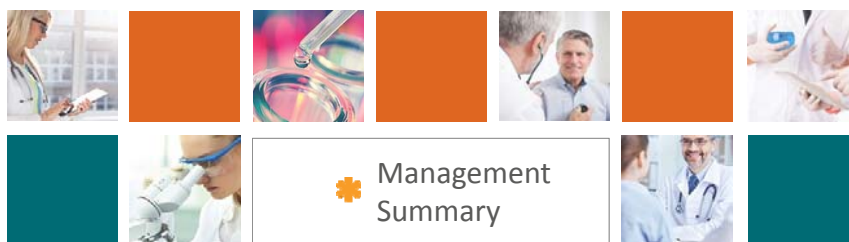




European Federation of Pharmaceutical
Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2017 Data

* Date: 08 / May / 2018 * Public Version



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EFPIA Annual Inspection Survey

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



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Survey Outcomes 2017

- **Most active inspectorates from 2017 survey**
 - Russia, US followed by Turkey, Brazil, EU, Japan, South Korea, Belarus
- **Notable changes**
 - **Increase**
 - Inspections by Russia, Turkey, Japan, Canada, Iraq, Ukraine
 - Inspections by US and Japan in Europe
 - Inspections by (pre-)accession Inspectorate in country of PIC/S members
 - Inspections in affiliates, specifically on GDPs, and desk assessments
 - **Decrease**
 - Foreign inspections by Belarus, South Korea, Kazakhstan, Nigeria, Argentina
 - Companies reported that the EU waived inspections in US
 - **Two joint inspections**
 - Alliance of UK / MHRA - Canada / HC - Australia / TGA
- **Number of foreign inspections* demonstrated an increase**
 - Based on data from 26 research-based pharmaceutical companies
 - One-year event or trend?

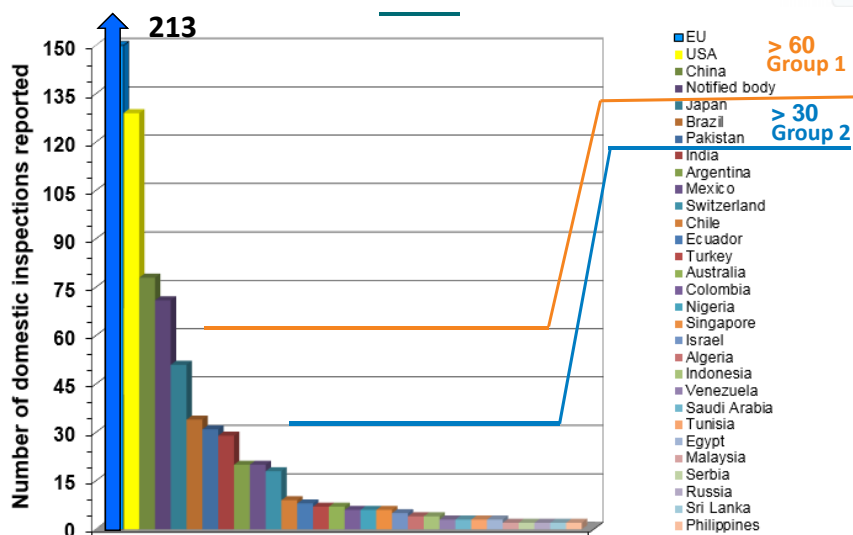


* Foreign inspection: inspection conducted outside of the inspectorate's own country/region
 Domestic inspection: inspections conducted in the inspectorates own country/region

