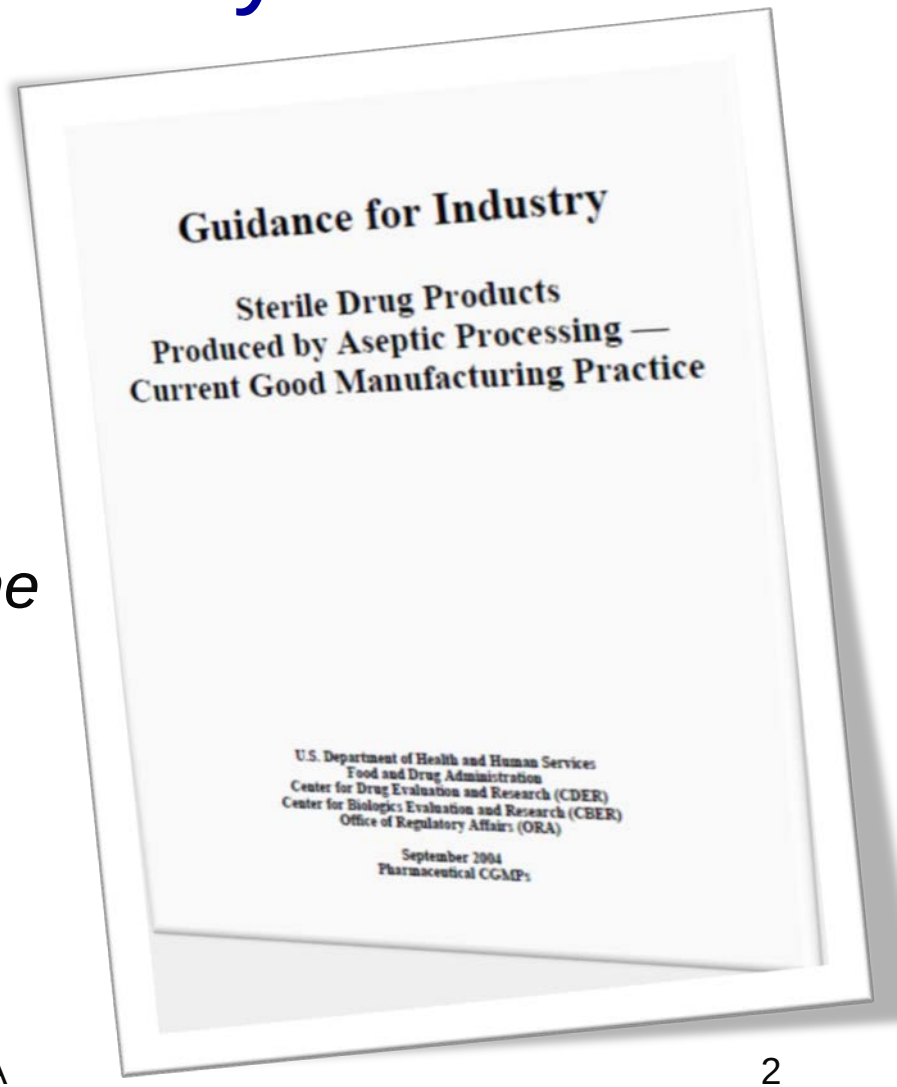
“Global Inspections and a *trend* to come ?”

