LES DEFIS DU SYSTEME EUROPEEN AU SUJET DE L'EVALUATION ET SUPERVISION DES MEDICAMENTS

OS DESAFIOS DO SISTEMA EUROPEU NA AVALIAÇÃO E SUPERVISÃO DOS MEDICAMENTOS

THE CHALLENGES OF THE EUROPEAN SYSTEM FOR THE EVALUATION AND SUPERVISION OF MEDICINES

Reunião em Lisboa

16 fevereiro 2018

Ordem dos Farmacêuticos

Georges FRANCE, Académie Nationale de Pharmacie

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to any organization with which the presenter is employed or affiliated.

Tkx to Anders Vinther, Ph.D.
Chief Quality Officer
Sanofi Pasteur
PDA Workshop 2017

Future of the European Model ?
An interesting time

- Global Environment major changes
  - Politico-Economy / Supply chain / Regulatory environment
- 2 opposite trends
  - Globalization versus Protectionism & Turning inward
- Challenges
  - Regulatory convergence or Regulatory fragmentation
  - Science knowledge: Constrain or Booster
  - More regulations or better regulations
- Examples
  - Challenges of Post Approval changes
  - Multiplication of Foreign inspections

*Added value for **patient ?***

Global Political/Economical trends

World Health Organization

SIXTY-NINTH WORLD HEALTH ASSEMBLY
Agenda item 16.4

A69/8/CONF./3
25 May 2016

WHA69.25
28 May 2016

Addressing the global shortage of medicines and vaccines

The Sixty-ninth World Health Assembly,

Having considered the report on addressing the global shortages of medicines, and the safety and accessibility of children's medication;[1]

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http://apps.who.int/medicinedocs/documents/s22423en/s22423en.pdf

Lower Drug Prices: New Proposals Carry Lots of Promises

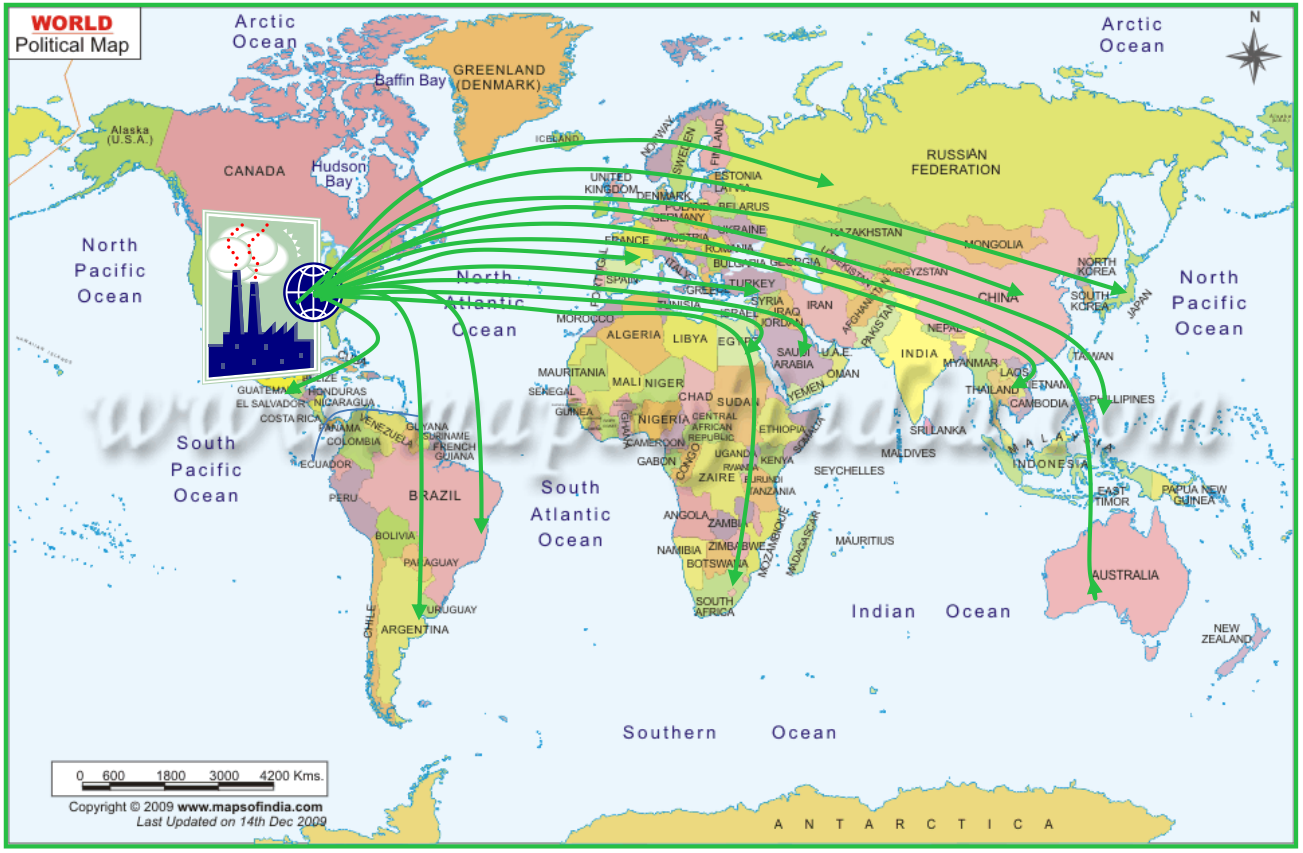
The New York Times

The White House is considering a plan to lower out-of-pocket costs for people in Medicare drug plans, who often pay inflated prices for their drugs.

