2014 PDA ANNUAL MEETING

Biopharmaceutical and Sterile Manufacturing – Embracing Innovation to Meet Global Challenges

April 7-9, 2014

JW MARRIOTT SAN ANTONIO HILL COUNTRY
SAN ANTONIO, TEXAS

EXHIBITION: APRIL 7-8
POST-CONFERENCE WORKSHOP: APRIL 9-10
COURSES: APRIL 10-11

www.pdaannualmeeting.org

Welcome to the Inspection Trends Interest Group

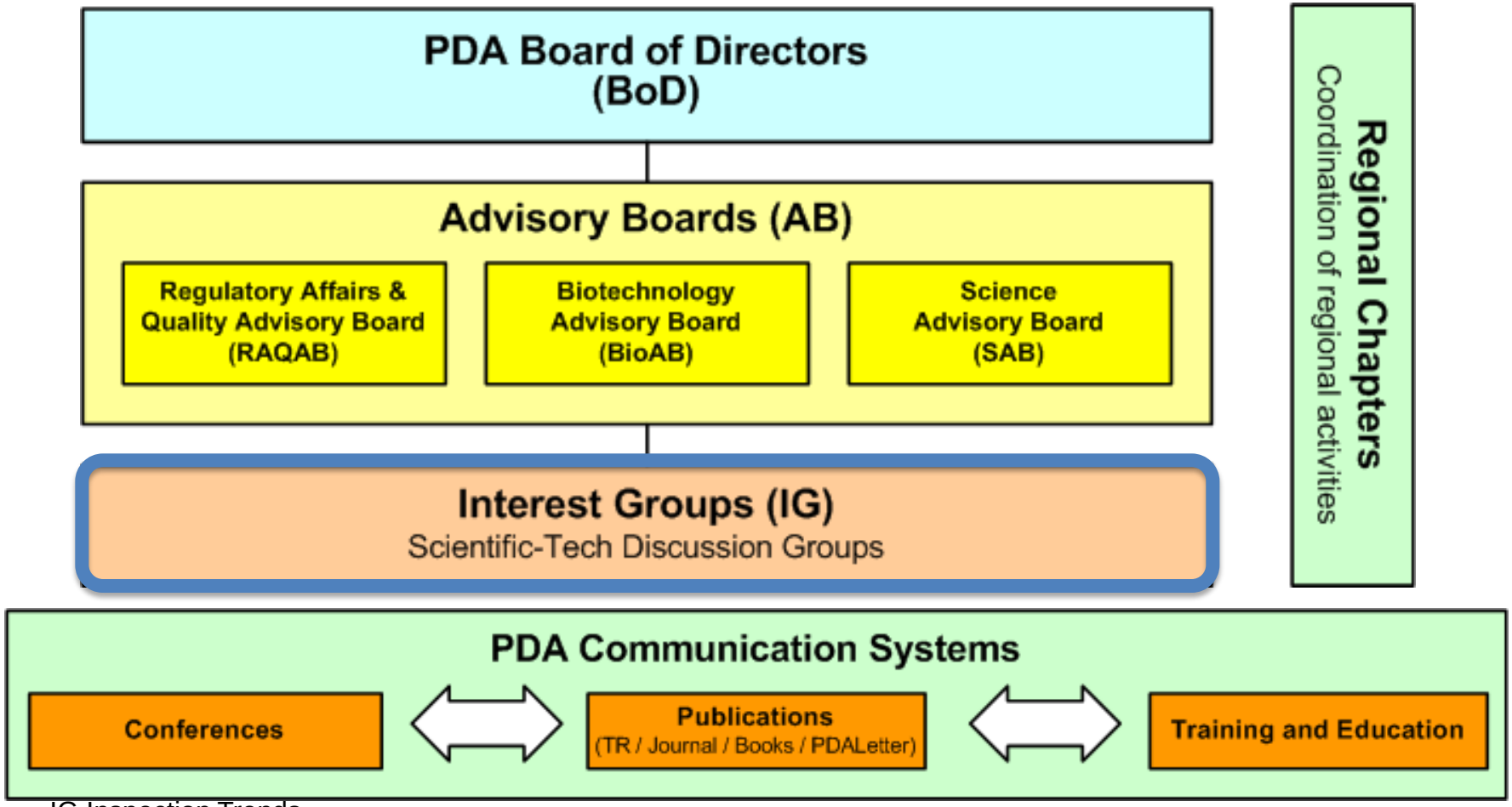
Inspection Trends Interest Group

Stephan Rönninger, Amgen
Brian Laskowski, Hospira
Bob Dana, PDA

Acknowledgement:
Zena Kaufmann, Hospira
Stephanie Garcia, Hospira

PDA Parenteral Drug Association

What is an Interest Group @ PDA?



What is the Inspection Trends Interest Group?

- Provides a forum for sharing experiences and knowledge
  - Area of general Inspection Trends
  - Areas, subjected to inspections
- Meeting format varies
  - Data on current inspection findings and trends are presented
  - Panel discussions featuring industry and FDA participants
  - Podium presentations on inspection-related activities
  - Informal discussions on new regulatory and compliance initiatives
  - Programs and an open forum for questions and answers relative to company experiences with government inspections

http://www.pda.org/Science-and-Regulatory-Affairs/Volunteer-Opportunities/Interest-Groups/InspectionTrendsRegulatoryAffairsIG.aspx

What is the Program for Today?

What is the Program for Today?