New England - PDA
Woburn, MA
November 9, 2016

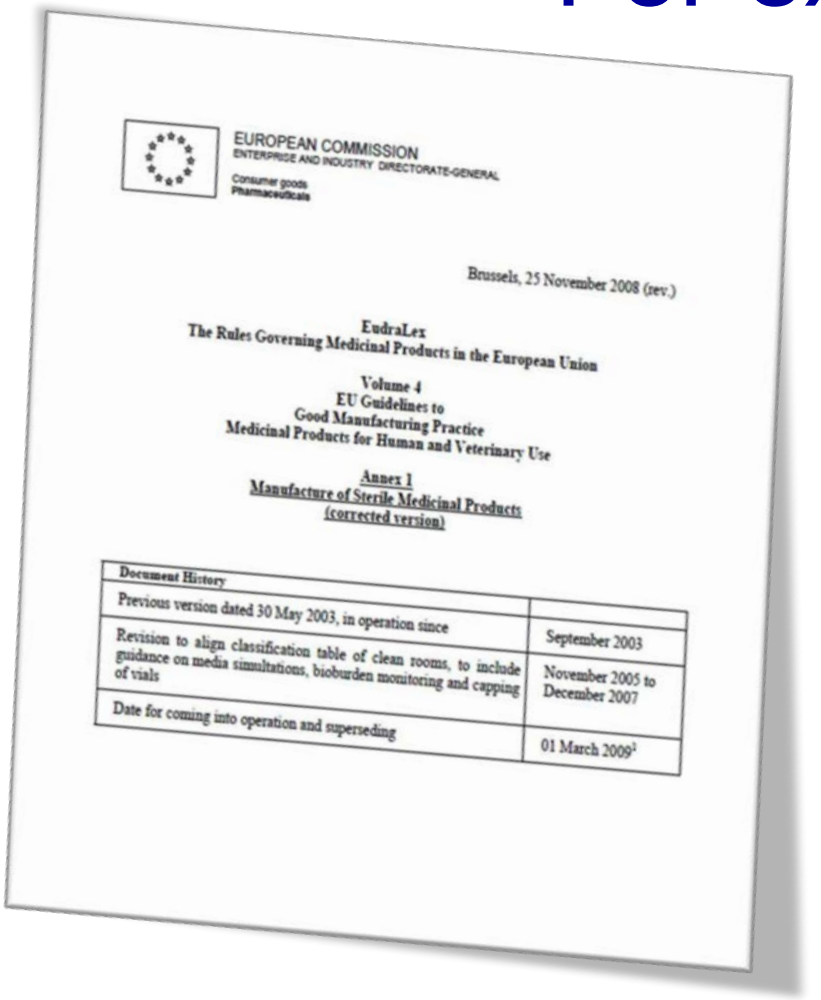
Fundamentally

- We continue to consider the information provided in our Guidance Document, and

- *"You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."*



For example



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Brussels, 25 November 2008 (rev.)

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)

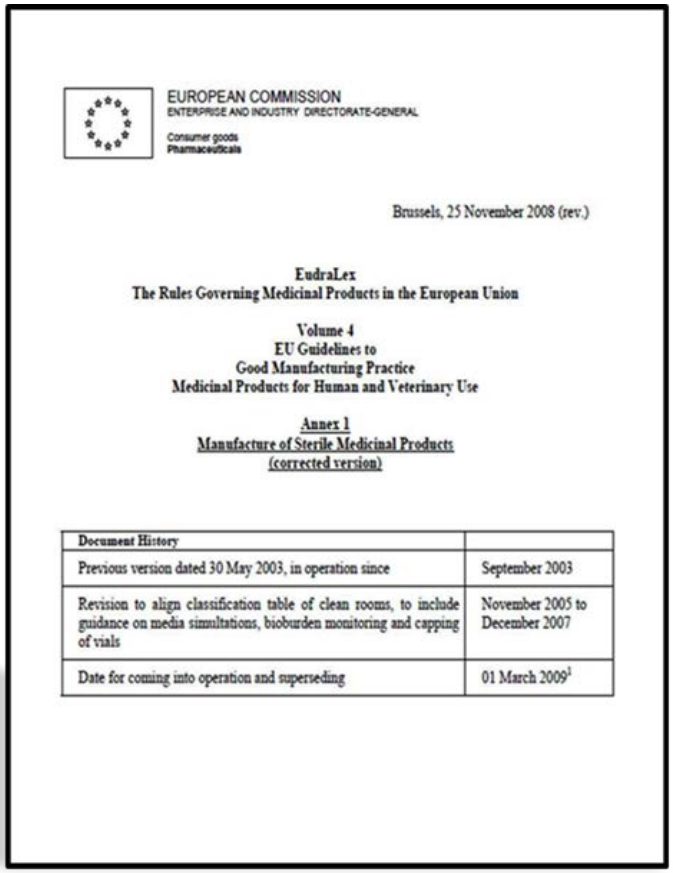
Document History	
Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009[1]

Technical Report No. 22
(Revised 2011)
Process Simulation for
Aseptically Filled Products

PDA

2011

mindful of potential adjustments with the EU Annex-1 Revision



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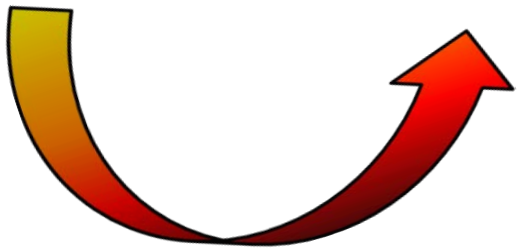
- There are many similar principles of manufacture and considerations noted between the FDA Aseptic Guidance and the current EU Annex-1 Guideline document

For example

1. Aseptic Process Simulations
2. Cleanrooms classification and monitoring
3. Controls to prevent the ingress of microorganisms
4. Design of equipment & facilities
5. Personnel clothing / gowning requirements
6. Container Closure System
7. Quality Control testing

As a note - with the Aseptic Guidance Document

- Compliance Program 7356.002 provides general information on the system based approach to conducting inspections of drug manufacturers.