By KATIE THOMAS and REED ABELSONFEB. 9, 2018

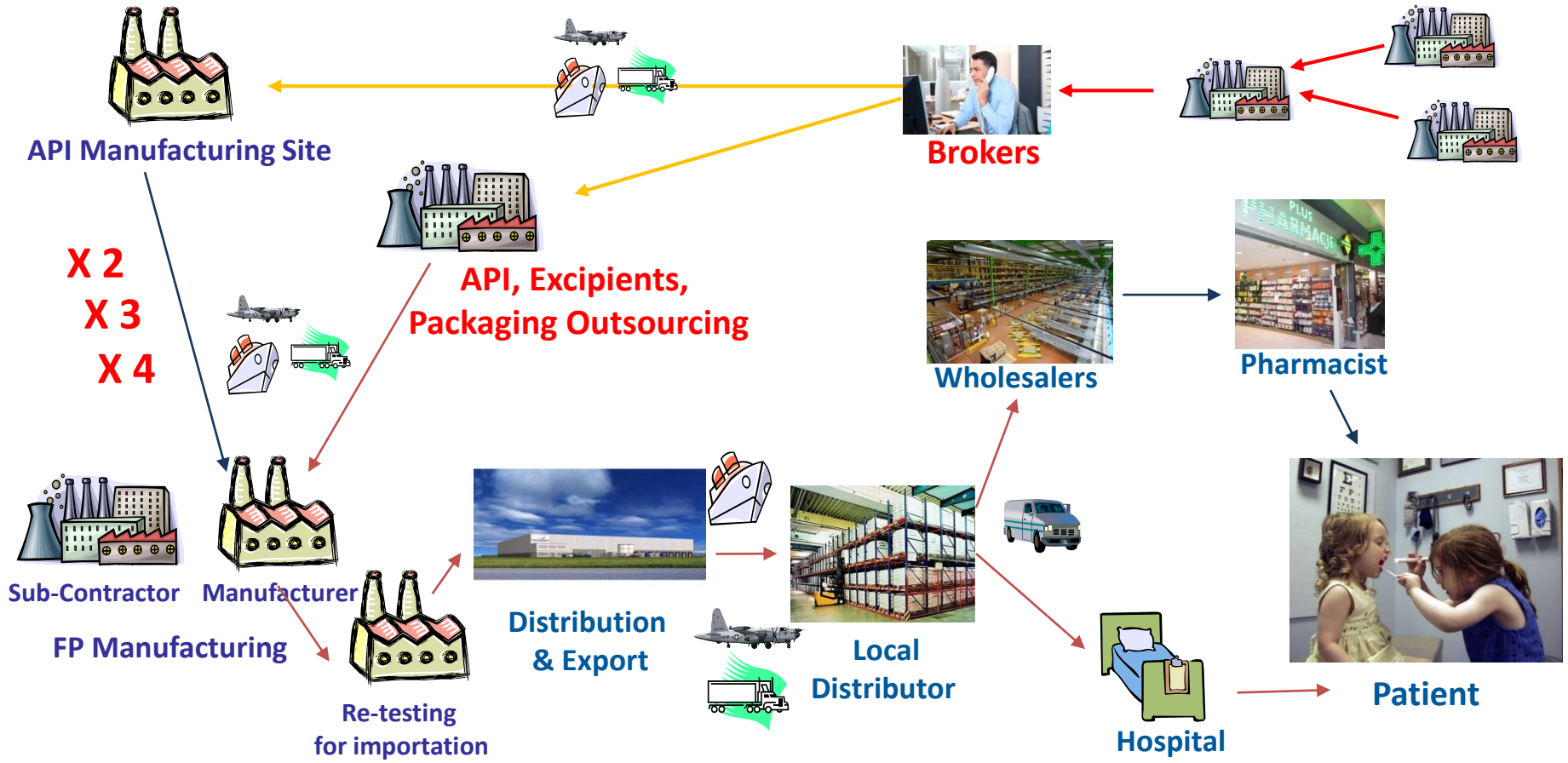
Major changes in the Supply Chain

Major changes in the Supply Chain Concentration on one side



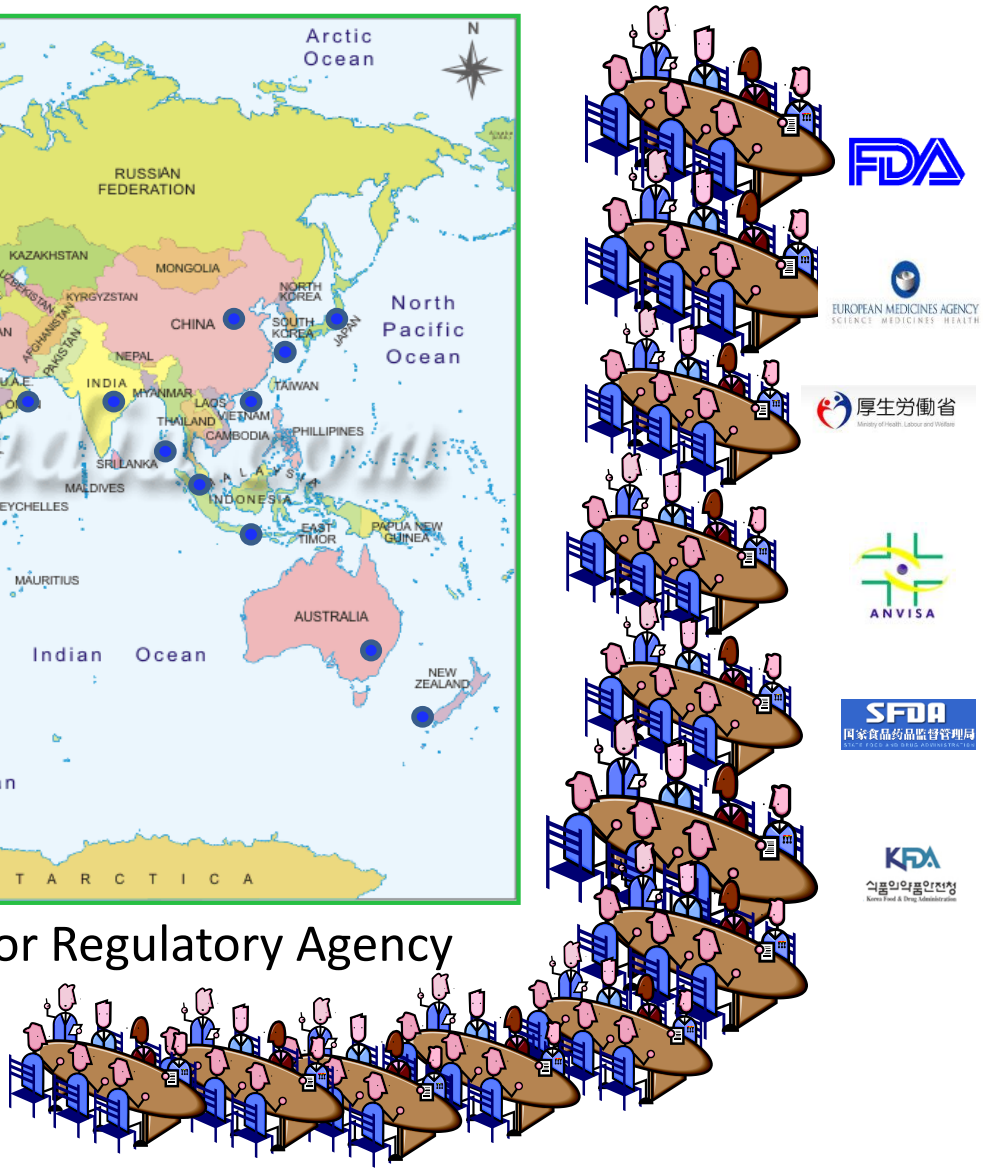
Manufacturing site with Regional/Global coverage

Fragmentation and Complexity on the other side



Historical Traditional Supply Chain moving to a pretty more complex model upstream and downstream

Major changes in the Regulatory Environment



Regulatory Environment : Emerging Major Regulatory Agency

Reference Standard are essential and the backbone of quality international organisation

However

Drug tested against USP

Same drug tested against European Pharmacopeia/BP/...

Multiple standards: *Added value for **patient ?***

Brexit: Adding a layer to the complexity

- Unclear Scenario
  - Timing / Scope
  - Worst case considered, not realistic, multiple options
- Certification vs Retesting processes
- Multiple Regulatory Changes (Artwork and Labelling, etc.)

- More complexity
- Non value added changes and cost
- Shortages

*Added value for **patient ?***

Benchmarking with another Global industry

We are expecting maintenance tests to be similar and the same Standard to be used in these Airports and all others,

aren't we ?

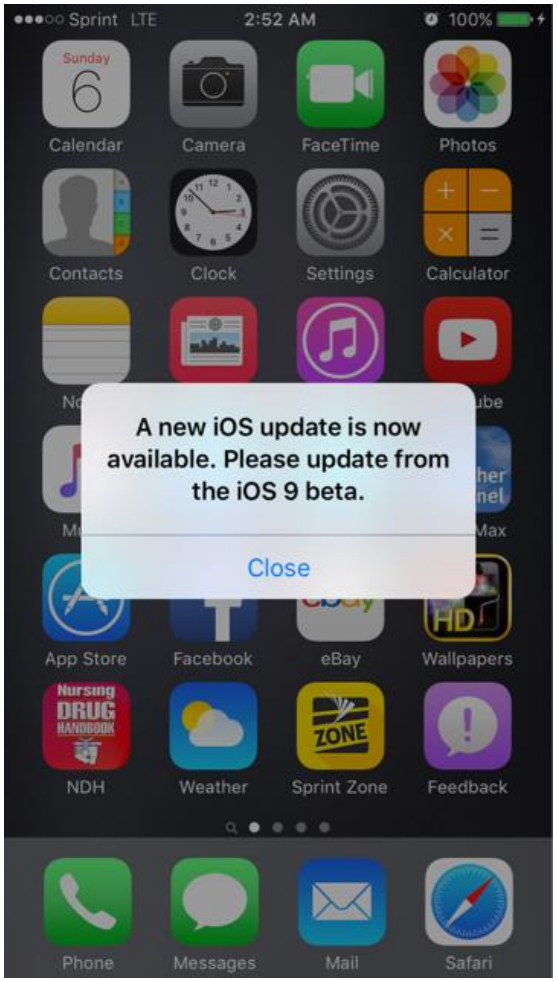
Pharmaceutical: Room for improvement Benchmarking

- With other industry sectors
  - Continuous manufacturing
  - Real Time Release Testing (RTRt)
  - Process Analytical Technology (PAT)
  - Design Space

➢ an “old story” in food & chemical

- Sub-optimal asset utilisation

- Cycle times



However some challenges to “upgrade” our industry

Post Approval changes

- Variation for “upgrading”
  - ➢Timing: From “do and tell” to 1,2 to 5 years depending of local regulatory requirement.
    - ➢Over Stock, multiple specifications
    - ➢Risk of **non compliance** and **shortage**

*Added value for **patient** ?*

- Regulatory framework to support
  - **QbD** (ICH Q8,9 & 10): Challenge where accepted (Dossiers with and without)
  - **LCM & PAC** (ICH Q12)

Transformational Guidelines or ... ?

ICH Q10 w Q9 & Q8 ➡ Benefit ?

Annex 1

"Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles"

"Opportunity to optimize science- and risk-based post approval change processes to maximize benefits from innovation and continual improvement"

ICH Q10 June 2008

The Right Quality Culture

Change Management	CAPA	Internal Audit
• Fully integrated Q9 principles, clear risk based PAC plans • Alignment of risk assessments between company and regulators	• Integrate knowledge from deviations, trends and complaint/recall incidents in risk based PAC plans • Monitor PAC effectiveness	• Assess effectiveness of risk based decision making for PAC management
Process Performance & Product Quality Monitoring	**Outsourcing**	**Management Review**
• Early and proactive detection of control drifts, variability, trends, adverse events/complaints • Drive continuous improvement	• PQS effectiveness should be assessed for each CMO/Supplier • Clear agreement between CMO/Supplier and MAH for PAC notification and management	• Risk based decision making on product, process and quality system performance metrics

Integrated Quality Risk Management & Knowledge Management

PtC PQS, www.pda.org/pac

8

Concept or Reality ?

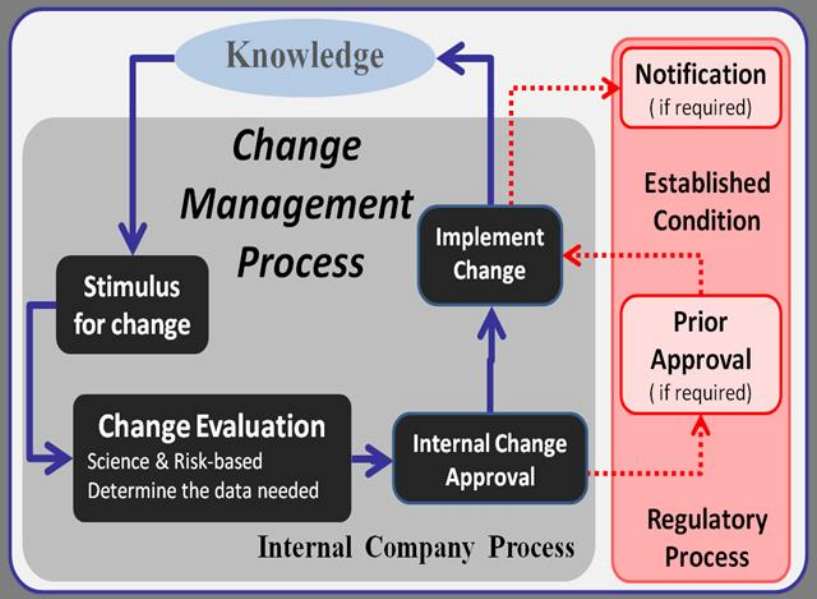
Q12 : Product Life Cycle Management

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation

QTPP (Quality Target Product Profile) Defined
CQA (Critical Quality Attribute) Identified
CPP (Critical Process Parameters) Determined
KPP (Key Process Parameters) Determined
CS (Control Strategy)

Changes

Enablers



Efficient PQS

Tools

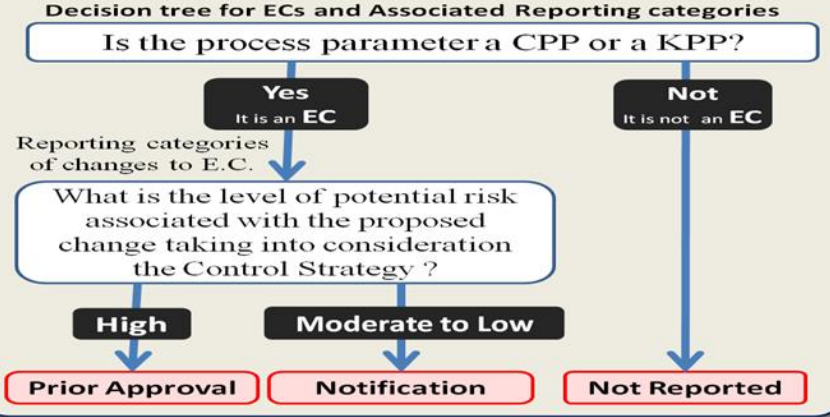
Elements of PLCM documents

- Summary of Control Strategy (CSs)
- Product Established Conditions (ECs)
- Reporting categories Associated to ECs
- PACMPs
- Post-approval CMC Commitments

- Product Established Conditions (ECs)
- Reporting categories Associated to ECs
- Post-Approval Change Management Protocols
- Analytical Processes for existing product

