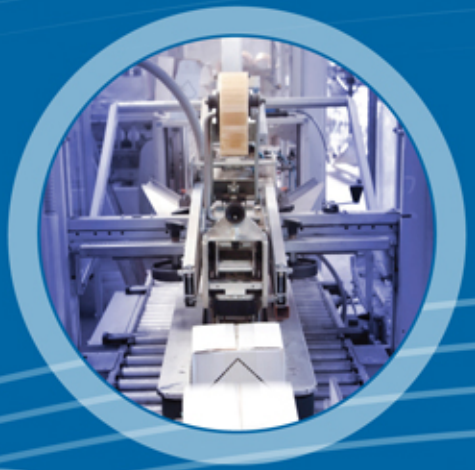
Connecting People, Science and Regulation

Regulatory Inspection Trends

Parenterals Conference, Munich
05 November 2014



Dr.-Ing. Stephan Rönninger,
Amgen (Europe) GmbH

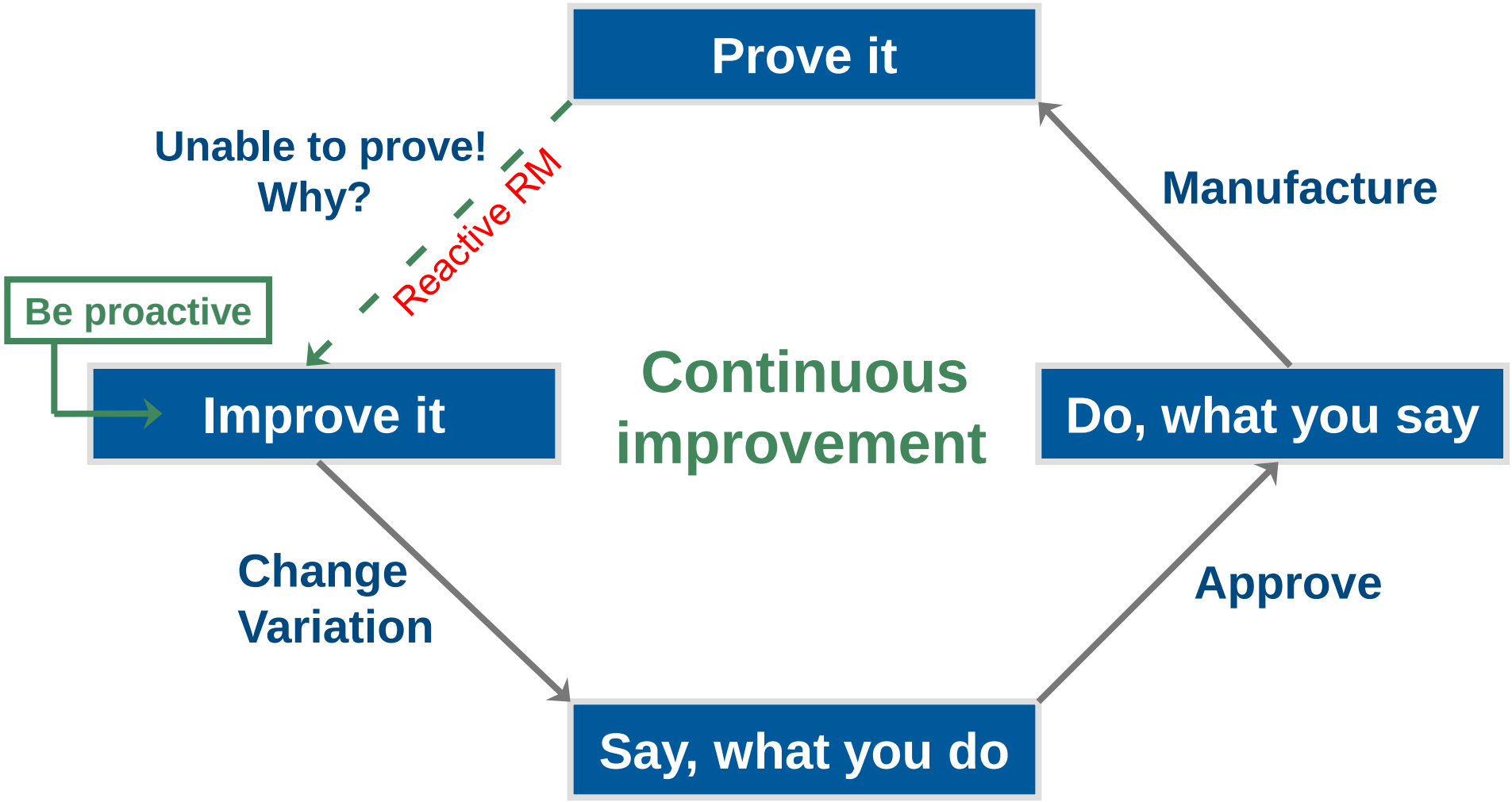
Inspections

- **Current hot topics**
- **Be prepared for upcoming inspections**
- **Inspection practice and opportunities**
- **Conclusion**

Inspections

- **Current hot topics**
- **Be prepared for upcoming inspections**
- **Inspection practice and opportunities**
- **Conclusion**

Maintain Compliance and Manage Risk

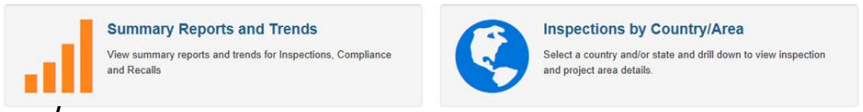


Communicated Inspection Trends

FDA's inspections observations (483s)

Reference Number	Short Description	Long Description	Freq.
21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically,***	155
21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically,***	131
21 CFR 211.100(a)	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***	106
21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically,***	99
21 CFR 211.67(b)	Written procedures not established/followed	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically, ***	77
21 CFR 211.113(b)	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically,***	76
21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, ***	71
21 CFR 211.165(a)	Testing and release for distribution	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically,***	66
21 CFR 211.110(a)	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically,***	65