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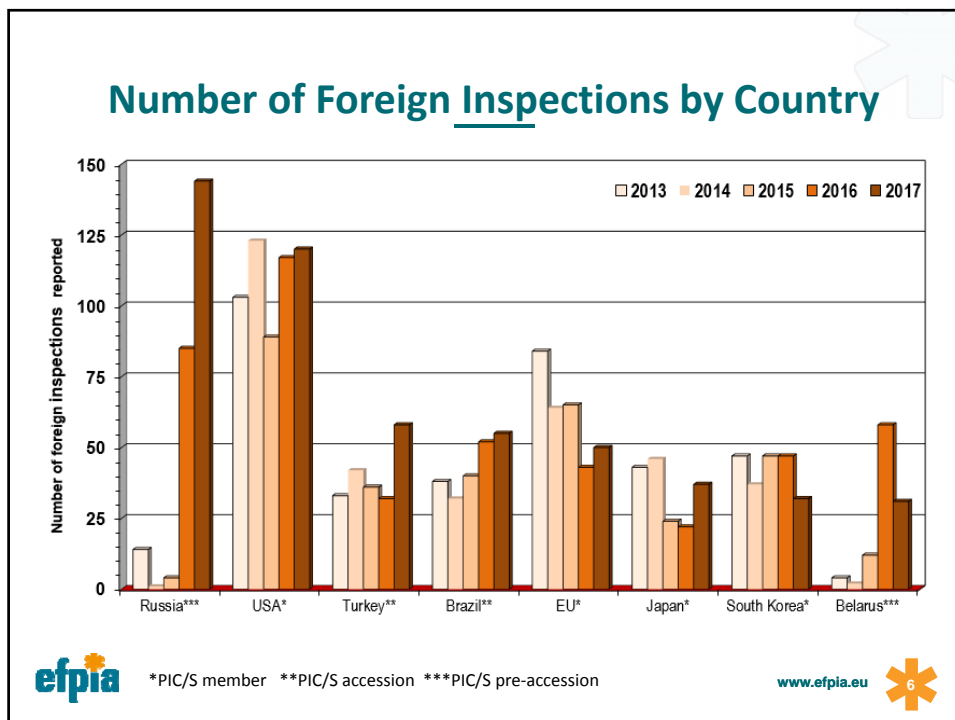
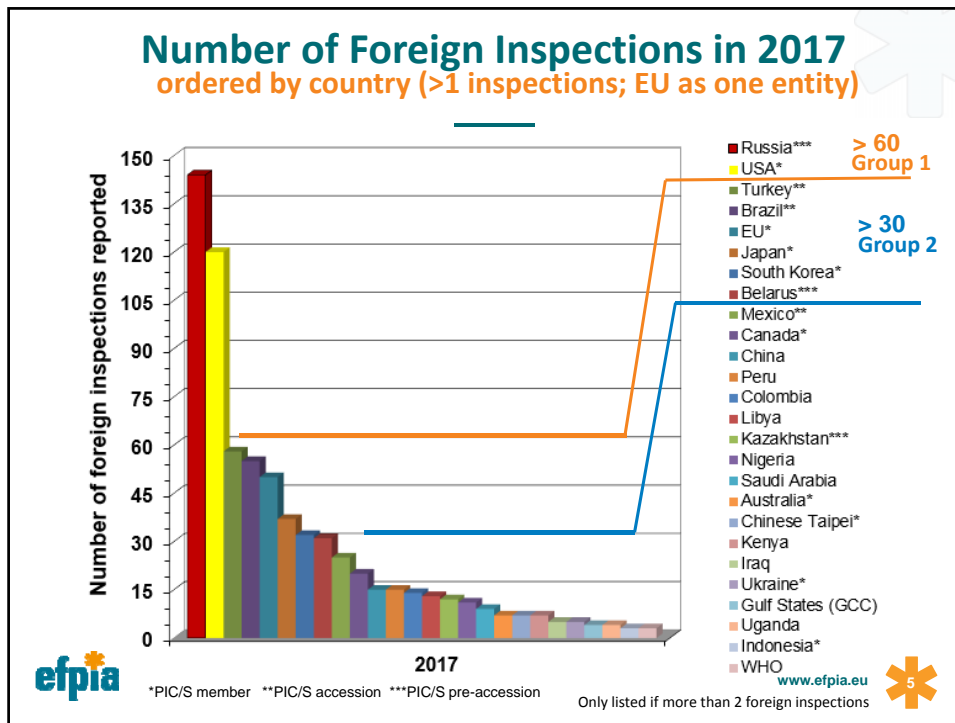
Number of Domestic Inspections in 2017 ordered by country (>1 inspections; EU as one entity)