Manufacturing Process Parameters

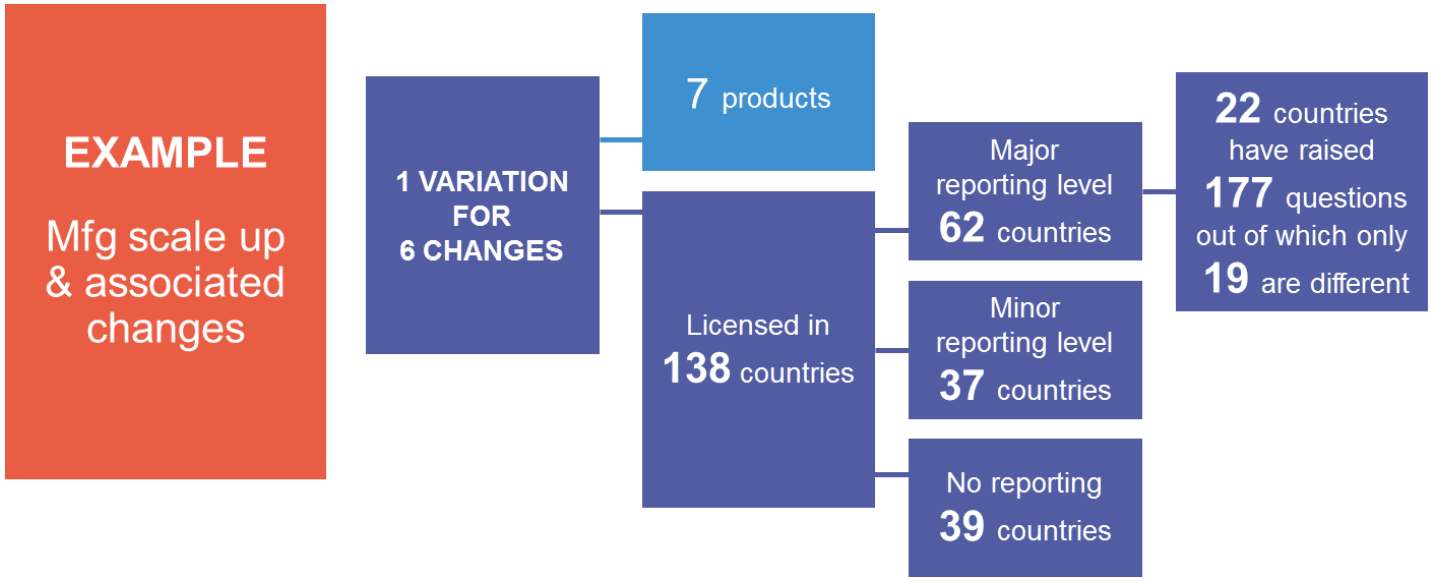
Decision tree for ECs and Associated Reporting categories



Regulatory Framework: Categorization of changes

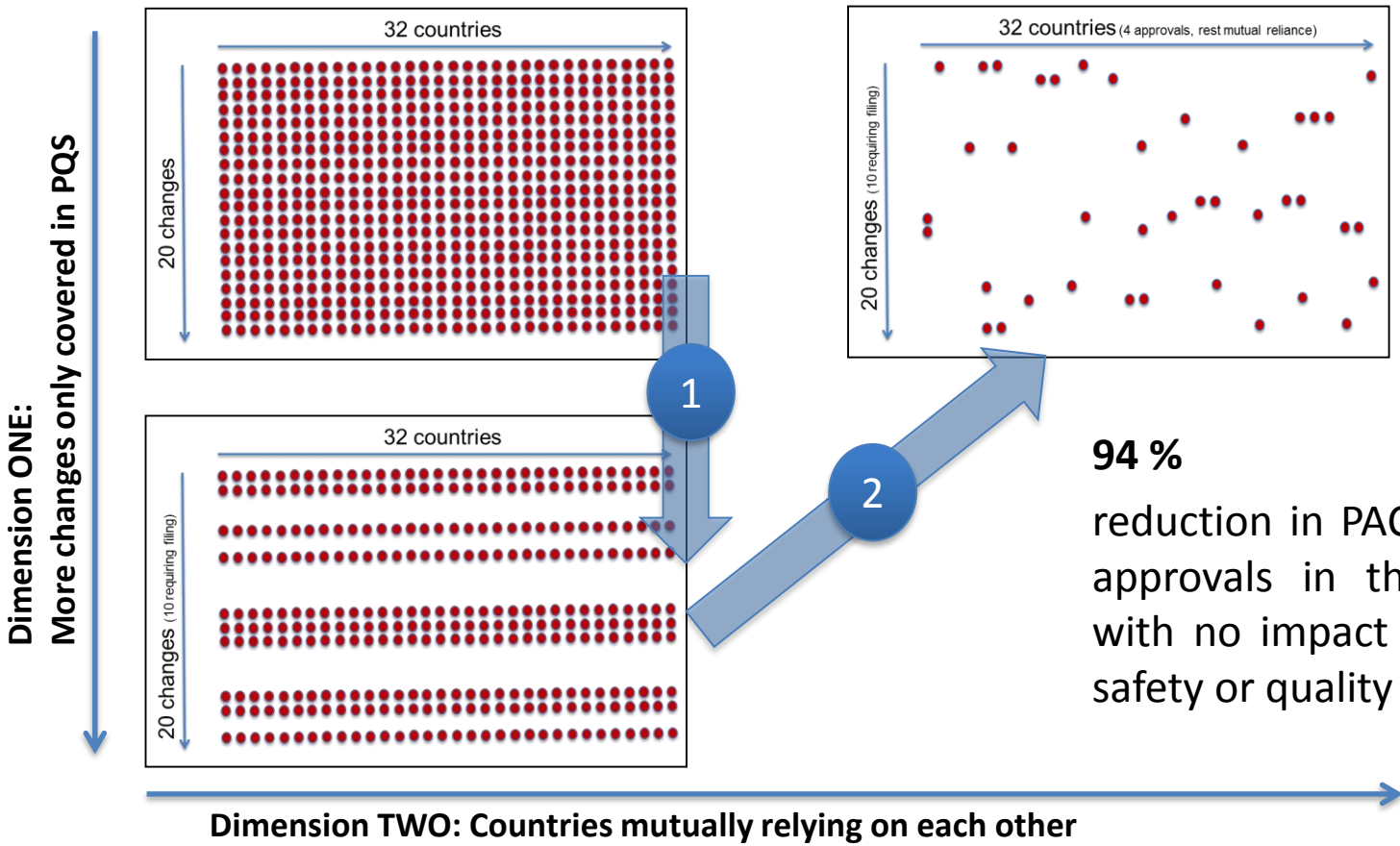
Challenges after The Finish Line – How Can We keep a Product in Supply after Its Initial Approval?

Anders Vinther



Real life example: One change assessed by 99 different countries individually according to different requirements and timelines

*Added value for **patient ?***



94 %

reduction in PAC regulatory approvals in this example with no impact on product safety or quality

Post Approval changes

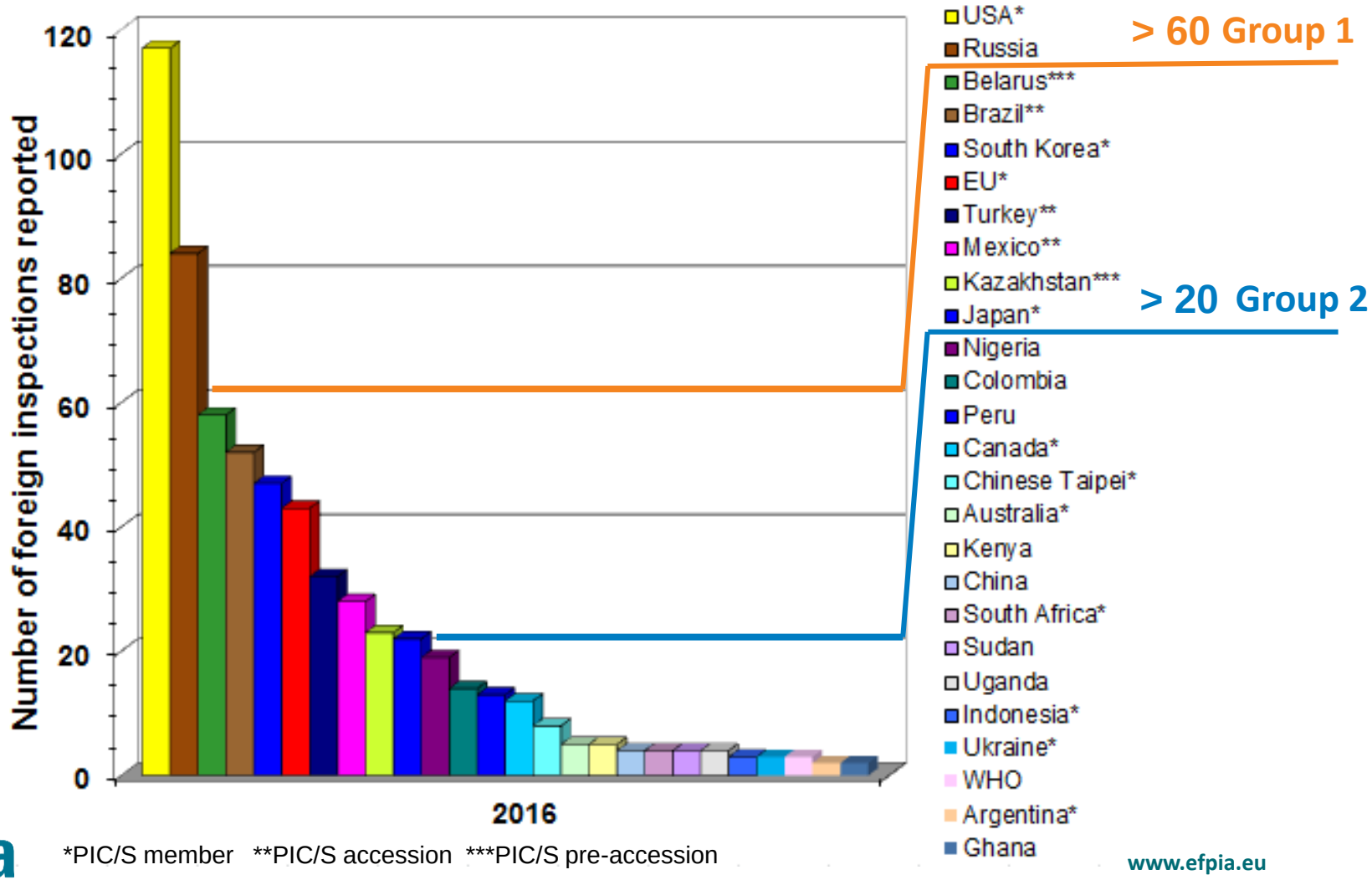
- How to secure
  - Very Robust **Change Control** process
  - Comprehensive and Robust **Pharmaceutical Quality System (PQS)**
  - **Third Party Quality management**
  - **Visibility to HA**
    - (Marketing Authorization Holder MAH / Manufacturing site)