- **PIC/S Recent changes**
- **International Inspections Trends**
  - EU update
  - US update
- **Conclusion**

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About PIC/S

Pharmaceutical Inspection Co-operation Scheme

- **Mission**
  To lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products
- **To be achieved by**
  Developing and promoting harmonised GMP standards and guidance documents; training competent inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations
- **Membership**
  Currently 44 inspectorates

PIC/S provides a co-operation and networking opportunity

List of PIC/S member inspectorates

Status 07.01.14

Europe

- Austria
- Belgium
- Cyprus
- Czech Republic (H/V)
- Denmark
- Estonia
- Finland
- France (H/V)
- Germany
- Greece
- Hungary (H)
- Iceland
- Ireland
- Israel
- Italy
- Latvia
- Liechtenstein
- Lithuania
- Malta
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Slovak Republic
- Slovenia
- Spain
- Sweden
- Switzerland
- United Kingdom (H/V)
- Ukraine
- *Turkey*
- *Armenia**
- *Belarus**
- *(Bulgaria)*
- *(Croatia)*
- *(Georgia)*
- *(Hungary (V))*
- *(Russia)*
- *(Serbia)*

Asia

- Chinese Taipei
- Indonesia
- Malaysia
- Singapore
- *Hong Kong, China*
- *Iran*
- *Japan*
- *Philippines*
- *South Korea*
- *Kazakhstan**
- *(Bhutan)*
- *(China)*
- *(Oman)*
- *(Saudi Arabia)*

Partner

- ASEAN
- EDQM
- EMA
- UNICEF
- WHO

America

- Canada
- Argentina
- USA
- *Brazil*
- *Mexico **

Africa

- South Africa - Chair
- *Uganda**
- *(Zambia)*
- *(Zimbabwe)*

Australia

- Australia
- New Zealand

Accession Country: membership evaluated
**Pre-accession country: in preparation for accession*
(Country): interested countries/parties

There are a lot of inspectorates organised under PIC/S world wide

About PIC/S Executive Bureau

Changes in the PIC/S Organisation

- Chair-person: Joey Gouws (South Africa/MCC)
  - Deputy Chair: Paul Hargreaves, MHRA
- Sub-Committees
  - Training (SCT)
  - Strategic Development (SCSD)
  - Compliance (SCC)
  - GM(D)P Harmonisation (SCH)
  - Budget, Risk and Audit (SCB)
  - Communication (SC COM)
  - Expert Circles (SCEC)

PIC/S is ready to take additional member inspectorates on board

Active Teams

PIC/S Expert Circle

- APIs
  - Joint PDA PIC/S basic training on ICH Q7
  - Q&As shared with the ICH Q7- IWG
- Quality Risk Management
  - Development of training modules
- Good Distribution Practices
  - Basic GDP Training Course for Inspectors
- Circle on Computerized Systems
- Human Blood, Tissues and Cells

There hot topics where experts are working on Aid Memoirs and Q&As

Good Manufacturing Practice

PIC/S GMPs

- Recently updated (valid 01 March 2014)
  - Part II of GMP Guide (Q7A): Introduction of risk management principles (see text from ICH Q9)
  - New: Annex 3 on radiopharmaceuticals
  - Revised Annex 2 (biological medicinal products for human use)
  - Revised Annex 14 (products derived from human blood or human plasma)

This is following the commitment to align PIC/S GMPs with EU GMPs

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The Environment (Examples)

	US 	Europe 
• Language	• 1	• > 22
• Agencies	• 1	• > 40
• Policy makers	• 1 Commissionaire	• > 28 NCA / HMA + EC (2 DG)
• The voice	• FDA	• Diffuse focus on countries
• Key regulators	• FDA office / district	• EMA (as coordinator)
• Key locations	• One country	• > 30 capital areas
• Requirements	• Inspections focus on products; PAI	• Inspections focus on sites; normally no PAI
• Inspections	• Domestic: Districts Foreign: Assign inspectors from districts	• Domestic: in local language Foreign: EMA asks NCA to conduct inspection
• Pharmacopoia	• USP is separate	• *APIs also EDQM involved*

Differences in the environment results in differences in the inspection practices

Inspections Trends

by European Authorities

What do you want to know?

Inspections Trends EU

by European Authorities

- Not an easy topic
  - No freedom of information regulation
- EU participating 28 National Component Authorities (NCA) organized in > 40 agencies
  - Usually do not disclose inspection findings
  - Often only a few manufacturers in a country
  - Providing inspection trends has the risk of telling trade secrets

Inspections Trends EU

Mirror image of the regulatory changes

- Legal level: Falsified Medicines Directive (FMD)
  - Transparency of the supply chain
  - Tractability (serialization requirements)
  - GDP for Medicinal Products (registration of distributors)
  - GMP for Excipients (risk based)
  - GMP for APIs (= ICH Q7)
  - GDP for APIs (new ?)
- Guidance level
  - EUDRALEX Vol. 4 (EU GMPs): 19 of 36 guidelines are changing
  - 'Scientific guidelines' (for registration)
    e.g. QP-declaration, Process Validation, Variations regulations

If you want to predict what could be asked, follow the current discussions

Inspections Trends EU

Current discussion: What concerns Inspectors

- EudraLex Vol 4 (EU-GMP guide)
  - Chapters 3 and 5 (premises and equipment and production); Dedicated facilities & QRM principles
  - Chapter 6 (quality control); new: transfer of analytical methods
  - Chapter 8 (complaints and product recall); new: product shortage & QRM concepts
  - Annex 1 (GMP for sterile products: issues on interpretation & guidance on biofilms, if needed
  - Annex 15 (Qualification / validation): allow Q8-11 concepts; link to CGHMP guidance
  - Annex 16 (Batch release & QP); new: Supply chain oversight
  - Annex 17 (parametric release); new: RTRT & CPP
  - Need for a guidance for importers?