FDA Inspection Dash Board http://govdashboard.fda.gov



/

MHRA

GMP Inspection Deficiencies 2013

Review of Deficiencies Observed in 2013

Medicines and Healthcare Products Regulatory Agency

http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con464241.pdf

PIC/S

Questionnaire among PIC/S in 1st quarter 2012

Most frequently cited deficiencies		Most severe deficiencies	
Production	24%	Production	27%
Quality system	20%	Quality system	20%
Quality control	14%	Premises + equipment	17%
Premises + equipment	14%	Validation	14%
Validation	12%	Quality control	9%
Personnel issues	8%	Regulatory issues	6%
Materials management	7%	Materials management	5%
Regulatory issues	1%	Personnel issues	3%

See details: Hans Smallenbroek , Boon Meow Hoe, *Top GMP Deficiencies*, **Pharm. Tech. Europe**, May, **2012**, 42-44

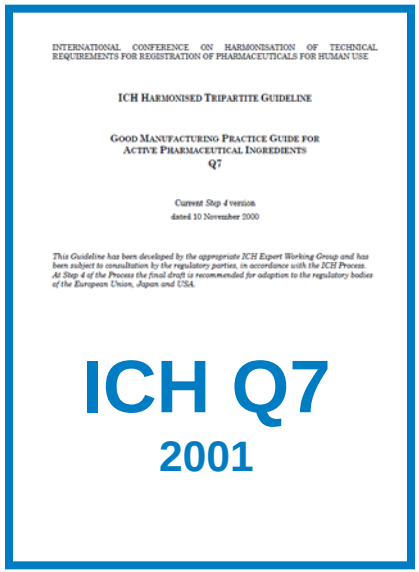
Hans Smallenbroek+, Boon Meow Hoe,
Top GMP Deficiencies, **Pharm. Tech. Europe**, May, **2012**, 42-44

- Procedures not in writing or fully followed
- Data integrity
- CAPA / Investigations / Complaints
- Inadequate lab controls incl. OOS
- Deficiencies in records and reports
- …

Basic principles of GMPs are not new; People might be.

Key Message on the ICH Q7 Q&As

- The ICH Q7 document is intended to be read in its entirety regardless of the nature of the manufacturing activities being conducted to fully understand the linkages between certain sections and successfully implement appropriate GMPs at all stages of the API supply chain, including distribution.