To achieve an Efficient Life Cycle Management

Multiplication of foreign inspections

Foreign Inspections in 2016

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



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

www.efpia.eu

Multiplication of foreign inspections

Potential barriers

- Local legal requirement
  - foreign inspection to legally protect public health (Country level)
- IP challenges
  - Lack of, or uncertain, arrangements for the protection of confidential commercial and trade secret information between authorities
- Mutual acceptance processes
  - GMP-certificates are not accepted if issued by other inspectorates
  - Insufficient Mutual Recognition Agreements (MRA) between national/regional authorities

*Added value for **patient ?***

Global Regulatory Convergence
A real value for the patients

- Increase transparency internally and externally
- Facilitate quality oversight
  - *Focus on weakness (QRM approach)*
- Decrease regulatory complexity
  - *Facilitate mutual acceptance*
  - *Avoid duplication of resources*
  - *Facilitate QRM approach for industry and for regulator/inspector and lead to better targeted use of resources*
- Indirectly facilitate visibility of substandard
- Facilitate the management of complex supply chain

Future of the European Model ?
Next steps

- How to keep focus on the essential with a good balance
  - Patient first
  - Continuous improvement based on Innovation, Science and Technology

- Options to consider
  - **Convergence** and **Mutual Recognition** until **Harmonization**
  - **Continuous improvement** (based on Innovation, Science and Technology)
    - Facilitate access to “better than …”
  - Regulation based on **Robust Risk Assessment**
  - Reconnect the **MA Holders** (country based) to **Manufacturing Sites**
  - Better Regulation versus More Regulation

"The Real Difficulty
in changing the course of any enterprise
lies not in developing new ideas,
but in escaping old ones"

John Maynard Keynes

From Hurdle Race

Innovation

To Fast Track

BACK UP SLIDES

- **Challenges after The Finish Line – How Can We keep a Product in Supply after Its Initial Approval?**

  Anders Vinther Chief Quality Officer Sanofi Pasteur

  2017 PDA Annual Meeting

EFPIA: Annual Regulatory GMP/GDP Inspection Survey 2016 Data

- Thanks to Stephen Roenninger

Challenges after The Finish Line – How Can We keep a Product in Supply after Its Initial Approval?

Anders Vinther

Chief Quality Officer

Sanofi Pasteur

Vaccines

- 2-3 million lives saved every year by immunization with vaccines[1]
- Vaccination saves 44 $ for every $ spent[2]
- In 2015 1 in 5 children didn't receive life saving vaccines[3]

% morbidity decrease in the US for vaccine preventable diseases

- Polio 99 %
- Hib 99 %
- Measles 99 %
- Mumps 99 %
- Pertussis 93 %
- Rubella 99 %
- Smallpox 100 %

(1) http://www.who.int/mediacentre/factsheets/fs378/en/
(2) Johns Hopkins Bloomberg School of Public Health; 2016
(3) WHO - Immunization highlights: 2015

Adapted from Farrant L. Vaccine infographic 2012. Available from: https://www.behance.net/gallery/2878481/Vaccine-Infographic

Focus on getting new medicines to market

- Many successful programs in place aiming at getting new medicines to the finish line (approval) faster with expedited regulatory reviews
- Good progress made on harmonized initial regulatory filing with Common Technical Document (CTD)

But what does it look like after the finish line?

Keeping the medicines in supply is a challenge

- Regulatory requirements for Post Approval Changes (PACs) differ from country to country
- These differences
  - are costly and a threat to innovation and medicines availability
  - have no scientific rationale
  - Makes supply logistics very challenging

Keeping medicines in supply is like a 'hurdle race'

Managing change is a necessity post first approval of the product

- Product & process knowledge grows
- New technologies emerge
- Industry practices change
- Regulatory requirements evolve
- Supply chain and suppliers change
- Safety knowledge increases

Managing change is a regulatory expectation

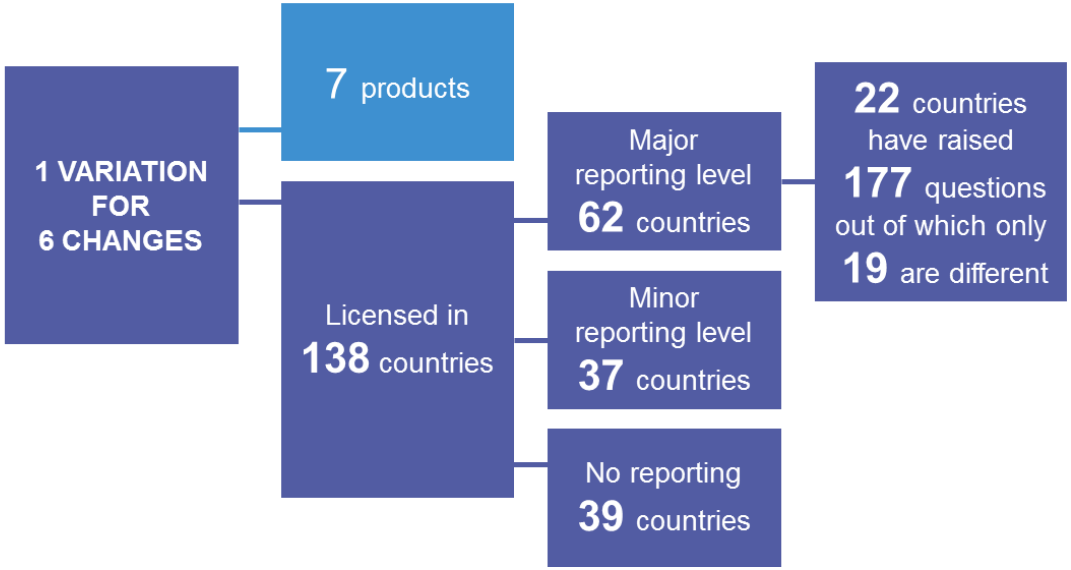
"Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of product and process knowledge"

(EU GMPs, Part I, Chapter 1)

PACs is a natural and important part of the product lifecycle

EXAMPLE

Mfg scale up & associated changes



Real life example: one change assessed by 99 different countries individually according to different requirements and timelines

- Each time we travel, we entrust the technicians who check that our airplane is safe to fly
- Imagine each passenger wanting to check safety according to his/her checklist before plane could take off

Imagine applying the same approach to boarding a plane - would we ever take off ?!

- ***Medicines shortages is a global problem*** that is handled at national level – which will not solve the problem globally
- Medicines shortages is a 'wicked problem' – highly resistant to solutions

World Health Organization

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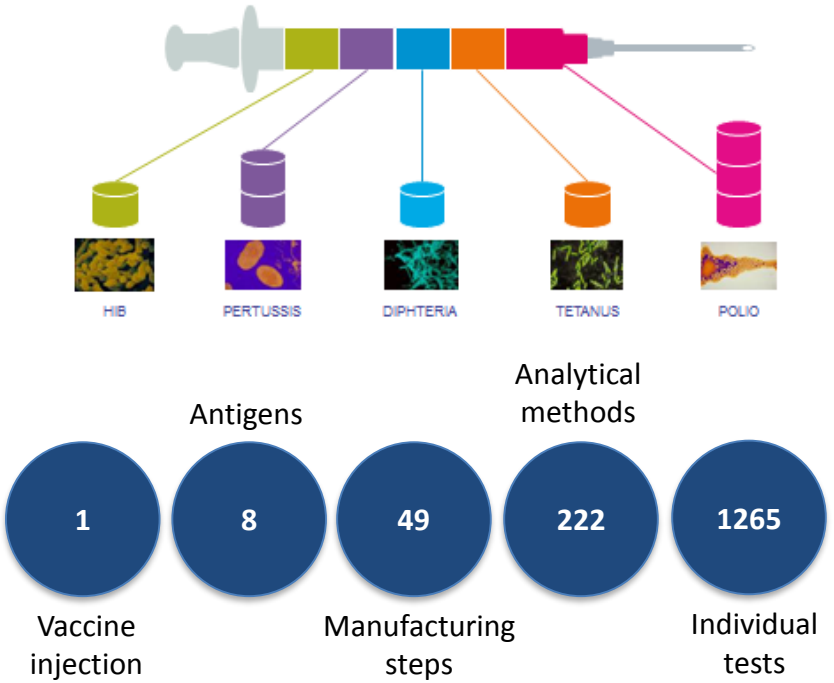
DIRECTOR-GENERAL

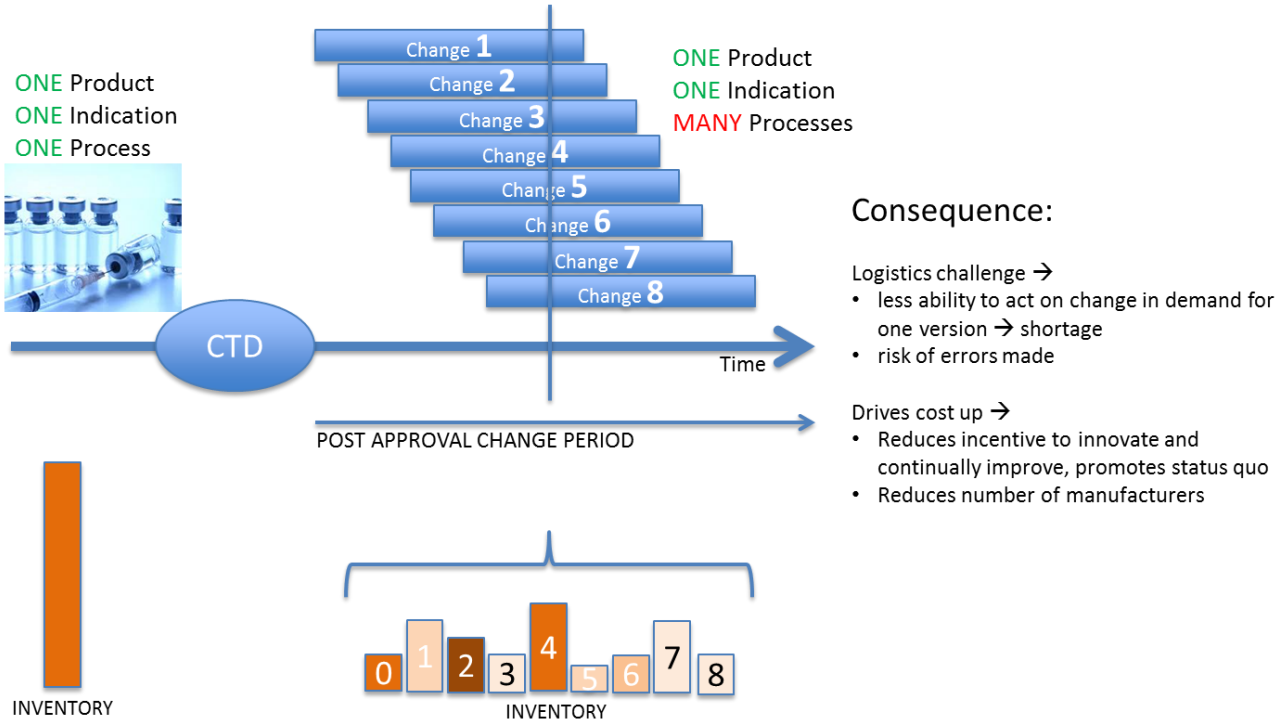
http://apps.who.int/medicinedocs/documents/s22423en/s22423en.pdf