EMA IWG Working plan 2014
EMA/INS/GMP/693231/2013

Inspections Trends EU

GDP

Companies, Contractors
See ICH Q7, Chap 7 and 17

API Manufacturing → **Drug Product Manufacturing** → **Supply Chain** → **Pharmacy Patient**

Repackers, Relabelers
(ICH Q7, Chap 17)

Large Quantity
Single Product
Drums, Containers

Small Quantity
Multiple Products
Different Packages

Agents, Brokers, Traders, Distributors
(ICH Q7, Chap 17)

GDP
(ICH Q7 Chap 10)

- **Warehousing**
- **Dispatch**
- **Transportation**

Outsourcing
(EU-GMP Part I, 7; Part II,16; Part III: ICH Q10, 2.7)

Inspections Trends EU

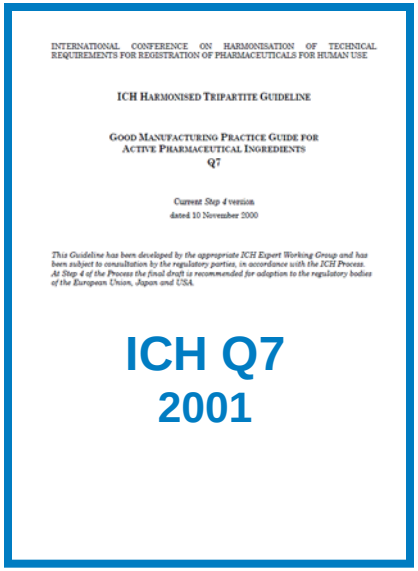
GMP for APIs

- ICH Q7-Implementation Working Group develops a Q&A

Key message

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.

ICH harmonisation for better health



PIC/S

Inspections Trends EU

Some topics shared by one NCA

- Comparison of contract manufacturing operations mentioned on manufacturing license with companies and facilities listed in audit schedule
- Rotational program for post-marketing stability studies accepted with justification
- Annual quality review reports – expectation to address regulatory variations
- Checks performed on regulatory implications of change controls
- OOS investigations

Inspections Trends EU

Inspections: Expectations for QbD

*Shared at **Joint Regulators / Industry QbD Workshop organised by PDA** January 28/29 2014, London*

Pre Approval Inspections

- Qualification procedures for PAT systems: URS, IQ,OQ
- Qualification of automation and IT infrastructure: CSV, transfer of data, interfaces between sensors and data storage systems
- Maintenance procedures
- Periodic re-qualification
- System SOPs (OOS, Change management,...)
- Education/training records
- Exchange with the assessor before and after the inspections
- Ideally assessor would take part in PAI

General GMP Inspection

- Method performance as part of PQR and CPV
- Deviations and changes
- Results from parallel testing
- Batch release procedures
- Procedure for identification, evaluation and implementation of continuous improvement

Inspections Trends EU

Inspections: Expectations for QbD

*Shared at **Joint Regulators / Industry QbD Workshop organised by PDA** January 28/29 2014, London*

GMP inspector will review

- Product knowledge
- How technology transfer between parties is ensure
- How product knowledge is managed and expanded during product maturity

Manufacturing process

- QMS supporting the life-cycle of a QbD product chosen control strategy
- Review risks assessed
- Correctly interpreted in process validation
- Handling of deviations in relation to design space and control strategy
- Handling of change control

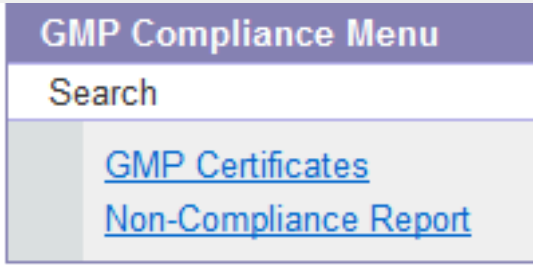
Inspections Trends EU

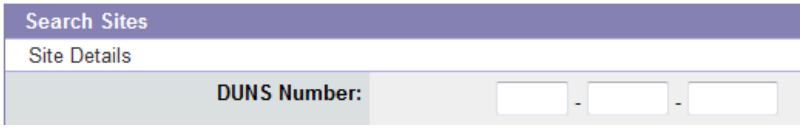
EU EUDRA-Data Base

EudraGMDP

MIA | GMP | API REG | WDA | GDP | Sites

- **MIA**: Manufacturing and Importation Authorisation
- **GMP**: Compliance with Good Manufacturing Practice
- **API Reg**: Registration of Active Substance manufacturers, Importers and Distributors
- **WDA**: Wholesale Distribution Authorisation
- **GDP**: Compliance with Good Distribution Practice