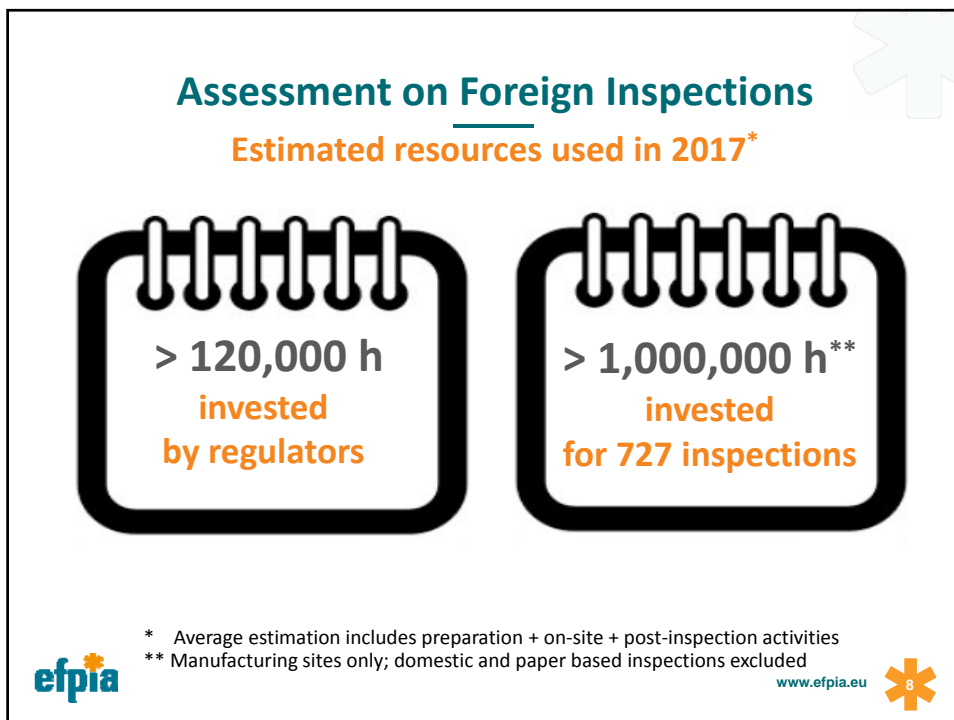
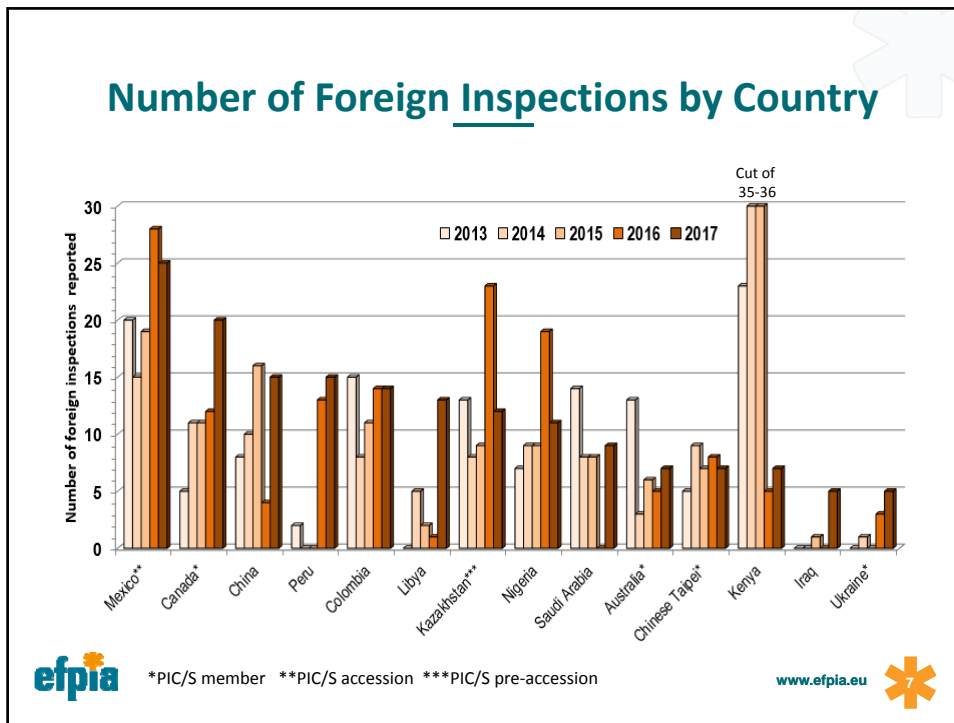