Medicines shortage is a global problem that requires a global solution

Specificities about vaccine manufacture

- Biologics manufacturing
- Often more than one antigen (drug substance) formulated into one vaccine (drug product)
- 2 years total time from start to finish for each batch (70 % of the time used for QC testing)



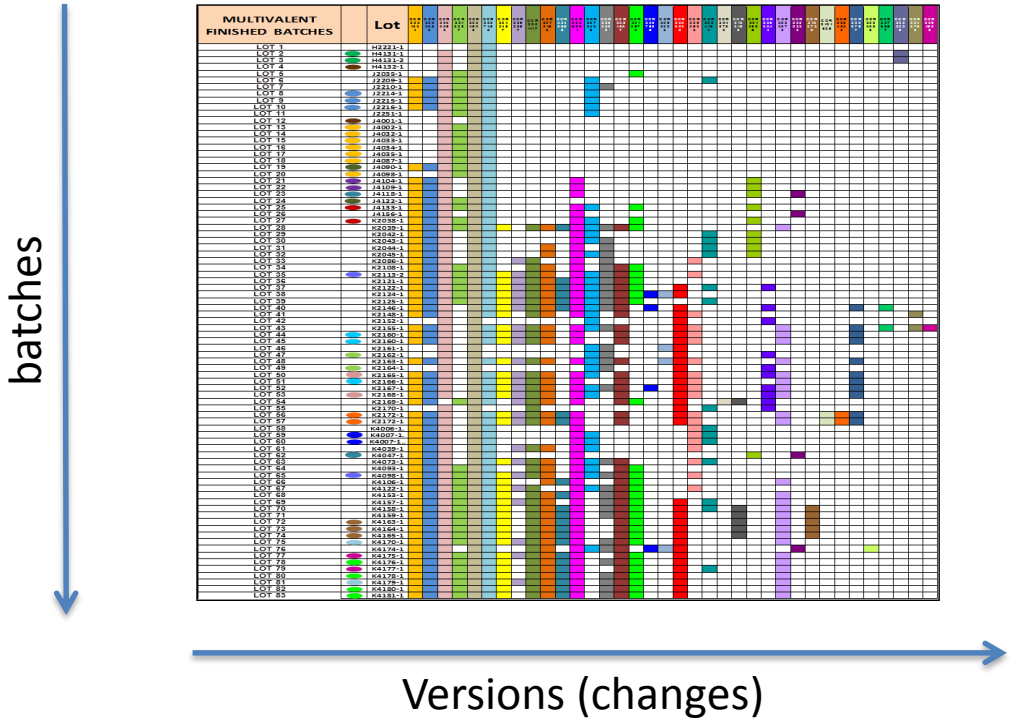


Options to manage multiple versions:

- Keep inventory of old version(s) as projected with known forecast.
  Risk: change in actual demand
- Run old and new version in parallel
- *Risk: costly and no incentive for innovation*

The logistics issue of regulatory complexity explained

83 batches : 55 variations of the same process…



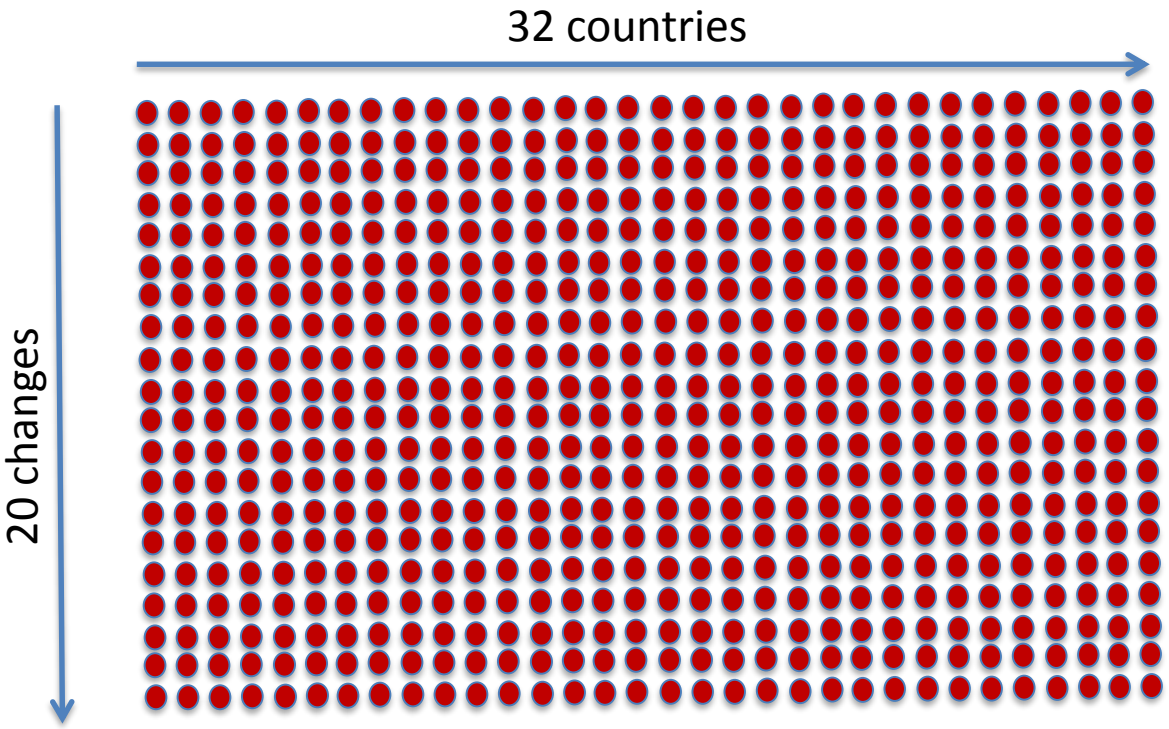
Regulatory complexity in reality: One pentavalent vaccine, one year

Time to talk solutions…..

Solutions

- ***Solution A***: Setting time limits for PAC approvals
  - Challenge: resources & prioritization
  - Benefit: Fewer open changes (versions) at any given time

- ***Solution B***: Harmonize documentation requirements and reporting level for regulatory submissions
  - Challenge: country specific legal framework
  - Benefit: Everyone works from the same requirements -Start from WHO guidance



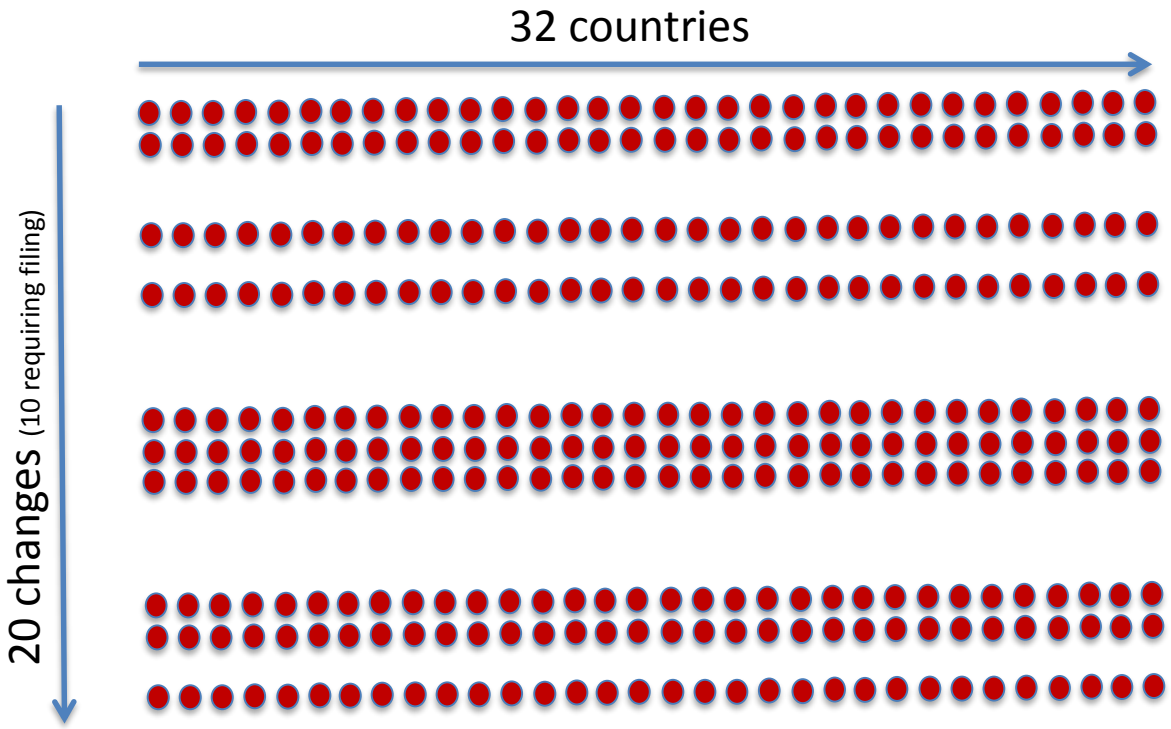
Illustrative example: 20 changes requiring 640 approvals