www.eudragmp.ema.europa.eu

Inspections Trends EU

EU EUDRA-Data Base

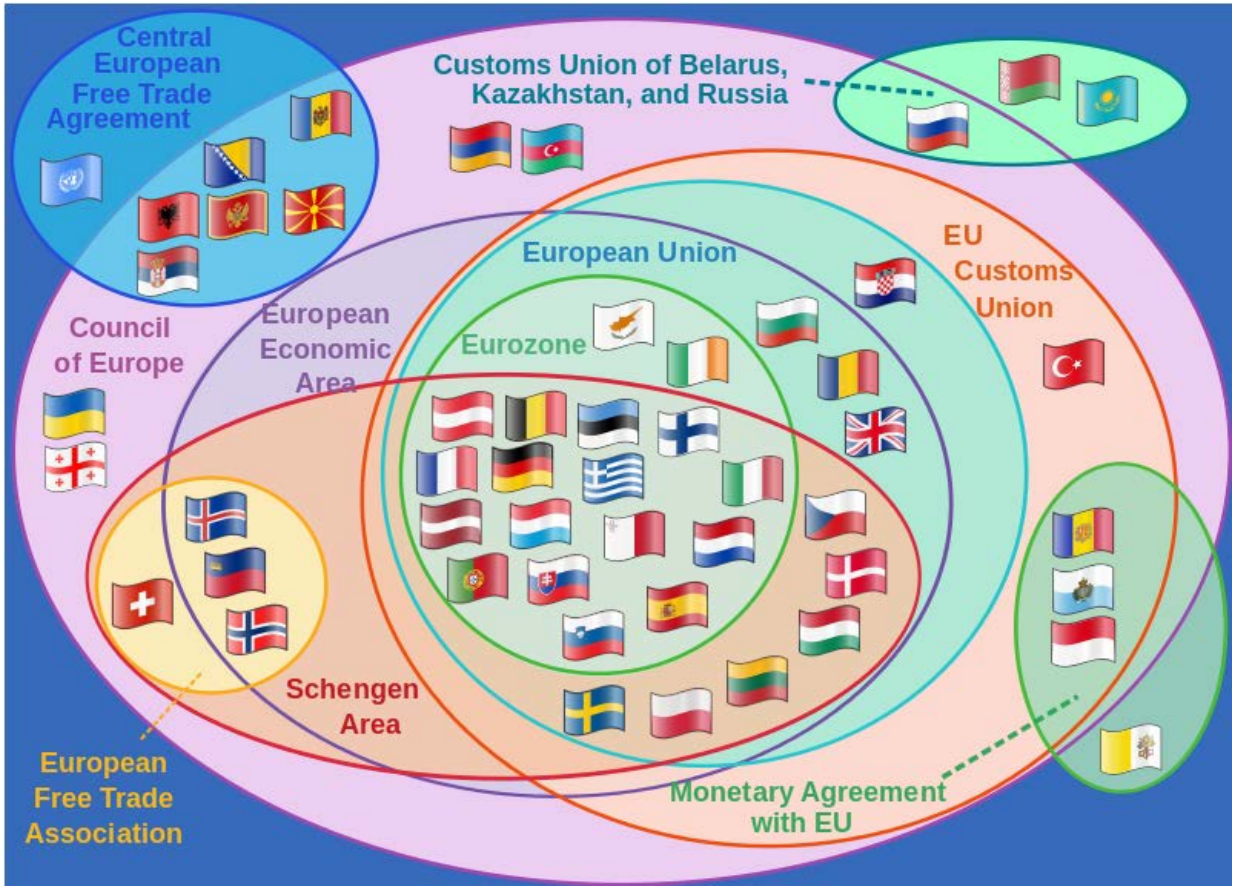
- Not all data of the NCA is available now
- API manufacturer: The absence of a GMP certificate should not be understood as meaning that the in question does not comply with GMP
  - API inspections are based on risk
- EMA is not responsible for the contents of the database
  - Any questions on its content should be addressed to the relevant National Competent Authority.
- Granted GMP-Certificates
- Non-Compliance statements

Inspections Trends EU

Remember: Is Europe a Union?

Relationships between various multinational European organizations and agreements

