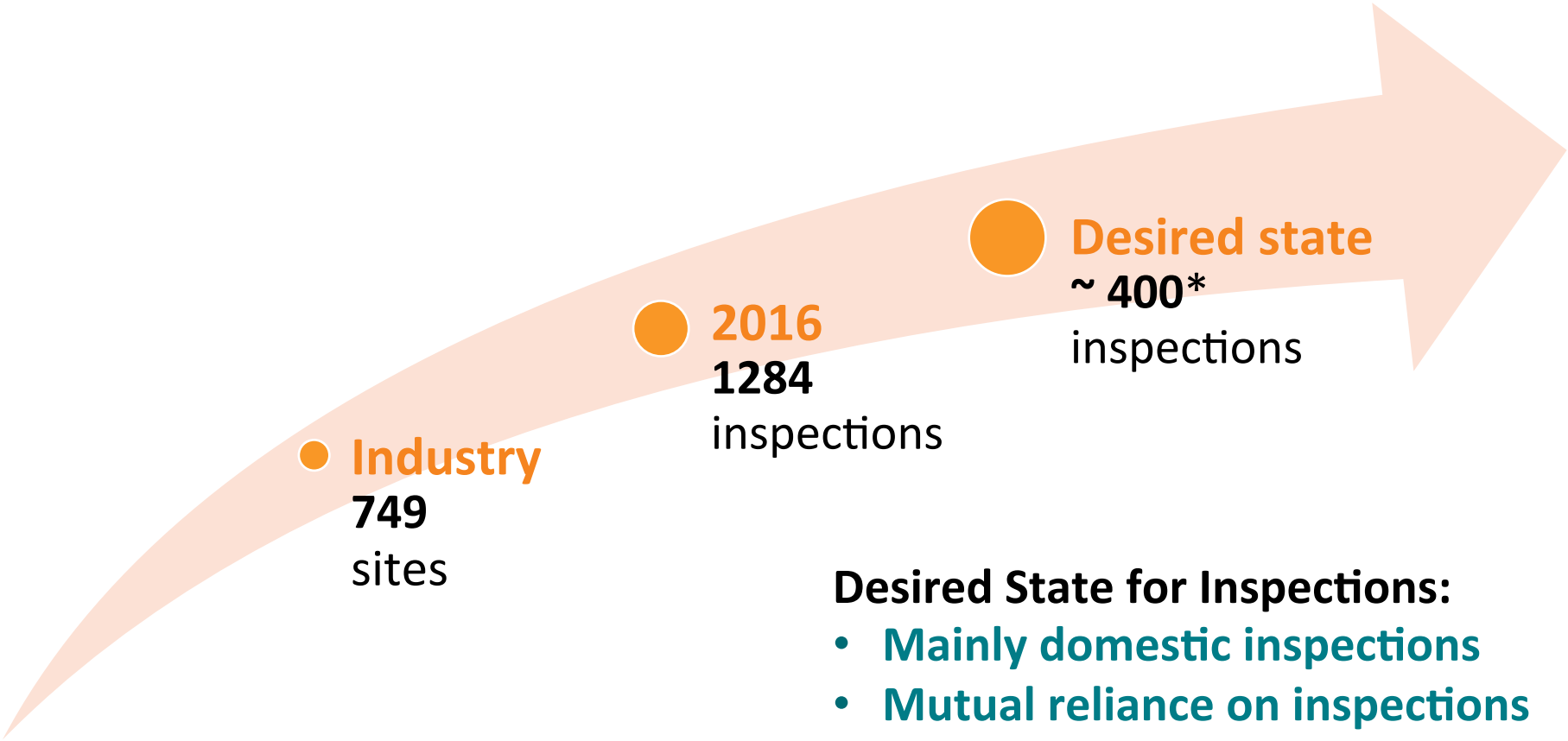
Call for Action to Regulators on Inspections

- **Leverage PIC/S membership to optimise use of inspection resources**
  - Rely on local inspections rather than undertaking foreign inspections
  - In case a foreign inspection is considered, existing schedules by the inspectorate in the 3rd country could be recognised