Solution C: More changes only covered in Quality System (PQS) requires

- Science and risk based approach to PACs
- Effective PQS for PACs

Benefit: reduced regulatory burden with no impact on quality and safety

PDA PtC Effective PQS for PACs



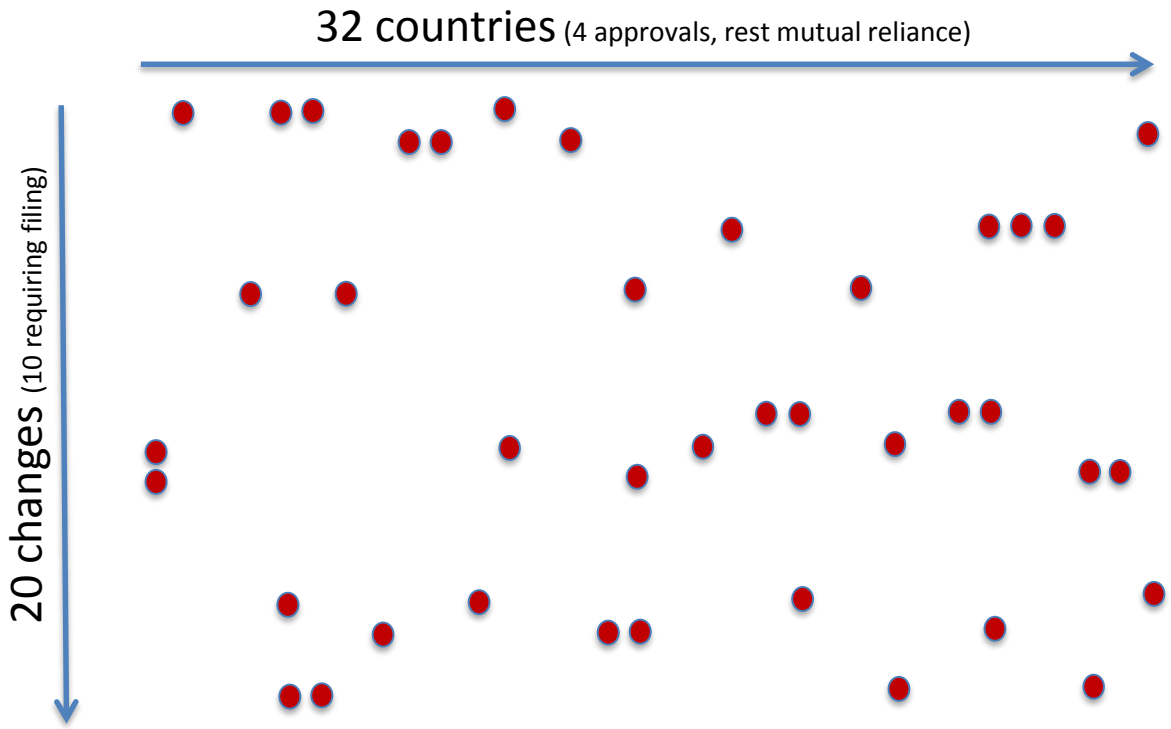
Applying science and risk based approach to achieve regulatory relief

Solution D: Regulatory convergence requires

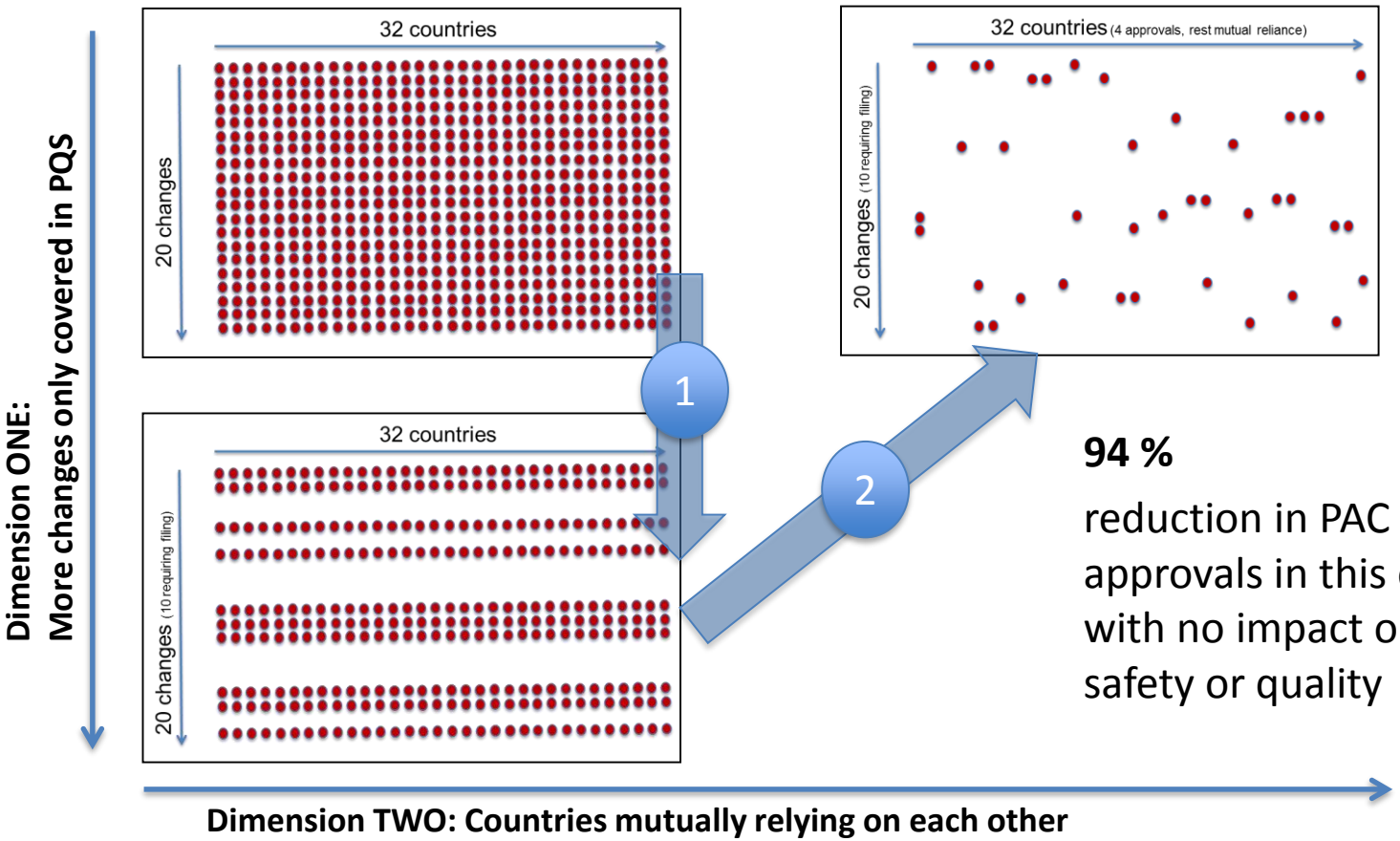
- Clearly defined regulatory reliance guidance
- Extended collaboration between countries

Benefit: leveraging technical experts outside national borders

WHO guidance



Drastic reduction of workload with no impact on product quality and safety



94 %

reduction in PAC regulatory approvals in this example with no impact on product safety or quality

Summary

- Keeping medicines on the market after initial approval is a ‘hurdle race’ and the global regulatory complexity is increasing
- Industry must do it’s part by developing medicine shortage prevention plans, continually innovate, and demonstrate an effective PQS
- Solutions to reduce regulatory complexity includes setting maximum PAC approval timelines, harmonizing PAC documentation requirements, rely more on the company’s PQS and enhance regulatory convergence
- It is time that we together tackle this ‘wicked problem’

Medicines shortage is a global problem requiring a global solution

PDAs involvement…..

- Global organization with >10,000 individual members
- Connecting People, Science and Regulation
- Committed to developing scientifically sound, practical technical information and expertise to advance pharmaceutical and biopharmaceutical manufacturing science and regulation so members can better serve patients.
- www.pda.org
- Website for PAC iAM sm **pda.org/PAC**

PDA PAC iAM^{sm} Deliverables

- ✓ Call For Action
- ✓ Points to Consider
  - ✓ Lifecycle Management
  - ✓ Effective PQS for Management of PACs
  - – QRM and Knowledge Management for PACs
- Industry Survey
- Technical Report: Post Approval Change Implementation for Biologics and Pharmaceutical Drugs
- Global Post Approval Change Management Protocol Library of Examples
- Workshops, Trainings, Tools & Templates

European Federation of Pharmaceutical Industries and Associations

Annual Regulatory GMP/GDP Inspection Survey 2016 Data

* **Date:** 15 / May / 2017 * **Version:** Final






* 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

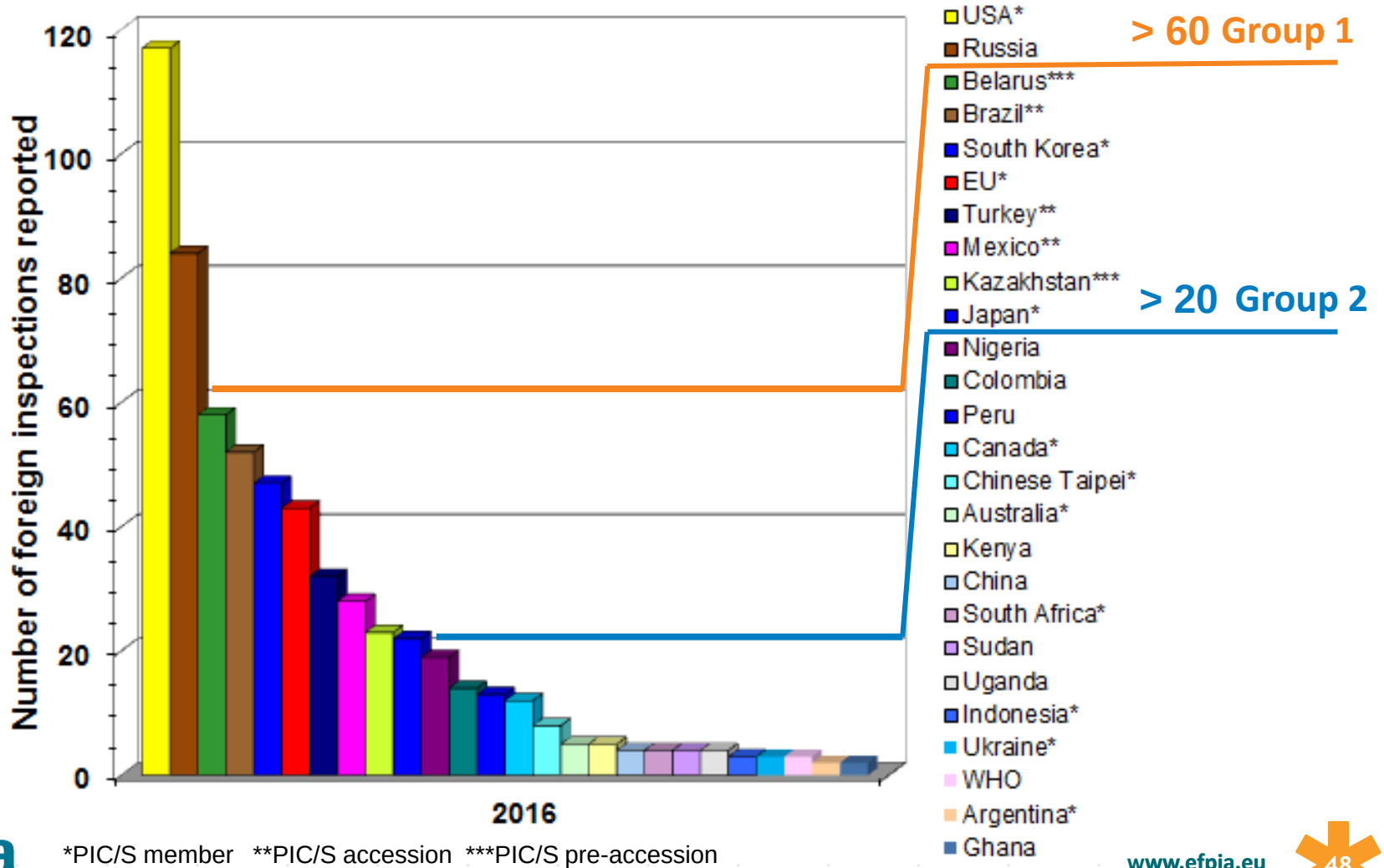
- **Number of foreign inspections* has remained consistent over several years**
  - **Based on data from 23 research-based pharmaceutical companies**
- **Most active inspectorates from 2016 survey**
  - **US, Russia followed by Belarus, Brazil, South Korea, EU**
- **Notable changes**
  - **Increase**
    - **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