source: http://en.wikipedia.org/wiki/File:Supranational_European_Bodies-en.svg



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Inspections Trends US

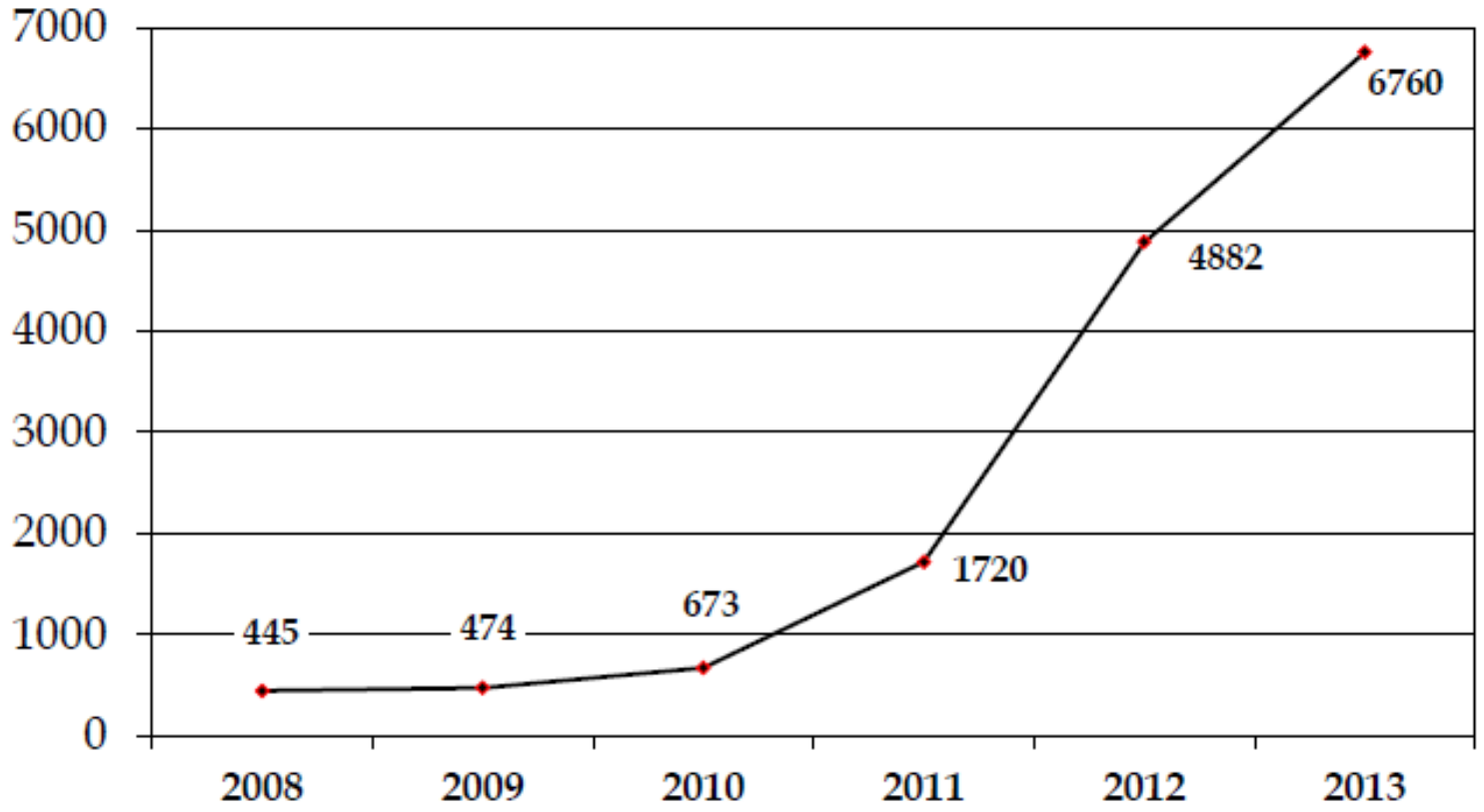
- FDA's inspections observations (483) for 2013
  http://www.fda.gov/ICECI/EnforcementActions/ucm381526.htm
  - Identifies only the regulations that the firm was observed not to be compliant with – no example.
  - Does not include forms 483 issued to API manufacturers and may or may not include foreign inspection results.

Center Name	483s issued
Foods	2386
Devices	1099
Drugs	690
Veterinary medicine	328
Bioresearch monitoring	273
Biologics	191
Human tissue for transplantation	121
Parts 1240 and 1250	91
Radiological health	32
Sum Product Area 483s from System*	**5211**
Actual Total in system 483s**	**5050**

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

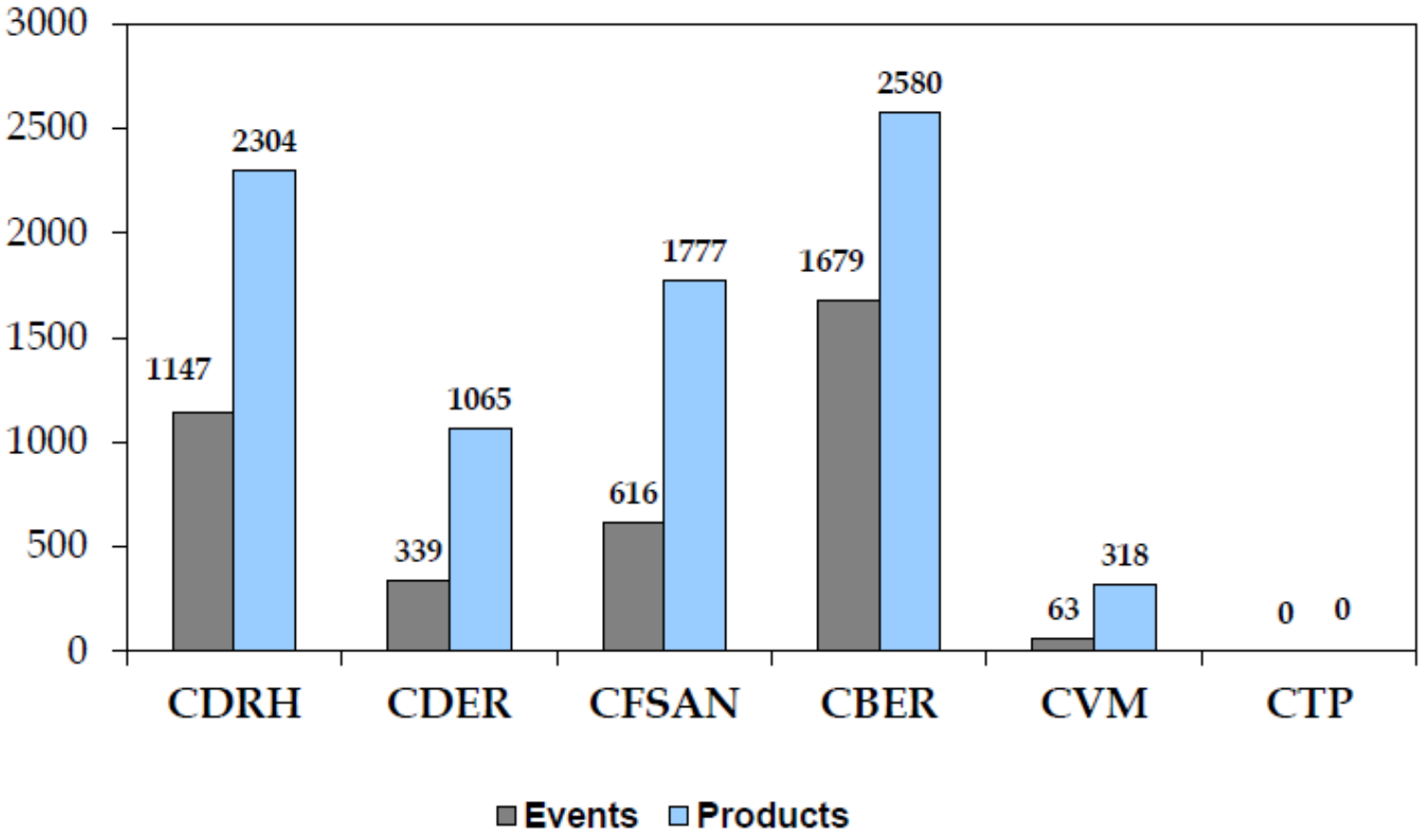
FDA: http://www.fda.gov/ICECI/EnforcementActions/ucm381526.htm