- Six Systems -
  1. Quality System
  2. Facilities & Equipment
  3. Materials
  4. Production
  5. Packaging & Labeling
  6. Laboratory

you may find it worthy of your considerations

- the PDA *Global Sterile Manufacturing Regulatory Guidance*
  (PDA - Global Sterile Task Force)

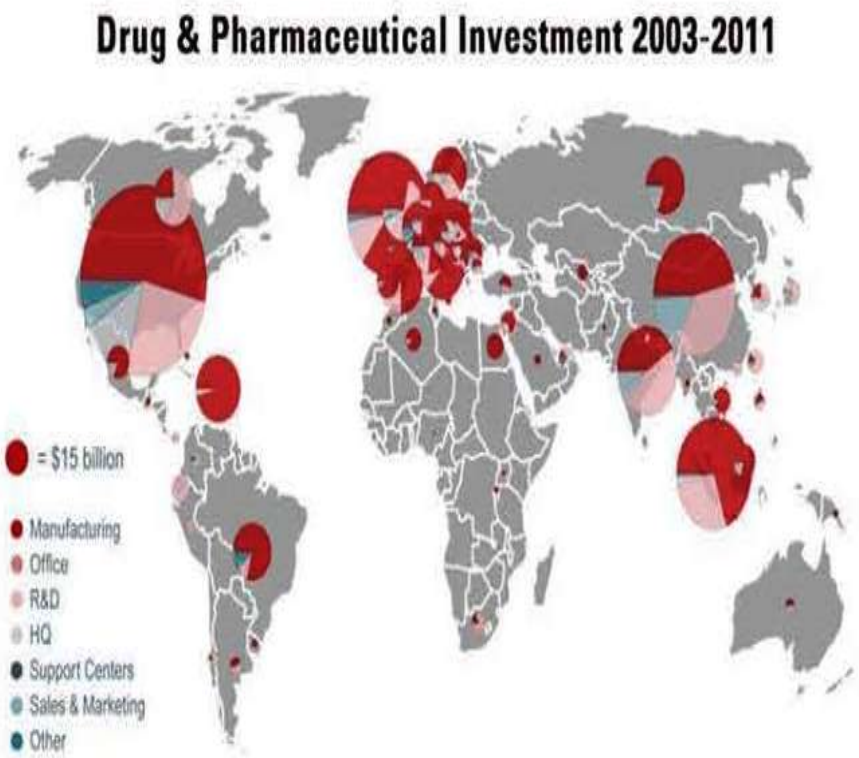
✓the text compares the regulations/guidance from the ménages de quatre i.e., European Union, the US, PIC/S and the WHO.

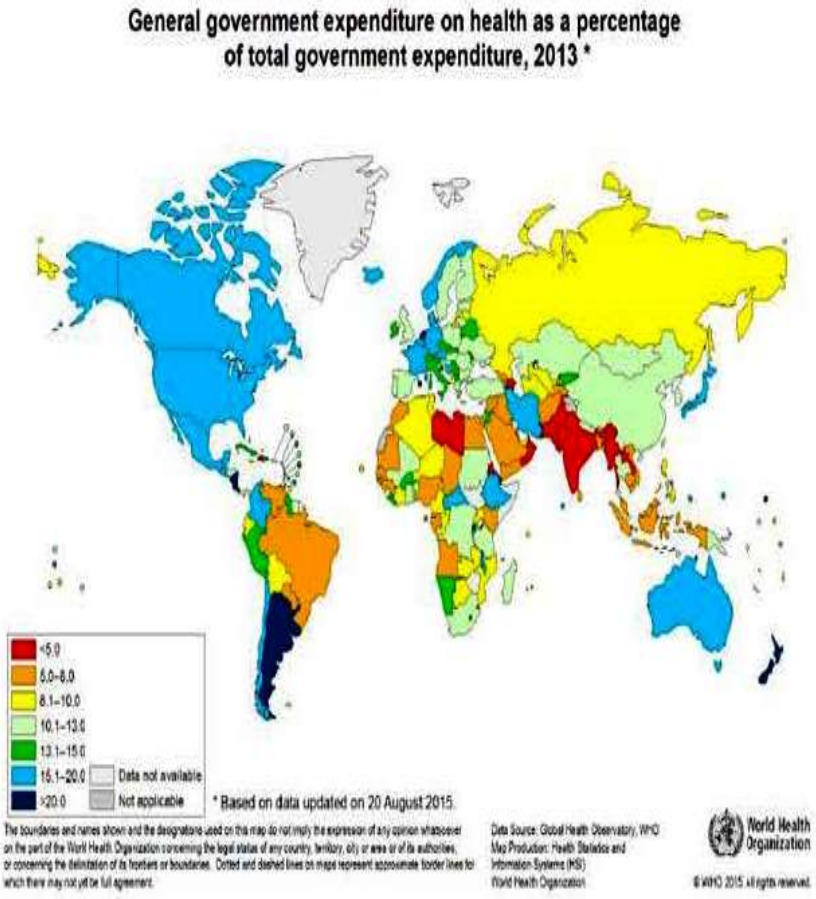
So then, what does all this mean to you folks?