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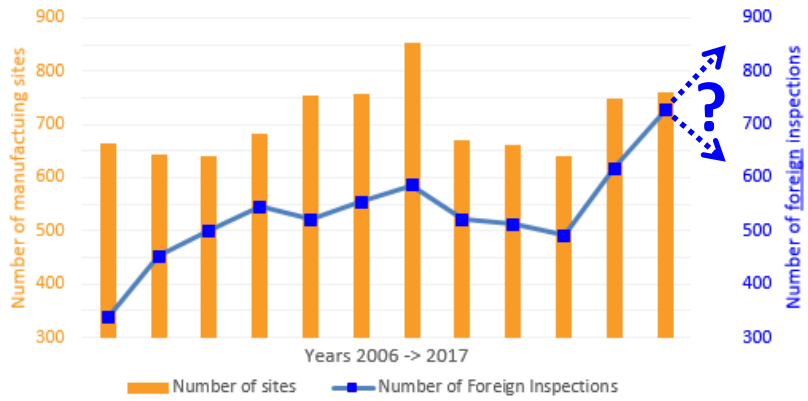


Only listed if more than 2 domestic inspections





Evolution of Number of Foreign Inspections versus Manufacturing Sites



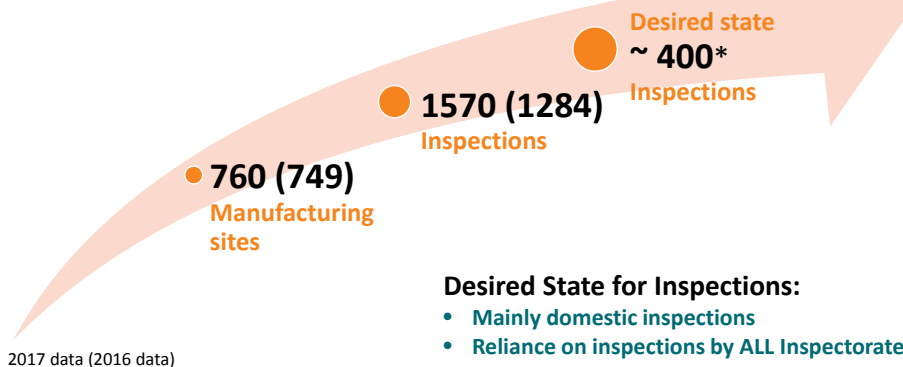
In the last 12 years the numbers of **foreign inspections** doubled while the number of **manufacturing sites** remained relatively constant



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What is the Desired State for Inspections?