This key message might be true for many other areas

New Guidance Provide Uncertainty

- **Pharmaceutical Quality Systems**
  - More than ICH Q10
  - Lack of/inadequate SOPs
  - What is described: current or future processes?
  - ‘Enabler’ (= help, make easy): Risk and Knowledge Management
- **Equipment cleaning, maintenance & validation**
  - Dedicated facilities, continued process verification
- **Statistical Methods**
  - Design of experiments, ‘Models’ data review tools and control charts, Sampling plans and testing

Best practices are developed to facilitate harmonised interpretation

Prevent and Detect Data Integrity issues

1. Is the data reliable, trustworthy and verifiable?
2. Was the data generated following GMPs ?
3. Is the data traceable and/or referenced to original raw data and reviewed by a reliable quality structure ?
4. Are the appropriate controls in place to ensure that all data is reported?
5. How long in a process can an employee go w/o direct oversight?
6. How do you know all the data is available?
7. Do you have mechanisms to ensure the data is authentic, retrievable?
8. Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

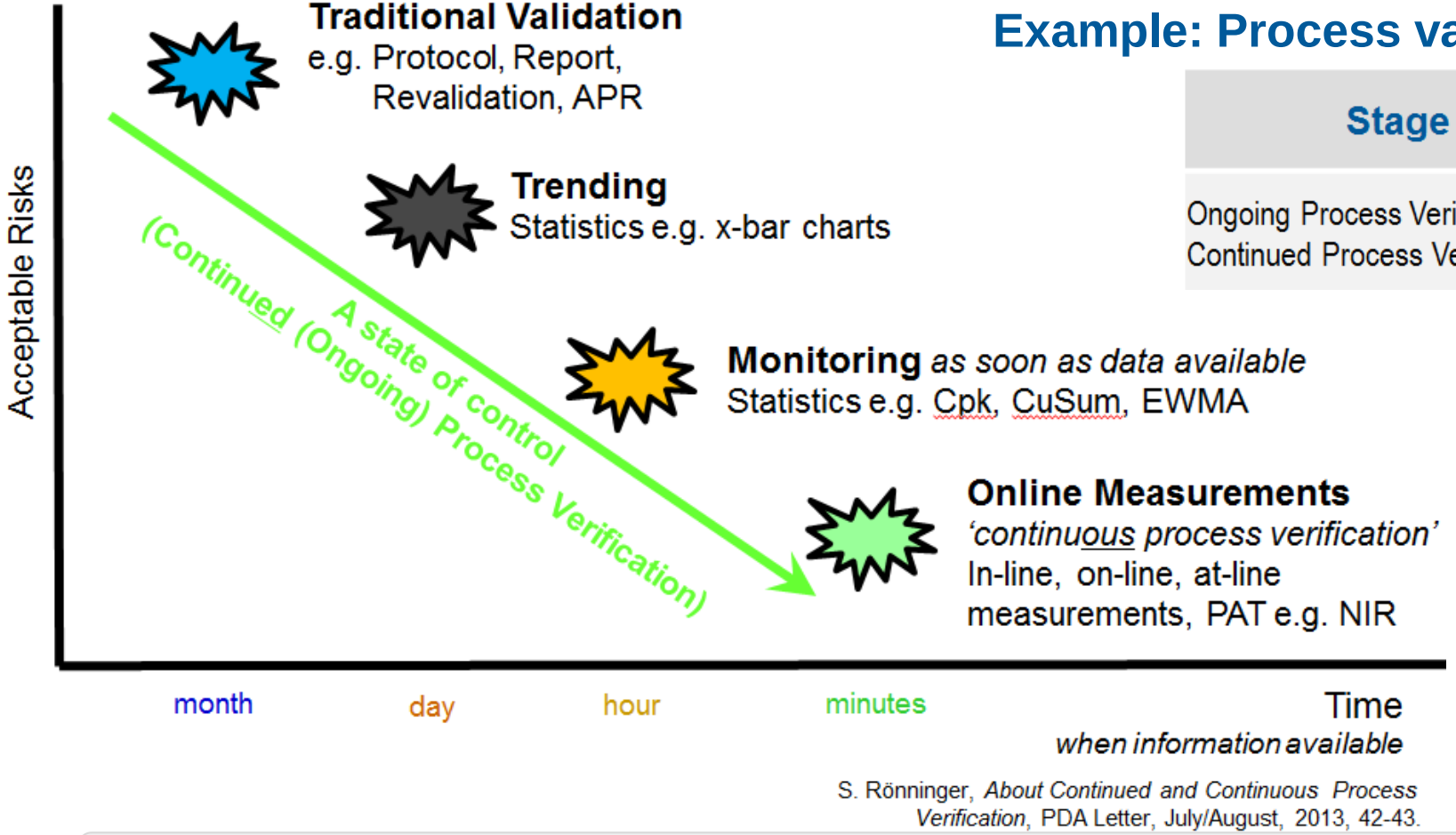
Carmelo Rosa at PDA-PIC/S Q7 training, Bethesda, Feb 2014