FDA Warning Letters Fiscal Years 2008 – 2013



IG Inspection Trends

Recalls By FDA Center - All Classes Fiscal Year 2013



Inspections Trends US

Inspections of APIs

- Quality System
  - Failure of the Quality Unit (QU) to release/reject APIs
  - Failure of the QU to review and approve all quality-related documents
  - Failure to ensure that quality-related complaints are investigated
  - Failure to conduct regular quality reviews of APIs
  - Failure to evaluate the potential impact of proposed changes on the quality of APIs

Karen D'Orazio, FDA at PDA-PIC/S Q7 training, Bethesda, Feb 2014

Inspections Trends US

Inspections of APIs

- Inadequate lab controls
  - Lack of/inadequate method validation
  - Failure to have scientifically sound and appropriate specifications and test procedures
  - Failure to adequately investigate out-of-specification (OOS) results
  - Failure to document lab controls at the time of performance
  - Failure to have an adequate stability testing program to assess the stability characteristics

Karen D'Orazio, FDA at PDA-PIC/S Q7 training, Bethesda, Feb 2014

Inspections Trends US

Inspections of APIs

- Equipment cleaning, maintenance & validation
  - Equipment not properly maintained
  - Inadequate cleaning procedures (ex. not detailed)
  - Failure to validate cleaning procedures
  - Failure to clean, store, sanitize or sterilize (if applicable) equipment to prevent contamination or carry-over that would alter the quality of API
  - Inadequate qualification of critical equipment

Karen D'Orazio, FDA at PDA-PIC/S Q7 training, Bethesda, Feb 2014

Inspections Trends US

Inspections of APIs

- Deficiencies in records and reports
  - Failure to prepare adequate batch production records
  - Failure to include complete data derived from all tests in the lab control records
- Lack of/inadequate SOPs
  - Failure to establish written procedures related to: production activities, QU responsibilities, laboratory processes, materials management, laboratory controls etc.

Karen D'Orazio FDA at PDA-PIC/S Q7 training, Bethesda, Feb 2014
For further reading: Carmelo Rosa, **Deficiencies found in APIs manufacturers**, *PharmTech*, Dec **2013**

Inspections Trends US

Data Integrity

- A Warning letter to an API site
  - Site Management informed FDA investigators that they were unaware of information generated at the XXX plant that may have an impact on the quality of API.
  - Your Site Management, at the local and corporate levels, is responsible for assuring that strict corporate standards, procedures, resources, and communication processes are in place to detect and prevent breaches in data integrity, and that such significant issues are identified, escalated, and addressed in a timely manner.

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

Inspections Trends US

Data Integrity

- Key to Prevent & Detect Data Integrity
  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?

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

Inspections Trends US

Data Integrity

- Key to Prevent & Detect Data Integrity (cont.)
  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

Inspections Trends US

Data Integrity

- Considerations
  - Know the Who-When-What-How: Is Data collected ?, Is Data processed?, Is Data reviewed?, Is Data reported?
  - The inability to detect and prevent poor data integrity practices raises serious concerns about the lack of quality system effectiveness
  - It is imperative that the data generated and used to make manufacturing and quality decisions at a firm is trustworthy and reliable

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

Inspections Trends US

Data Integrity: Conclusions

- We need to know the difference between falsification and poor / bad GMPs
- Existing systems should be able to ensure data integrity , traceability and reliability
- Companies who outsource operations should have systems in place to verify and compare the data generated by their contractor
- Once DI Practices are found, known or uncovered, A CHANGE TO AN SOP OR FIRING AN EMPLOYEE IS NOT ENOUGH!!!!
- QRM approaches to prevent, detect and control potential risk are essential
- If it looks to good to be true, it probable is not true, so keep your eyes WIDE opened