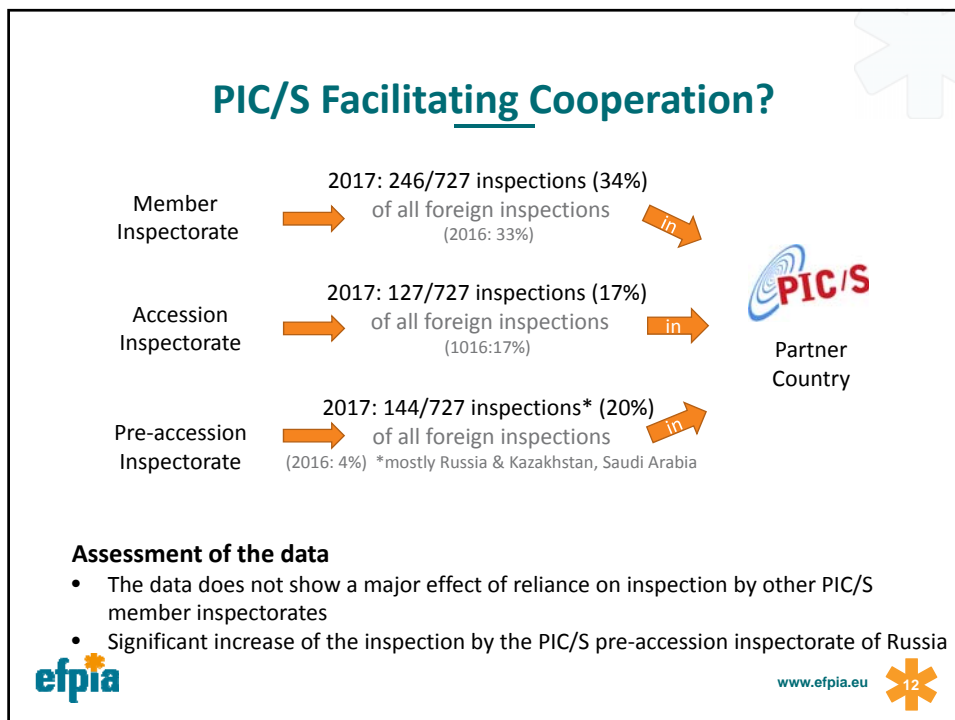
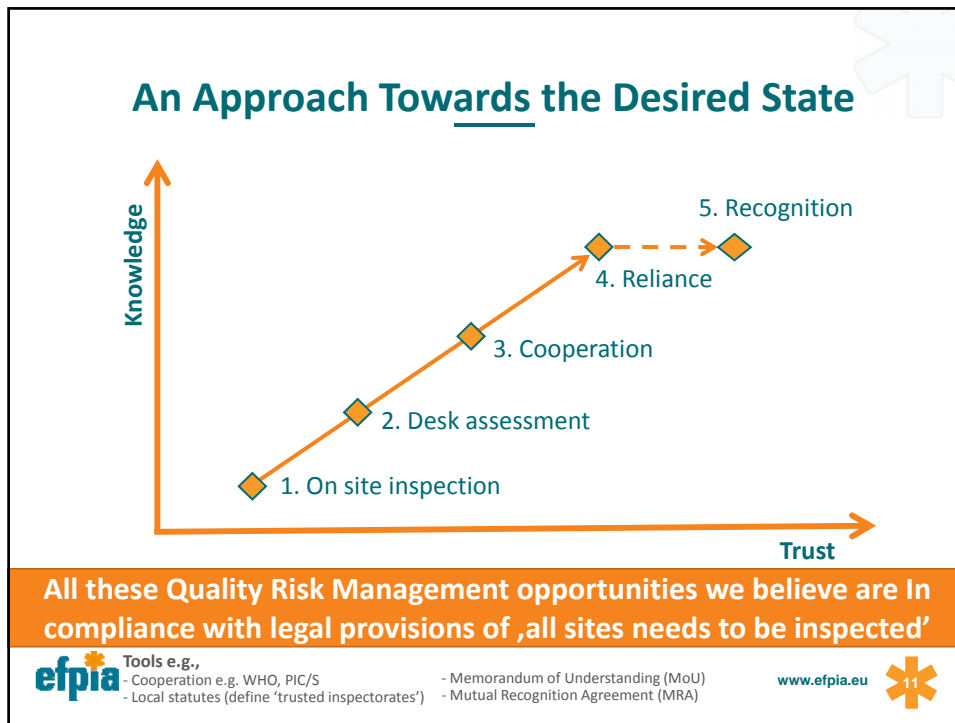
How can we get there?



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

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Significant Resources Required by both Inspectorates and Industry

per foreign on-site Inspection

Resources	Inspector	Industry
Preparation	4 person days (experience from industry audits)	90 person days (due to specific requirements by individual inspectorates)*
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. 350k EUR

- **Points to consider**
 - 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



• The above cost is not all inclusive e.g. contracted interpreters

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*including translations, as applicable



One Real Example

A new site submitted applications in several countries

	Domestic Inspectorate	Foreign Inspectorate 1	Foreign Inspectorate 2	Foreign Inspectorate 3
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 +1h travel	48h on site +80h travel	420h on site +240h travel	80h on site +96h travel
Resources at site**	> 1'930 h	> 1'440 h	> 5'040h	> 2'400h
PIC/S member	yes	yes	yes	yes