At the end of the day…

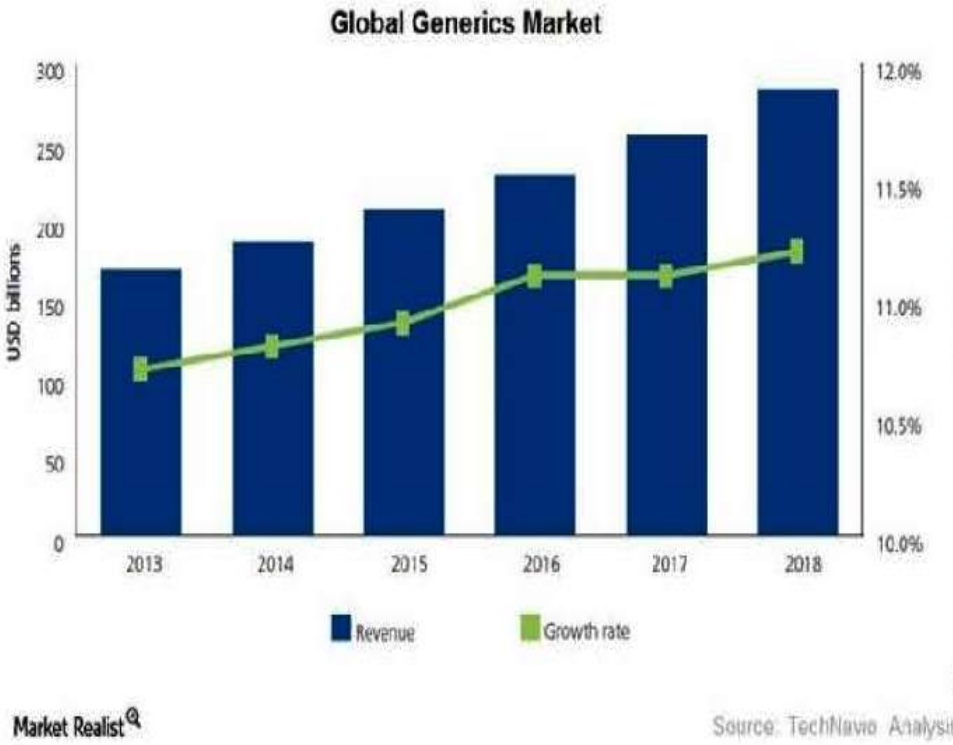
- I would offer that we (e.g., Industry/FDA/ EMA/ Global regulators) may in fact be engaged with basically assessing, if not the same, similar principles of manufacture, the Quality Control tests and verifying that the scientific data supports the conclusions made by a pharma company