Be honest, otherwise all good practices might be under question

Inspections

- Current hot topics
- **Be prepared for upcoming inspections**
- Inspection practice and opportunities
- Conclusion

Use Harmonis/zed Terminology



S. Rönninger, *About Continued and Continuous Process Verification*, PDA Letter, July/August, 2013, 42-43.

Example: Process validation

Stage 3
Ongoing Process Verification (EU) Continued Process Verification (US)

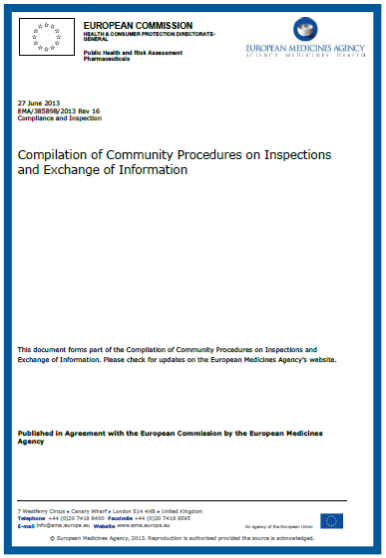
Have a look, what processes inspectors have to follow

Inspection process in the EU

221 pages

Compilation of Community Procedures

- **Procedures Related to Rapid Alerts**
- **Procedures Related to GMP Inspections**
  - Risk Based Planning for Inspections
  - Conduct of Inspections of manufacturers or Importers
  - Training and Qualifications of GMP Inspectors
  - Issuing GMP/GDP Certificates
  - Dealing with GMP/GDP Non-compliance
  - Coordination of inspections
- **Forms Used by Regulators e.g.**
  - Inspection Report
  - Manufacturer's, Importers, and Distributors Authorization


EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Public Health and Risk Assessment
Pharmaceuticals

EUROPEAN MEDICINES AGENCY

27 June 2013
EMA/385898/2013 Rev 16
Compliance and Inspection

Compilation of Community Procedures on Inspections and Exchange of Information

This document forms part of the Compilation of Community Procedures on Inspections and Exchange of Information. Please check for updates on the European Medicines Agency's website.

Published in Agreement with the European Commission by the European Medicines Agency

7 Westferry Circus ▪ Canary Wharf ▪ London E14 4HB ▪ United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

It is important to know, which guidance inspectors follows

Be Aware: FDA

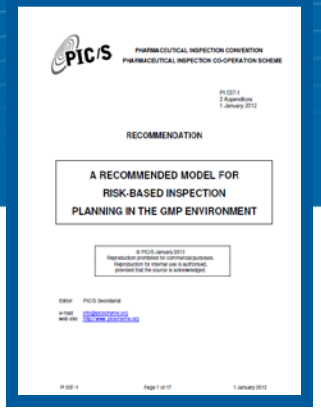
Guidance for Industry
Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection

- **Delay of inspections**
  - Delay Scheduling Pre-announced Inspections
  - Delay During an Inspection
  - Delay Producing Records
- **Denial of inspection**
- **Limiting of inspection**
  - Limiting Access to Facilities and/or Manufacturing Processes
  - Limiting Photography
  - Limiting Access to or Copying of Records
  - Limiting or Preventing Collection of Samples VI.
- **Refusal to permit entry or inspection**

FDA Oct 2014, http://www.fda.gov/RegulatoryInformation/Guidances/ucm122044.htm

Is there a risk to protect our intelligence?

Needs for an Inspector?


PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME
RECOMMENDATION
A RECOMMENDED MODEL FOR RISK-BASED INSPECTION PLANNING IN THE GMP ENVIRONMENT

- **'A Recommended Model for risk-based inspection planning'** (e.g. PIC/S approach, PI-037-1)
  - A simple and flexible QRM tool for the frequency of GMP based inspections implementing a risk ranking approach
  - Inspection Planning: complexity of the site, its processes and products, criticality of the products or services; the intrinsic risk associated with the site (B), compliance-related risk based on the last inspection (C)
- **Inspection Execution: Scope and Duration**
  - Adopt according to available information
    e.g. "plant tour", QMS topics, Quality Control
  - Inspection time used for clarification
    e.g. country specific filing and documentation and processes (e.g. batch release, contracts)
  - Mutual understanding of interpretation of the harmonized GMPs

Make use of the processes used by regulators

Manage Expectations from Inspectors

- **Inspectors like to see …**
  - All processes running, all effected areas and equipment
  - Quality management system practices are in place (training, maintenance, monitoring, cleaning validation...)
  - Deviations and changes
- **Companies like to show…**
  - Routine processes and level of work performance
  - Improvements and developments, established standards and innovations
  - System design by presentations (QA, QC, Manufacturing)

Harald Scheidecker, Boehringer Ingelheim
PDA / PIC/S Inspection trends WS, Geneva May 2012

Should we re-think how we prepare for inspections?

Quality Metrics

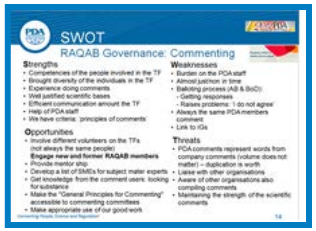
- **Current discussion in US**
  - Use as a risk ranking model of manufacturing sites
  - Opportunity to help with prevention of e.g. Drug Shortages while also assessing quality and compliance risk
- **Do we have existing elements in place?**
  - **Systems:** The EMA (= PIC/S) risk based inspection guidance to provide the site information/ranking
  - **Product:** The Annual Product Quality Review;
  - **Site:** Site Master File ration of personal (manufacturing vs. QA vs. QC), level of changes in the senior management
  - **Companies Key Performance Indicators** (KPI) systems

Challenge: Define specific metrics as GMPs focus on “what”
Metrics focus on the “how”; Identical metric interpretation is required

Know Where You Are and What To Do

- **Experience: Use a simple technique QRM tool for informal risk ranking e.g.**

  Strengths, Opportunities, Weaknesses, Threats (SWOT)


SWOT
RAQAB Governance: Commenting
Strengths
Weaknesses
Opportunities
Threats

1. Select a governance process
2. Brainstorm on SWOT
3. Identify interconnections and overlaps
4. Filter and rank the 3 major themes from the opportunities and threats
5. Formulate conclusions to drive further activities
6. Review immediate actions and shuffle as necessary based on risk-ranking to address weaknesses and threats

Be simple and focused

Inspections

- Current hot topics
- Be prepared for upcoming inspections
- **Inspection practice and opportunities**
- Conclusion