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

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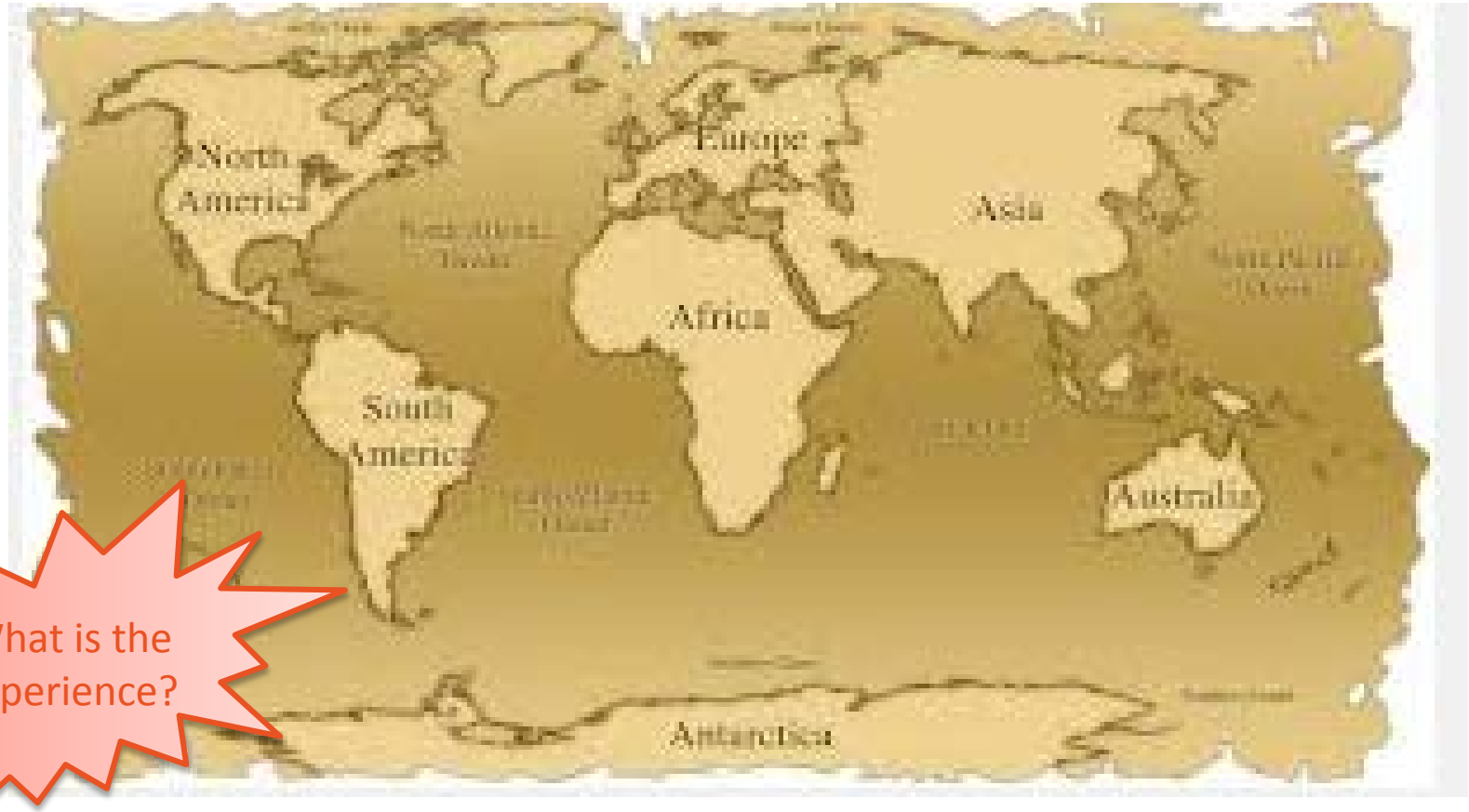
Inspection issues with Technical Topics

International Inspection Trends



What is the Experience?

http://www.freeworldmaps.net/download/maps/political-world-map-big.gif

Q and A Summary

Following the prepared presentations at the April 8th IG meeting, a question and answer session followed. Here are the most significant interchanges which occurred during that session.

1. It was observed by one participant that his analysis of FDA483 observations which were reported in Fiscal Year 2013 showed a marked increase in the numbers of references to deficiencies in microbiologic environmental monitoring and training as opposed to FY2012.

2. Q: Have there been observations with respect to monitoring for Relative Humidity during shipping?
   - A: Such observations have been made but not frequently (e.g. two people responded "yes").

Acknowledgement:
Based on the notes by Bob Dana, PDA

Q and A Summary

3. Q: Can product be released if results for some control tests exceed alert limits, but fall within action limits?
   - A: Yes, but an investigation is needed into why alert limits were exceeded, especially if no root cause is apparent.

4. Q: What's the future look like as far as the role of virtual sponsor companies when non-compliance is found at their CMO's?
   - A: One can refer to the FDA guidance on Quality Agreements. Warning Letters have been issued for lack of adequate oversight.
   - A: For virtual companies, the lack of infrastructure makes proper oversight difficult. The FDA guidance on Quality Agreements is really designed for large pharmaceutical companies overseeing CMOs.
   - A: The registration (license) holder is responsible for releasing product to market and for the overall compliance of the product.

Acknowledgement:
Based on the notes by Bob Dana, PDA

Q and A Summary

5. Q: What has been the experience with other non-US inspection agencies?
   - A: Not much information available. One participant stated his experience was that Brazil frequently included engineers in the inspection team, but that was an anecdotal observation.

6. Q: What has been the experience with the Chinese FDA?
   - A: No experience from the group with Chinese FDA inspections.

7. Q: How might one determine the trends in Europe, where not much information on inspection findings is published officially?
   - A: Sources of information included industry surveys, inspectors joining local interest groups, and inspectors conducting training sessions.