Conclusion

- 3 inspections which could have been waived by reliance on the report of the domestic inspection (PIC/S member)



* Inspectors left a day earlier than scheduled

**about 40+20 experts from the site and SMEs, some needs travel arrangements

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Response to PIC/S*

'Regulatory Authorities are concerned about the effective use of their resources and under pressure from Governments to reduce expenses'

- **Why inspections are increasing or decreasing**
 - The data does not tell the reason why the number of inspections are increasing or decreasing
 - Russia is a major factor in the increase of foreign inspections
 - Excluding Russia the number of foreign inspection are comparable
 - The data does not show a major effect of reliance on inspection by other PIC/S member inspectorates
- **Analysis on the reasons which prevent Regulatory Authorities from decreasing the number of inspections**
 - Most responded they are not aware of legal requirements or barriers
 - There is no trend seen as some regulators say they can rely on GMP reports or certificates, others say they cannot

➔ Benefits of reliance not yet realised



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*Discussion EFPIA with the PIC/S, December 2017

Continued Call for Action

- Traditionally reliance on inspection was the norm
- PIC/S member inspectorates should continue working towards reliance
 - Industry and regulators have not yet fully realised the benefit of reliance on inspections
 - Pre-accession inspectorates should focus on domestic inspections rather than significantly being active in foreign inspections
- 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 reliance on inspections within local statutes

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



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Drivers to Increase Complexity

- Are there different expectations for Good Manufacturing Practice?
 - In the past
 - General GMP inspections for API and medicinal product
 - GDP inspections
 - Now
 - GMP for medicinal products (commercial)
 - GMP for APIs
 - GMP for Sterile
 - GMP for Biologics
 - GMP for ATMPs
 - GMP for IMPs
 - GDP for ...
 - + Certification of QS for medical device
 - + IDMP ISO compliance

We see the need for basic GMPs with risk-based principles that all stakeholders understand and follow



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Role of Notified Bodies versus Inspectorates

- Our data is lacking consistency on 'certification'
 - 'GMP-certificate' also marked as 'ISO-certification'
 - Next survey will be modified for clarification
- Interpretation of current data
 - Systematic issues of parallel view from two perspectives in Europe
 - Inspection of a product with a quality system behind and
 - Audit of quality system with a product behind

	Medicinal Product	Medical Device
Terminology	Inspection	(Certification) Audits
Manufacturing standards	GMP guidelines	ISO standards
Enforcement	By inspectorates	By a for-profit Notified Body
Registration	Marketing Authorization	Registration & CE mark
Agencies	EMA & member states	Heads of Medicinal Agencies (HMA)
European Commission	D.G. SANTE	D.G. GROWTH



- Inspectorates - also in EU - not relying on certificates issued by Notified Bodies (re-verification of ISO 13485 compliance) www.efpia.eu



Message on Future for Global GMP/GDPs

- Regulations, rules and practices should be based on science principles and incorporate risk-based approaches
- Assessment on new products and technologies is interlinked with understanding of GMP requirements and oversight
- Expected outcomes
 - Innovation would be facilitated by adaptable GMPs based on a core set of risk-based principles
 - Resource-efficient
 - Time to Market and patient access would be accelerated by globally aligned GMP/GDPs principles



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Concluding Message

Optimise the effectiveness of inspectional oversight of GMDP operations by

1. Focusing resources on domestic inspections
2. Leveraging the opportunities in the application of existing local regulations, guidelines and initiatives that recognize equivalent GMDP frameworks, including MRAs
3. Promoting international development, implementation and maintenance of harmonised GMP standards and quality systems of Inspectorates in the field of medicinal products
4. Deploying a common inspection practice using risk- and science-based methodology
5. Encouraging co-operation and reliance between inspectorates by actively participating in existing harmonisation forums



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'Authorities should give first priority to ensuring that manufacturers on their own territory are compliant through adequate local oversight'

'Foreign inspections should only be conducted if absolutely necessary'

David Cockburn (EMA), on Good Regulator Practices, APEC 2015



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 - IFPMA Infographic: https://www.ifpma.org/wp-content/uploads/2018/02/GMP_IFPMA_02-20-2018-WEB.pdf



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



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