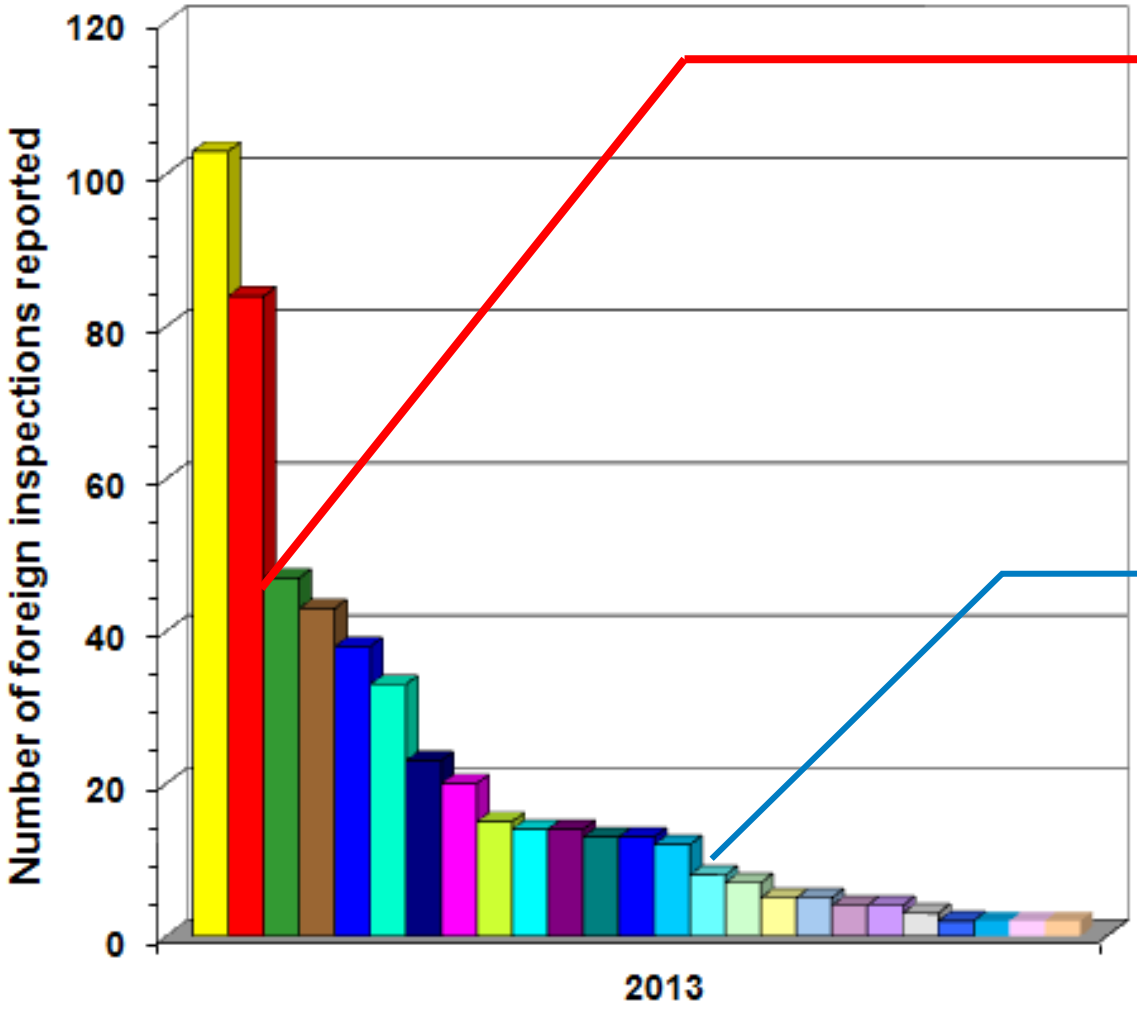
Data Based Arguments

- **European Federation of Pharmaceutical Industry and Associations (EFPIA) Annual Inspection Survey**
  - Scope: Regulatory GMP/GDP inspections conducted inside and outside the Regulatory Authority's own borders
  - Source data: Survey of EFPIA member companies: 22 companies
- **2013 Inspection Survey Outcome**
  - Numbers of foreign inspections have stabilised at a high level
    However more countries are conducting GDP and Vaccine inspections
  - Most active inspectorates: US-FDA, EU; as well as South Korea, Japan, Brazil, Turkey, Kenya and Mexico
  - Notable changes
    - Decreasing number of foreign inspections by Brazil and Canada
    - Increased involvement by Colombia (in South America only), Kazakhstan, Nigeria, China, and others

The survey evaluation supports understanding of reality and expectation

Number of Foreign Inspections in 2013

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



- USA
- EU
- South Korea
- Japan
- Brazil
- Turkey
- Kenya
- Mexico
- Colombia
- Russia
- Saudi Arabia
- Australia
- Kazakhstan
- Uganda
- China
- Nigeria
- Canada
- Chinese Taipei
- Belarus
- WHO
- Iran
- Argentina
- Peru
- Sierra Leone
- South Africa

>50 Group 1

50-10 Group 2

≤ 10 Group 3

& 6 countries with 1 foreign inspection

Data by EFPIA 2013 Regulatory GMP/GDP-Inspection Survey 2013

Who is going? Where do they go?