Acknowledgement:
Based on the notes by Bob Dana, PDA

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Manage Expectations from Inspectors

Can we do better?

- 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)
- 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

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

Should we re-think how we prepare for inspections?

Next Activities of the IG

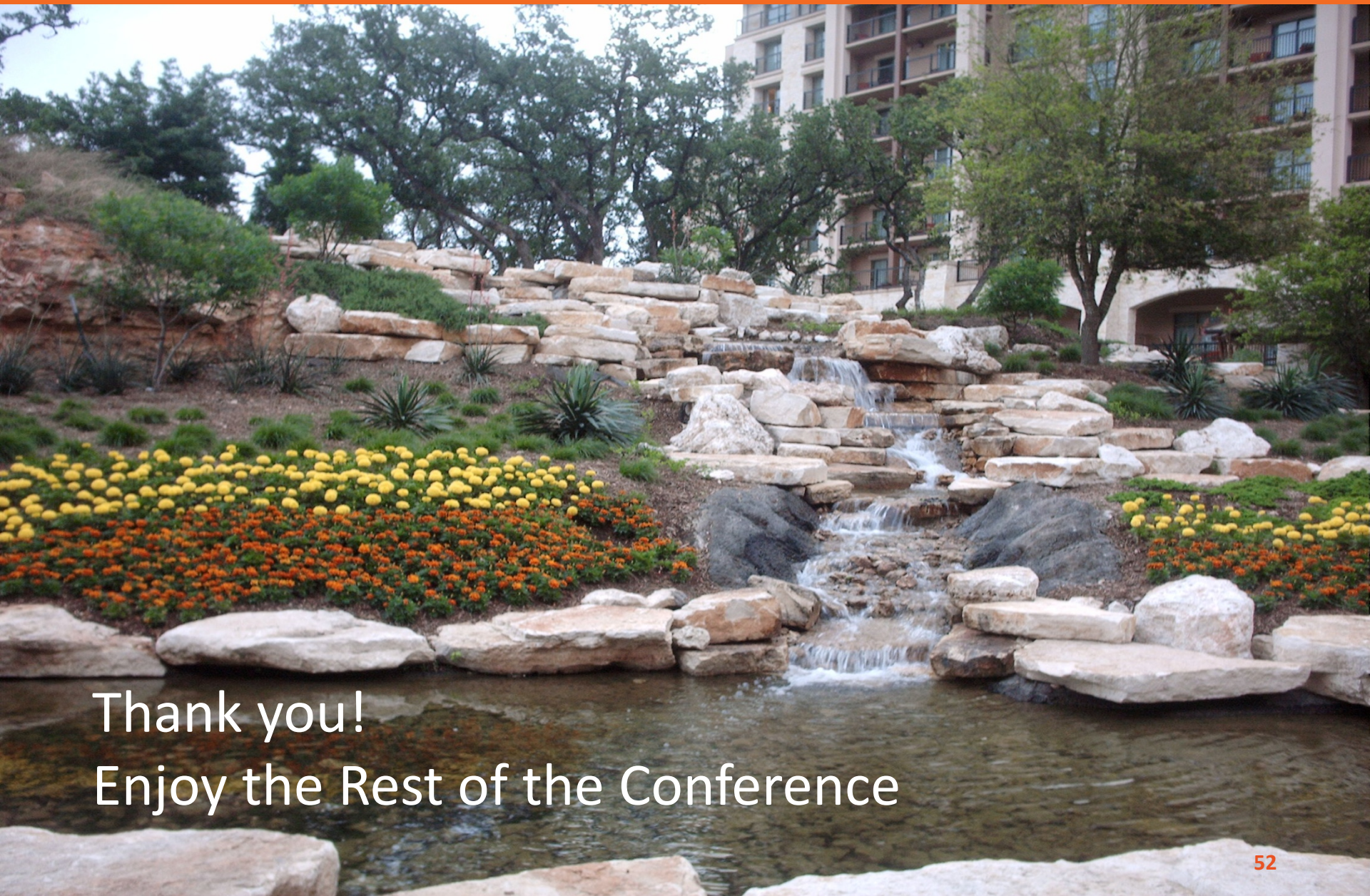
US: http://www.pda.org/Science-and-Regulatory-Affairs/Volunteer-Opportunities/Interest-Groups/InspectionTrendsRegulatoryA
EU: https://europe.pda.org/index.php?n1=667&n2=705&n3=707

- EU: Parenteral Manufacturing Conference, Istanbul, June 24-25 2014
  Break out session with presentations and Q&As on Inspection Trends
  https://europe.pda.org/index.php?n1=665&n2=689&id=1511&content=Overview
- US: Next IG meeting at PDA/FDA September 08-10 2014
  Interactive sessions – New format with regulators
  http://www.pda.org/GlobalEventCalendarandRegistration/2014-PDAFDA-Joint-Regulatory-Conference.aspx
- EU: Next IG meeting at PDA Parenteral Conference, Munich, November 04-05
  Interactive session with regulators
  https://europe.pda.org/index.php?n1=665&n2=689&id=1516&content=Overview

Acknowledgement:
- Stephanie Garcia, Hospira
- Zena Kaufmann, Hospira
- Barb Unger, Amgen
- Mid West Discussion Group (MWDG)

How Do You Feel Now?

- Happy?
  - Sign up for our Interest Group
- Enthusiastic?
  - Approach us, if you are interested to plan IG meetings
- Tired?
  - Speed up to the 'PDA Dine Around'



Thank you!
Enjoy the Rest of the Conference