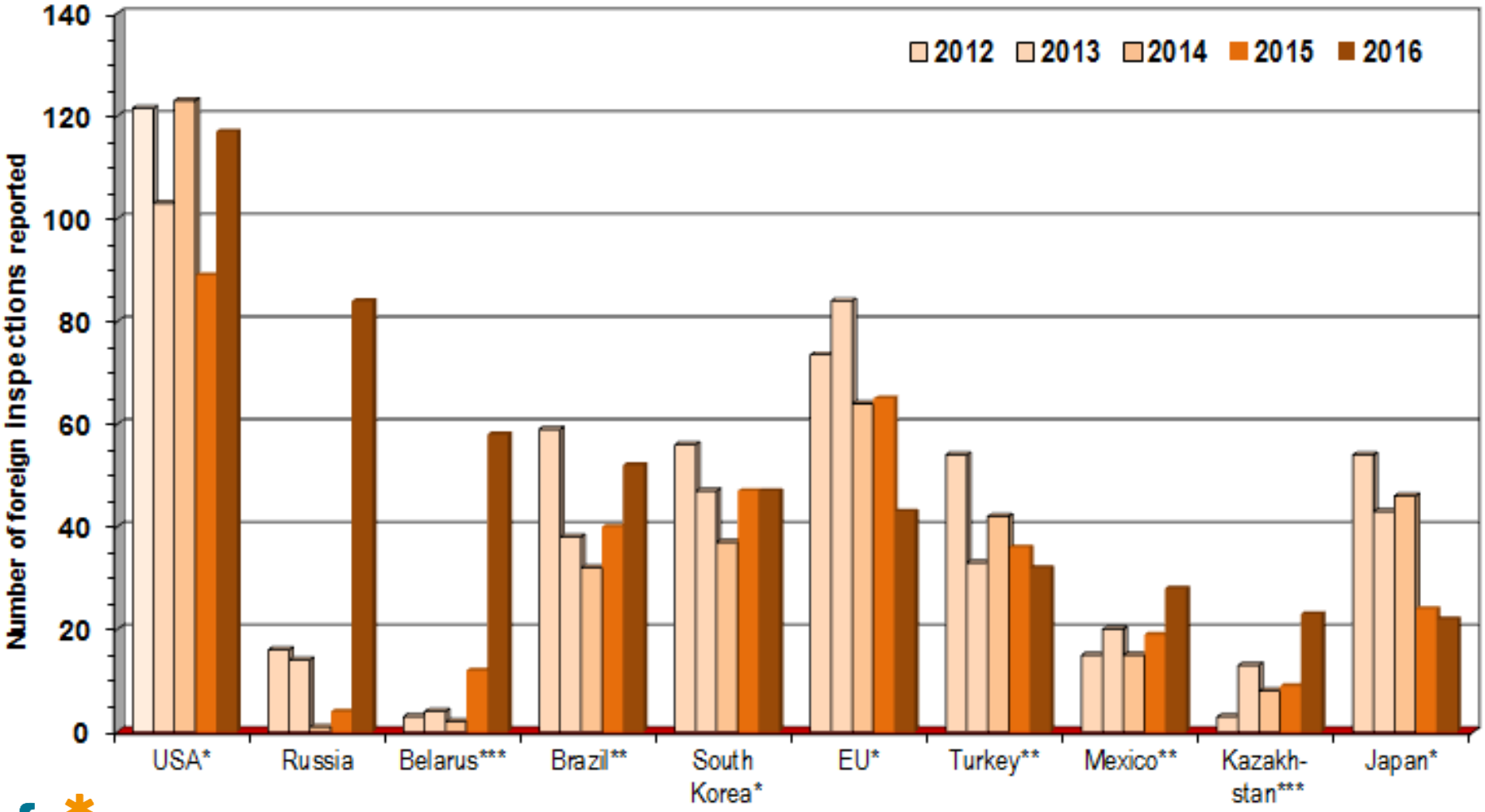
ordered by country (>1 inspections; EU as one entity)



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

Number of Inspections by Countries

Performing foreign inspections 2012 - 2016



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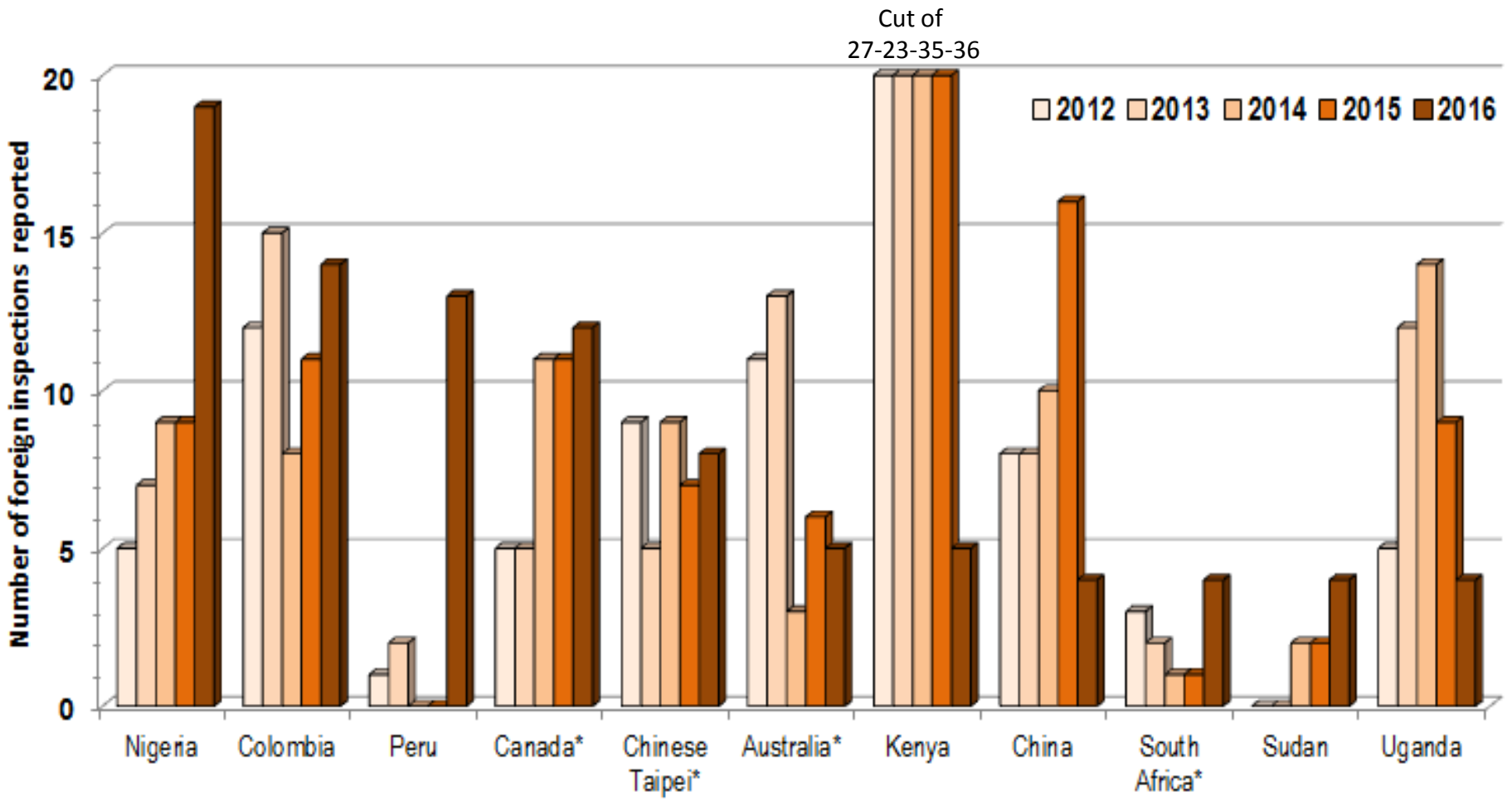

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Foreign Inspections at Manufacturing Sites