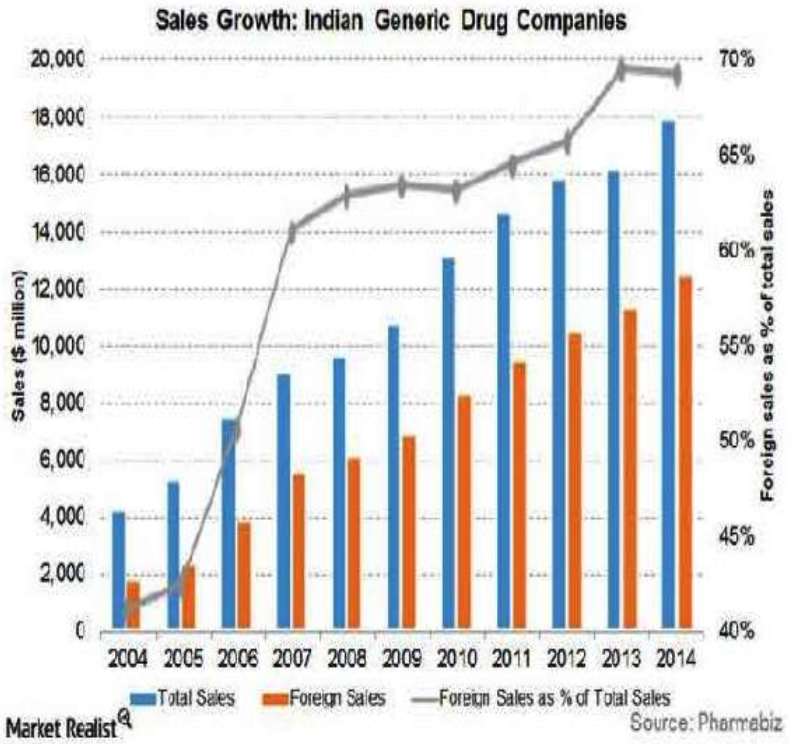
A snap-shot


Drug & Pharmaceutical Investment 2003-2011
= $15 billion
Manufacturing
Office
R&D
HQ
Support Centers
Sales & Marketing
Other


General government expenditure on health as a percentage of total government expenditure, 2013 *
<5.0
5.0–8.0
8.1–10.0
10.1–13.0
13.1–15.0
15.1–20.0
>20.0
Data not available
Not applicable
* Based on data updated on 20 August 2015.
World Health Organization

Let us consider what we know and a few facts





So then, a show of hands

1. How many of you folks perform internal audits, vendor audits?
2. Assess contract manufacturers, Quality Control laboratories?
3. Here's a rhetorical question; You pick your area/subject/topic of your most recent assessment/inspection. What was the outcome of your assessment?
4. And, if you could do something different what would it be and why?

Imagine this is your company and tasks du jour

Consider these imaginary numbers

- an inventory of 2,500 manufacturing sites that need to be assessed
- approximately 450 sites are within country/region;
- 25 – 30 GMP Inspectors;
- assuming re-inspection every 2 – 3 years; = approx. 30 – 60 inspections / inspector / year

Remember…
there's only 92-hours in a day

Global Harmonization - Risk Factors

- More outsourcing of manufacturing overseas
- Greater complexity in supply chains
- Increasing volume of imported products
- Imports coming from countries with less well developed regulatory systems
- Greater opportunities for economic fraud
- Multinational corporations and other companies must consider the risks of contracting and outsourcing across borders

Global Harmonization - Consider

Importance of Quality System (QS)

- QS facilitates compliance with current good manufacturing practices e.g.,
  - ICH Q10 helps bridge GMPs in various ICH regions

- Critical for managing compliance in a global industry
  - Across multiple plants within a multinational corporation
  - Contract manufacturers
  - Global supply chain

Global Harmonization - Consider

Importance of Quality System (QS)

- Quality agreements and contractual arrangements
  - Forethought and good planning!
  - Informed risk assessment
  - Informed decisions
  - Knowledge management
  - Well developed communication system within company and partners in other companies

Global Harmonization

Title 21 CFR 20.89 permits FDA officials to share non-public information with a foreign government or international organization that performs counterpart functions to FDA as part of cooperative law enforcement or regulatory efforts

FDA-European Medicines Agency (EMEA) Good Clinical Practice Initiative August 26, 2009,

FDA-European Medicines Agency (EMEA)
Good Clinical Practice Initiative - August 26, 2009

Confidentiality Arrangement (CA) or Confidentiality Commitment (CC)

- Written formal document or a pair of written documents that contains mutual commitments **not to publicly disclose non-public information** that is exchanged

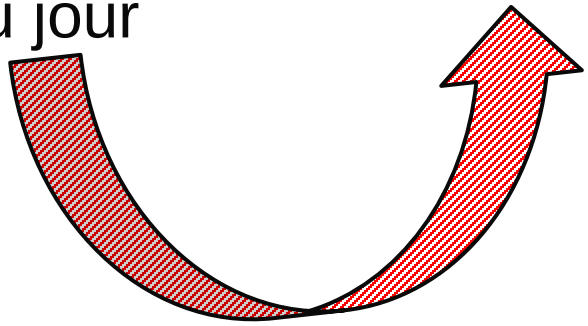
- If both information exchange partners sign a single document, it is usually termed a Confidentiality Arrangement

- If each partner signs a separate document, each document is usually termed a Confidentiality Commitment

FDA Safety and Innovation Act
(FDASIA – July 9, 2012)

Expands the FDA's authorities and strengthens the agency's ability to safeguard and advance public health which includes;

- …*ufa* du jour



- Prescription drug provisions (PDUFA V)
- Medical device provisions (MDUFA III)
- Generic Drug User Fee Amendments of 2012 (GDUFA)
- Biosimilar User Fee Act (BsUFA)