Inspectorates activity profiles mirror-image industry's global supply chain footprint

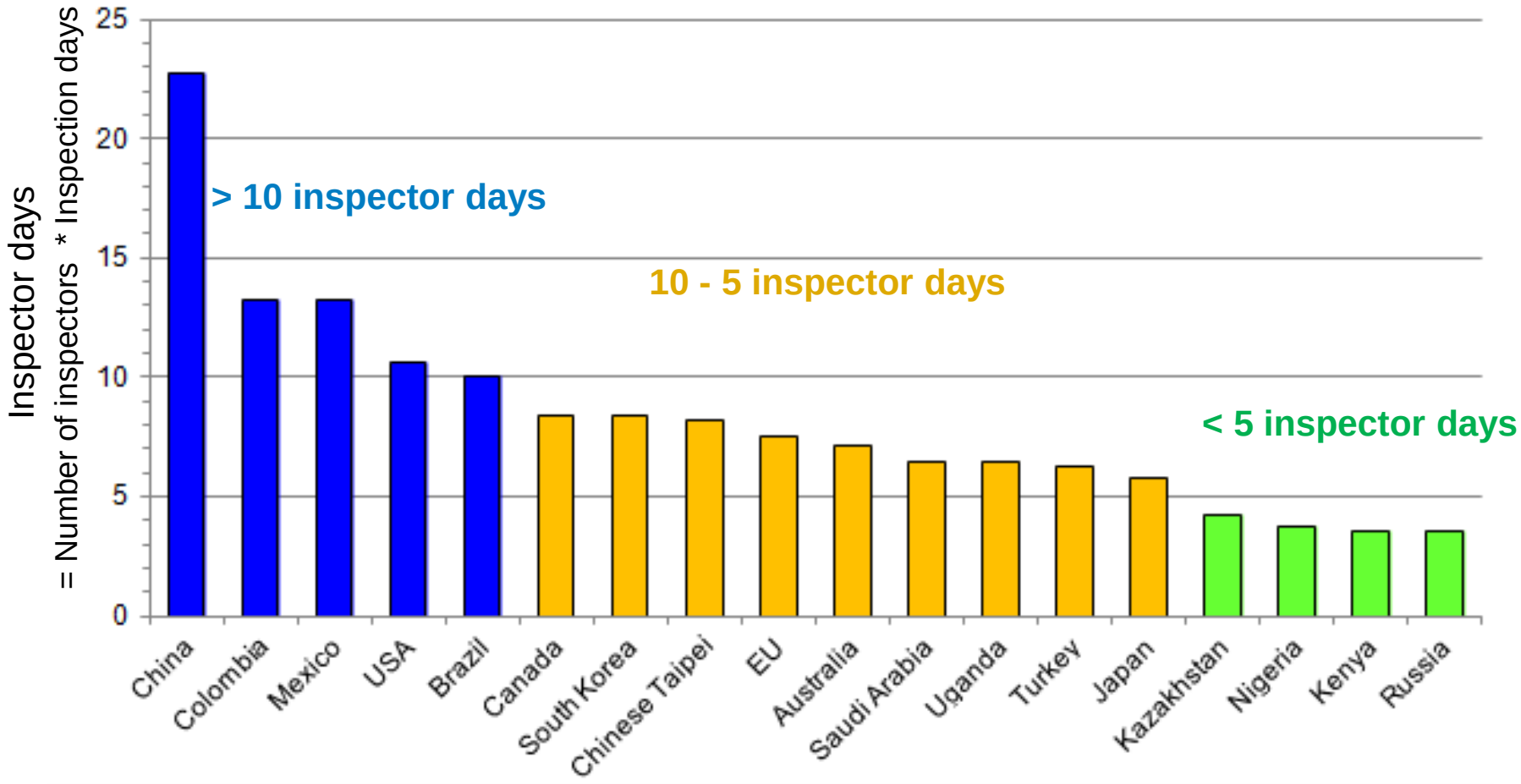
Europe	• 11 of 29 countries are performing foreign inspections (28 EU & EDQM) • 66% of the European foreign inspections target US & Puerto Rico
US	• 76 % of the reported US foreign inspections target Europe
Africa	• Increasing number of African countries perform foreign inspections, mainly in Europe • Talking point on Kenya: 18 times to Europe, 5 times to US
Asia & Australia	• Paper based inspections are used as additional instrument • South Korea: 32 to Europe, 10 to US/Puerto Rico/Canada, 5 others • Japan: 24 to Europe, 18 o US/Puerto Rico/Canada, 1 Singapore
South America	• Decreasing number of South American countries performing foreign inspections • Colombia: increasing number but in the South American region only • Brazil: 26 times to Europe, 9 times to US/Puerto Rico/Canada, 3 others
Middle East	• There was no GCC inspection reported in 2013

Assumption: Harmonised GMPs (according to WHO, PIC/S?) and mutual reliance would reduce resources on both sides industry and regulators

Data by EFPIA 2013 Regulatory GMP/GDP-Inspection Survey 2013

Average Duration of Foreign Inspections

by country (EU as 1); *Country counted only if more than 4 inspections*



Significant resources involved in foreign inspections

Estimated Inspections Resources

Per on-site inspection

Resources	Inspector	Industry
Preparation for specific requirements by individual inspectorates	4 man days (experience from industry audits)	90 man days
On site	8 man days (average from the survey)	55 man days
Post-inspection	4 man days (experience from industry audits)	15 man days
Sum	16 man days	160 man days
Fees/Travel	-	Approx. 30'000 EUR

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

Are inspectors and industry the resources used well?