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%

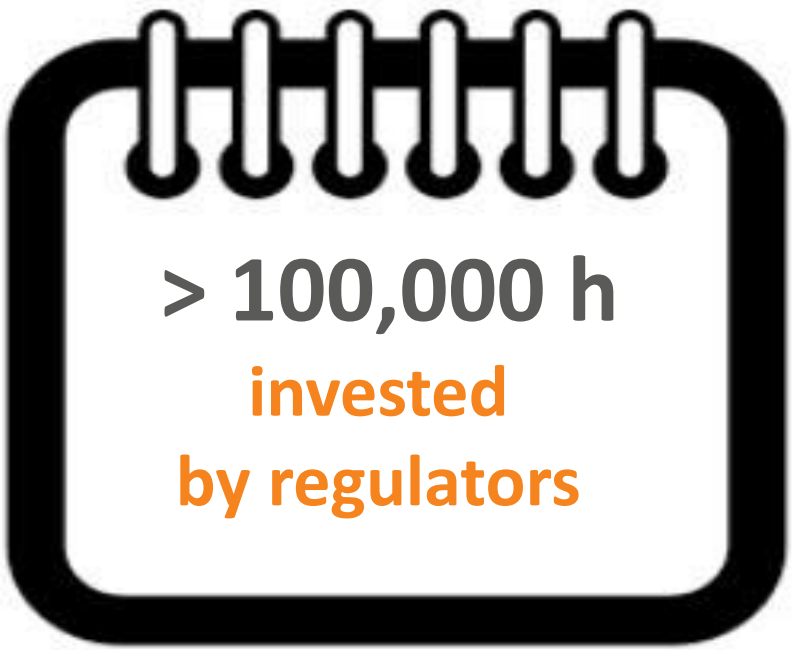
Call for Action to PIC/S members

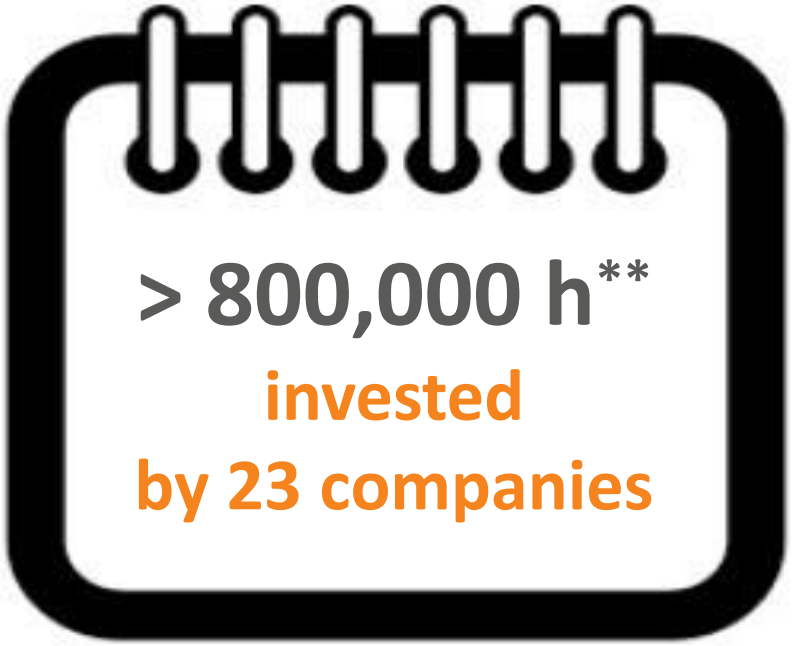
- **PIC/S member inspectorates should continue working towards mutual reliance**
  - **Industry and regulators have not yet fully realised the benefit of mutual reliance on inspections**
  - **Mutual reliance between PIC/S member inspectorates appears to be increasing; however 112 out of 119 inspections 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

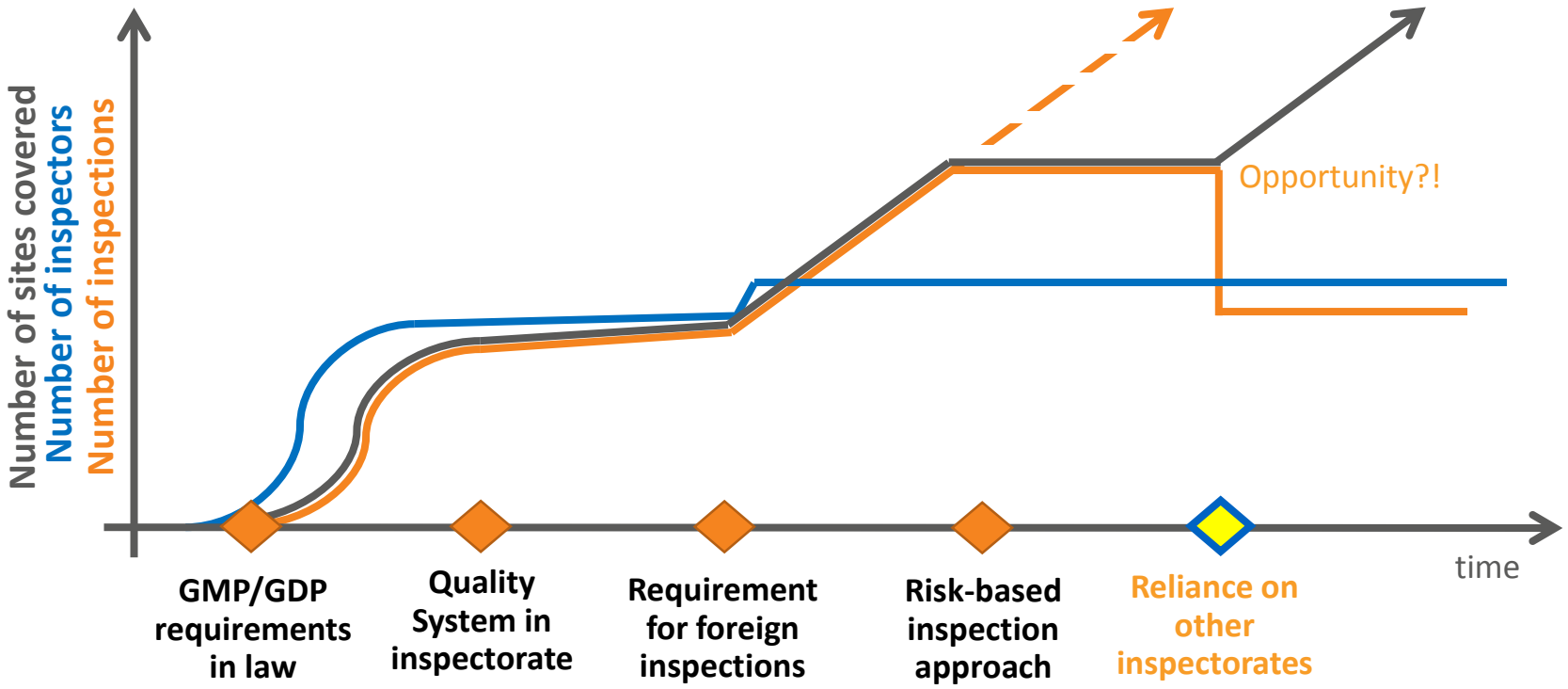
	Domestic Inspectorate	Inspectorate 2	Inspectorate 3	Inspectorate 4
When	August 2016	week 2 2017	week 3 & 4 2017	week 6 2017
Inspectors	2 inspectors 4 days	2 inspectors 3 days*	4 inspectors, 1 reviewer; 10.5 days	2 inspectors 5 days
Inspectors time	64h on site	48h on site	420h on site	80h on site
Resources 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

А.П. Мешковский, С. Роннингер, **Практика инспектирования по GMP: перспективы сближения национальных подходов, взаимного использования и признания результатов**, Новости GMP, 2017, 2-9; A. Meshkovskij, S. Rönninger, **GMP Inspection practice: a case for global benchmarking, convergence and mutual reliance/recognition**, *The GMP News, 2017, 2-9.*

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

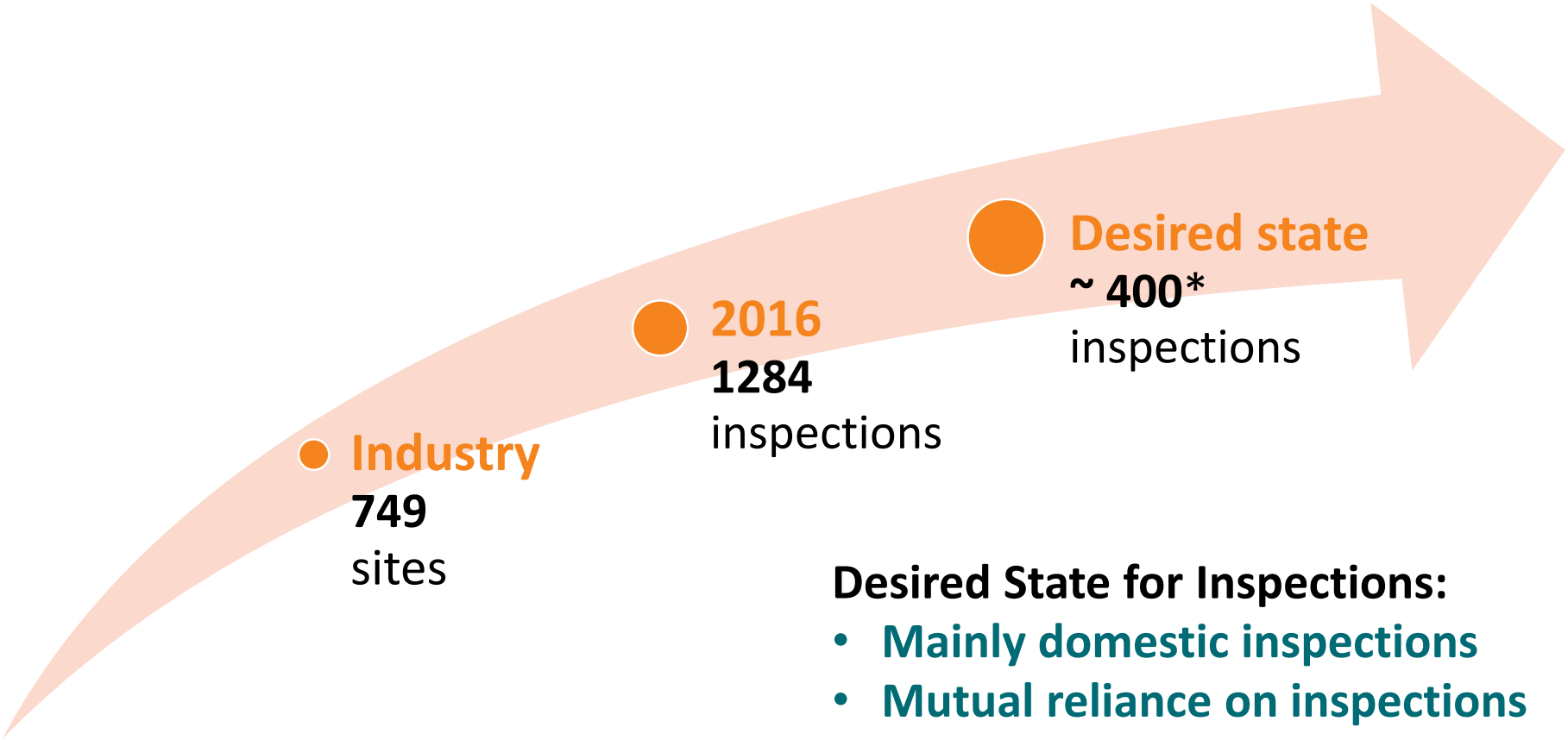
Call for Action to Regulators on Inspections

- **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?

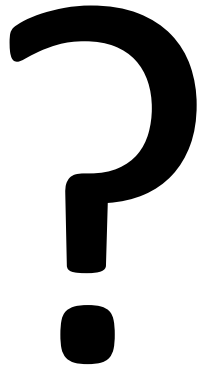
* Based on mainly domestic inspections with average inspection frequency of 2 years for approx. 750 sites

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?

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Contributors to the 2016 Survey

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- 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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