Generic Drug User Fee Program

- In particular has ***emphasis on a level playing field in manufacturing around the world***.
- So we are required under that law to make sure that we have ***equal scrutiny of firms and manufacturing*** no matter where it's going on around the world if they are selling product in the United States. So that's very challenging.
- …we need to ***work with other regulators***, but that means ***greater harmonization***, that means a lot of work in getting our inspectional standards more uniform…

Dr. Janet Woodcock (FDA/CDER)
Speech at ISPE - 2013

Generic Drug User Fee Program

- …I already alluded to the need for harmonization. The world cannot go on this way simply having all these regulatory programs with different requirements, particularly for manufacturing…So it's going to be very challenging, though, to figure out how to harmonize these efforts, and my team and others' folks are converging

- It's clear that FDA is no longer a domestic agency. We are to protect the domestic population, but ***we must go all around the world, or collaborate with the whole world, in order to effectively achieve our mission***.

Dr. Janet Woodcock (FDA/CDER)
Speech at ISPE - 2013

Global Harmonization

Regulators collaborating globally

- FDA joins Pharmaceutical Inspection Co-operation Scheme (PIC/S).
- FDAs "Pathway to Global Safety and Quality" for systems to collect and share data between competent authorities across the world.
- The Food and Drug Administration Safety and Innovation Act (FDASIA), Title VII

PIC/S consists of 49 member countries – regulatory/health authorities

- Considerations that are being discussed –

1. Reliance of inspection conducted by recognized regulators;
2. What would be the minimum information needed to approve or not-approve a manufacturing facility/application?

an example

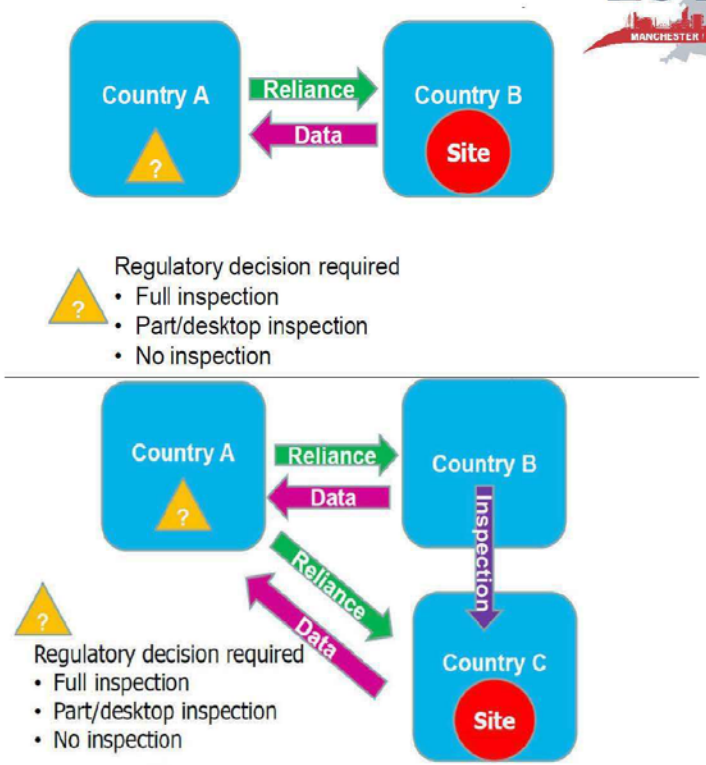
ICMRA – Mutual reliance framework

Initial Phase - 2 streams:

- Equivalency: determining the level of 'trust' that can be placed in the local regulator
- Data Requirements: what information is needed to contribute to an informed regulatory decision

Hypotheses tested

- Pilot: is utilisation of framework possible?
  ✓ Yes



Assuring Drug Quality through International Agreements

- **FDA-regulated products originate from more than:**
  - 150 countries
  - 130,000 importers
  - 300,000 foreign facilities

- **Number of FDA-regulated shipments at 300 U.S. ports has more than doubled during the last ten years.**
  - In 2006, approximately 15 million shipments of imported food and medical products crossed our borders. In 2015, 34 million.