- **The benefits of MRAs should materialise in future survey data**
  - Adopt Mutual Recognition Agreements (MRAs) where necessary to provide legal basis for mutual reliance on inspections
  - Expand the scope of MRAs to all types of pharmaceutical products and activities (e.g. EU/Japan, EU/US, ASEAN)

- **Utilise the various harmonisation forums and initiatives for faster, more efficient progress**
  - International Coalition of Medicines Regulatory Authorities (ICMRA)
  - International Pharmaceutical Regulators Forum (IPRF)
  - World Health Organization (WHO)
  - Asia Pacific Economic Cooperation (APEC)
  - Training activities e.g. PIA-PIC/S, AHC-APEC, ATC-PMDA, ICH

What is the Desired State for Inspections?



Desired State for Inspections:

- **Mainly domestic inspections**
- **Mutual reliance on inspections**

How can we reach the desired state?

* Based on mainly domestic inspections with average inspection frequency of 2 years for approx. 750 sites

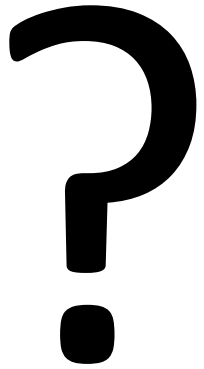
Future for Global GMP/GDPs

- **Principle-based GMPs/GDPs**
  - Innovation is facilitated by adaptable GMPs based on a core set of principles
  - Patient access is enhanced by global alignment of GMP/GDPs
- **Assessment of new products and technologies is interlinked with understanding of GMP requirements and oversight**
- **Regulations, rules and practices should be based on science and incorporate risk-based approaches**
  - This should lead to comparable outcomes from inspections

Inspections

- **Today**
  - General GMP inspections for API and medicinal product
  - GDP inspections
- **Tomorrow**
  - GMP for medicinal products (commercial)
  - GMP for APIs
  - GMP for sterile
  - GMP for ATMPs
  - GMP for IMPs
  - GDP for …

  + Certification of QS for medical device
  + IDMP ISO compliance



Are there different expectations for Good Manufacturing Practice?

Acknowledgement

Contributors to the 2016 Survey

- AbbVie
- Almirall
- Amgen
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- Bayer
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- Biogen
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- Eli Lilly and Company
- Grünenthal GmbH
- GlaxoSmithKline
- Johnson & Johnson
- Merck Serono
- Merck Sharp & Dohme
- Novartis
- NovoNordisk
- Pfizer
- Roche
- Sanofi
- Seqirus
- Servier
- Teva
- UCB

For Further Reading

- **Scientific Papers**
  - S. Rönninger, J. Berberich, V. Davoust, P. Kitz, A. Pfenninger, **Landscape of GMP/GDP inspections in research-based pharmaceutical industry**
    - **Part I: Data,** *Pharm. Tech. Europe*, **January, 2017,** 6-10**.** http://www.pharmtech.com/gmpgdp-inspection-landscape-part-i-data
    - **Part II: Considerations and Opportunities,** *Pharm. Tech. Europe*, **February, 2017,** 5-9**.** http://www.pharmtech.com/gmpgdp-inspections-landscape-part-ii-considerations-and-opportunities
  - A. Meshkovskij, S. Rönninger, **GMP Inspection practice: a case for global benchmarking, convergence and mutual reliance/recognition,** *The GMP News, **2017,*** 2-9 (Rus).
- **Industry Position Papers**
  - **EFPIA: GMP - Inspections of Global Pharmaceutical Supply Chains, May 2009**
  - **EFPIA: Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, 19. May 2014.**
  - **EFPIA / PhRMA: A Concept for Harmonized Reporting of Inspections, 29. May 2015**; ***addendum of the PhRMA White Paper: 'Mutual Recognition of Drug GMP Inspections by U.S. & European Regulators'*, 15. May 2015.** http://www.efpia.eu/uploads/EFPIA_Position_Paper_A_Concept_for_Harmonized_Reporting_of_Inspections_final.pdf
  - **IFPMA: Regulatory Convergence of Good Manufacturing and Distribution Practice and related inspection, 2017, in press**

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