Experience

- **Increase in the number of inspectorates inspecting**
  - Increase in variability among inspectorates
  - A need in our industry to adapt inspection management processes accordingly
- **New issues seen for the first time**
  - Variety of issues in interpretation of regulations identified (no trend)
  - No great consistency in examples
- **Specific and additional expectations**
  - Related to a variety of once-only issues (no trend seen)

Does this result of isolated only-once issues
show the lack of evidence on ‘Knowledge Management’?

Data by EFPIA 2013 Regulatory GMP/GDP-Inspection Survey 2013

Opportunities

EFPIA: Enhancement of GMP/GDP Inspection Efficiency


efpia

Position Paper

Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency

Executive Summary

Effective and balanced risk based regulatory oversight, allowing for improved resource utilisation, can be further enhanced by:

- **Continued regulatory agency collaboration**
  - To drive harmonisation and optimise use of global inspection resources;
  - For domestic inspectorates to act as the primary overseeing body, and by mutual recognition of each other's systems or reliance of inspection outcome
- **Harmonised GMP and GDP standards**
  - To support consistent interpretation of regulatory requirements.
- **Harmonised regulatory inspection processes including e.g.**
  - Globally accepted GMP/GDP certificate format to document compliance of an inspected site
  - Inspection planning and documentation, standard data packs, risk based approach to inspections, sharing of inspection results in database, standard terminology for the categorisation of observations, standard reporting template

http://www.efpia.eu/topics/innovation/regulatory-affairs

Build awareness and drive solutions

A Year At A Manufacturing Sites

- **My inspection plan**
  - Jan: Brazil
  - March: EU/EMA
  - May: Kenya
  - May: Mexico
  - July: South Korea
  - Aug: Turkey
- **My audit plan**
  - Feb: MAH 1 for product A
  - May: Corporate auditing group
  - Oct: MAH 2 for product B, C, D
- **In December: '*Two inspectors showed up at the main gate just now*'**
  - We are still manufacturing, but drop everything now. Serve the inspectors!

We serve patients – Should we?

Inspections

- Current hot topics
- Be prepared for upcoming inspections
- Inspection practice and opportunities
- **Conclusion**

Conclusions

- **Increasing collaboration within PIC/S and its influence in the global regulatory environment**
  - Optimise the use of inspection resources to leverage agreements
  - Implement a good inspection practices (e.g. standardised definitions, inspection templates) to facilitate opportunities for foreign inspectorates to accept the outcome of domestic inspections
  - A common database on accepted manufacturing sites (EudraGMDP)
- **Inspection Resources**
  - Deploy inspectorates resources based on risk assessment
  - Use more widely a risk based approach for scheduling and conducting inspections (e.g. product type, off-patent, geographic)

Need to leverage communication, collaboration and trust

Conclusions

Resources could be better leveraged by mutual recognition or reliance on inspection outcomes from trusted inspectorates

- **Exchange of inspection reports and companies responses**
  - Seems to be used as preparation resources
  - Seems not to reduce the number of inspections
- **Basis for reliance in a trusted inspectorate**
  - What qualifies a trusted inspectorate?
    (e.g. MRA/MOU, Confidentiality agreements)
  - PIC/S membership only?
  - Are there legal boundaries to allow better use of synergies?
  - Why do I need to see it myself?
  - Cultural issues?
- **How can we respect the reasonable needs of individual countries for a win-win situation (e.g. PIC/S, TTIP)?**

How can industry facilitate this process?

Inspectors are Coming - Be prepared

My site

Acknowledgement:
- EFPIA Efficacy in Ops network
- EFPIA TDOC
- PhRMA TDOC
- JPMA GMP team
- IFPMA RPTS
- Steve Mendivil