Dr. Robert M. Califf, Commissioner U.S. Food & Drug Administration – 6/22/16

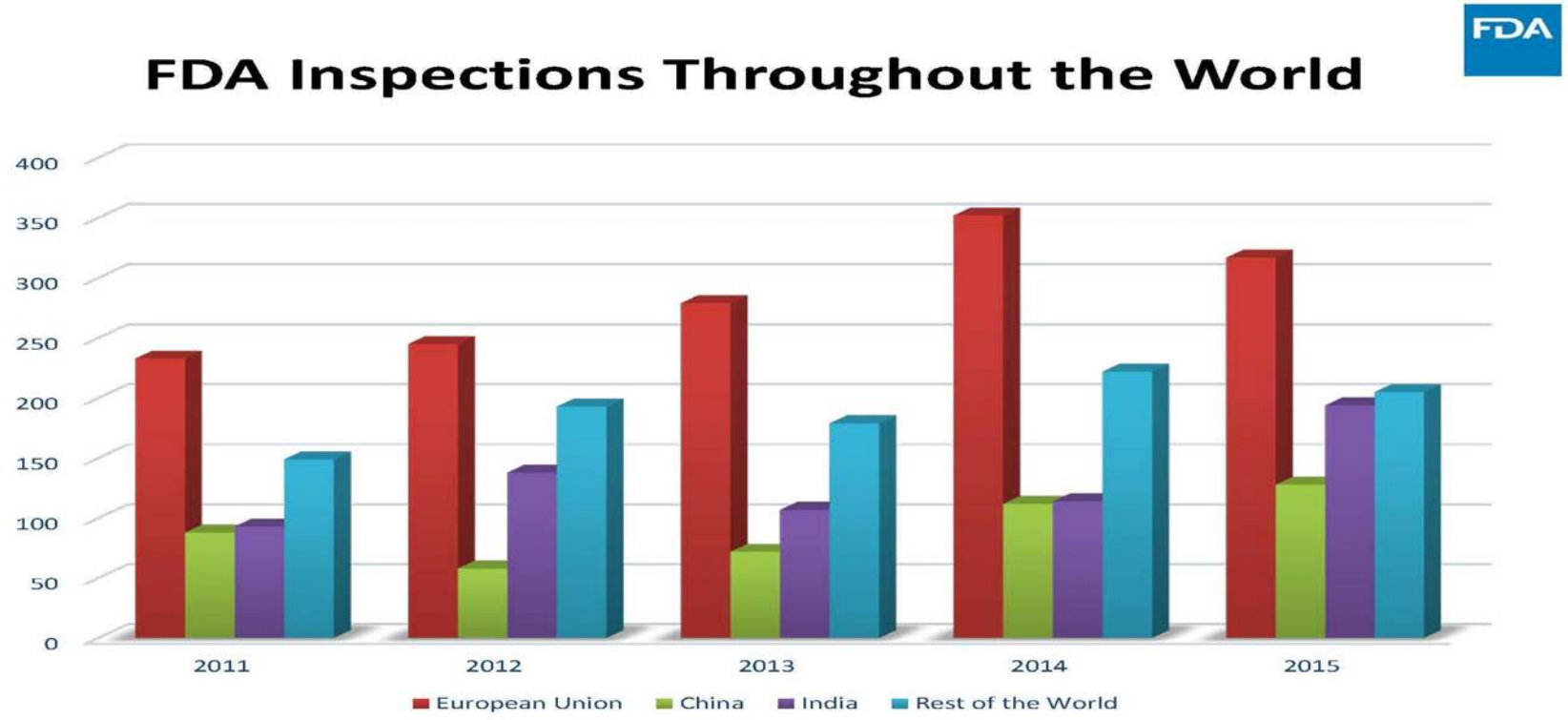
Assuring Drug Quality through International Agreements

- **Drugs and Devices**
  - Today, about 35% of medical devices Americans use are made overseas.
  - And approximately 80% of the manufacturers of active pharmaceutical ingredients (APIs) used in the U.S. are located abroad.

- **Food**
  - Approx. 15% of food consumed by U.S. households is imported.
  - Approx. 50% of fresh fruits and 25% of fresh vegetables consumed by U.S. households are imported.
  - Approx. 85% of seafood eaten domestically comes from outside the U.S.

Dr. Robert M. Califf, Commissioner U.S. Food & Drug Administration – 6/22/16

Assuring Drug Quality through International Agreements



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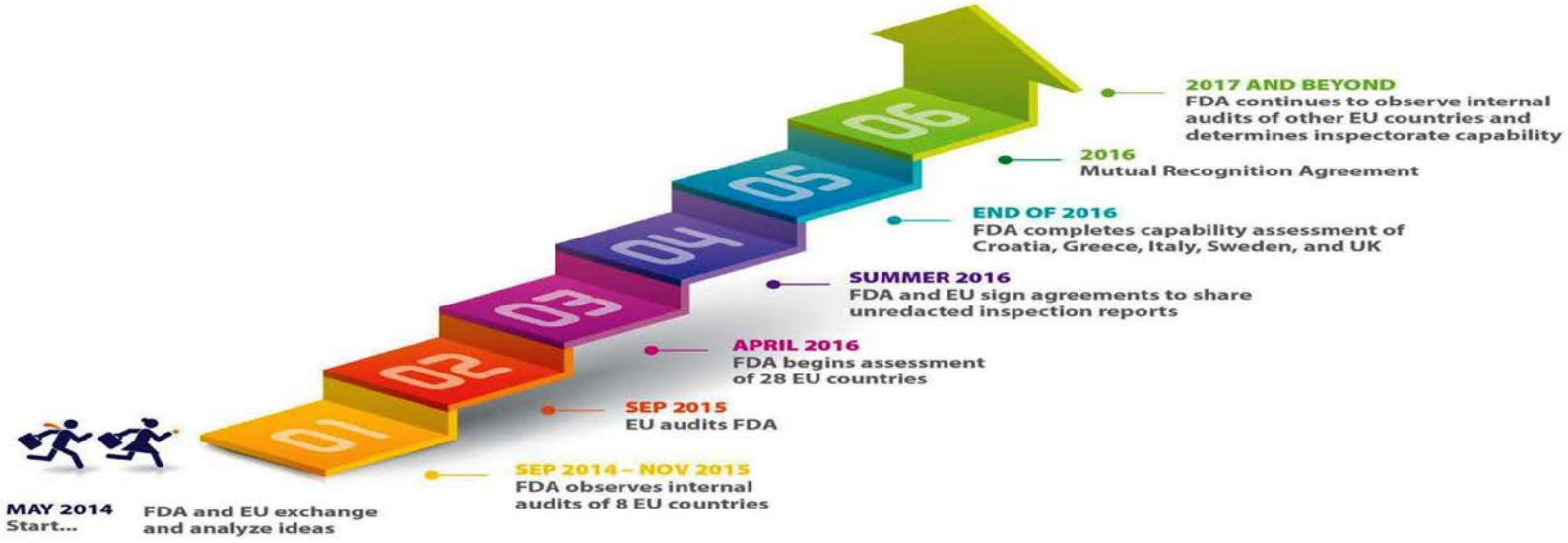
Dr. Robert M. Califf, Commissioner U.S. Food & Drug Administration – 6/22/16

Assuring Drug Quality through International Agreements

How Are We Getting There?



Dr. Robert M. Califf, Commissioner U.S. Food & Drug Administration – 6/22/16

What does all this mean ?

In my opinion;

- We will continue to collaborate with other regulatory bodies;
- Partner and/or leverage of our respective regulatory resources (e.g., inspection reports/scientific data);
- Which, may include considerations with respect to the minimum requirements / scientific data that is needed to approve the regulated commodities;

What does all this mean?

- With regards to "***regulatory reliance***" this may require consideration with respect to a more standardized manner of performing inspections / scientific review the varied medical product applications;
- The inspection team may consist of multiple scientific and regulatory disciplines; and
- With regards to capacity building and continual development of regulatory confidence, the inspection teams may consists of multiple regulatory bodies;

Global Harmonization

- It's not an ***"if"*** we will work with other regulators but rather…it "***is***" occurring.
  - ✓ Ultimately, it will provide in support of having safe commodities, a regulatory reliance based on the scientific & collective data provided by other regulatory authorities;
  - ✓ Which in turn would offer all of us (Regulators & Industry) an opportunity to reallocate/refocus some of our resources for other priorities.


Q&A

references

- FDA-European Medicines Agency (EMEA) Good Clinical Practice Initiative - Patricia M. Beers Block, B.S., B.S., CCRP, Cynthia F. Kleppinger, M.D. Field Drug Committee Meeting August 26, 2009;
- "Effective Leadership for a Robust Quality System" - Deb Autor, Esq. Director, Office of Compliance Center for Drug Evaluation and Research, CHPA - Manufacturing Controls Seminar New Brunswick, New Jersey, October 13, 2010
- FDA Safety and Innovation Act (FDASIA) July 9, 2012;
- Dr. Janet Woodcock (CDER) Speech at ISPE – 2013;
- Dr. Robert M. Califf, Commissioner U.S. Food & Drug Administration – 6/22/16;
- PIC/S International Conference on *"Inspectorate of the Future"* Manchester, UK July 5 – 8, 2016;
- "*Working Together*" Harry Rothenfluh, PhD., Manufacturing Quality Branch, Therapeutics Goods Administration (TGA) Australian Department of Health July 7, 2016 / PIC/S July 2016.

Thank You

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