



# Substandard Drugs within the Global Market

## (Recent Examples & FDA Efforts)

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# Agenda

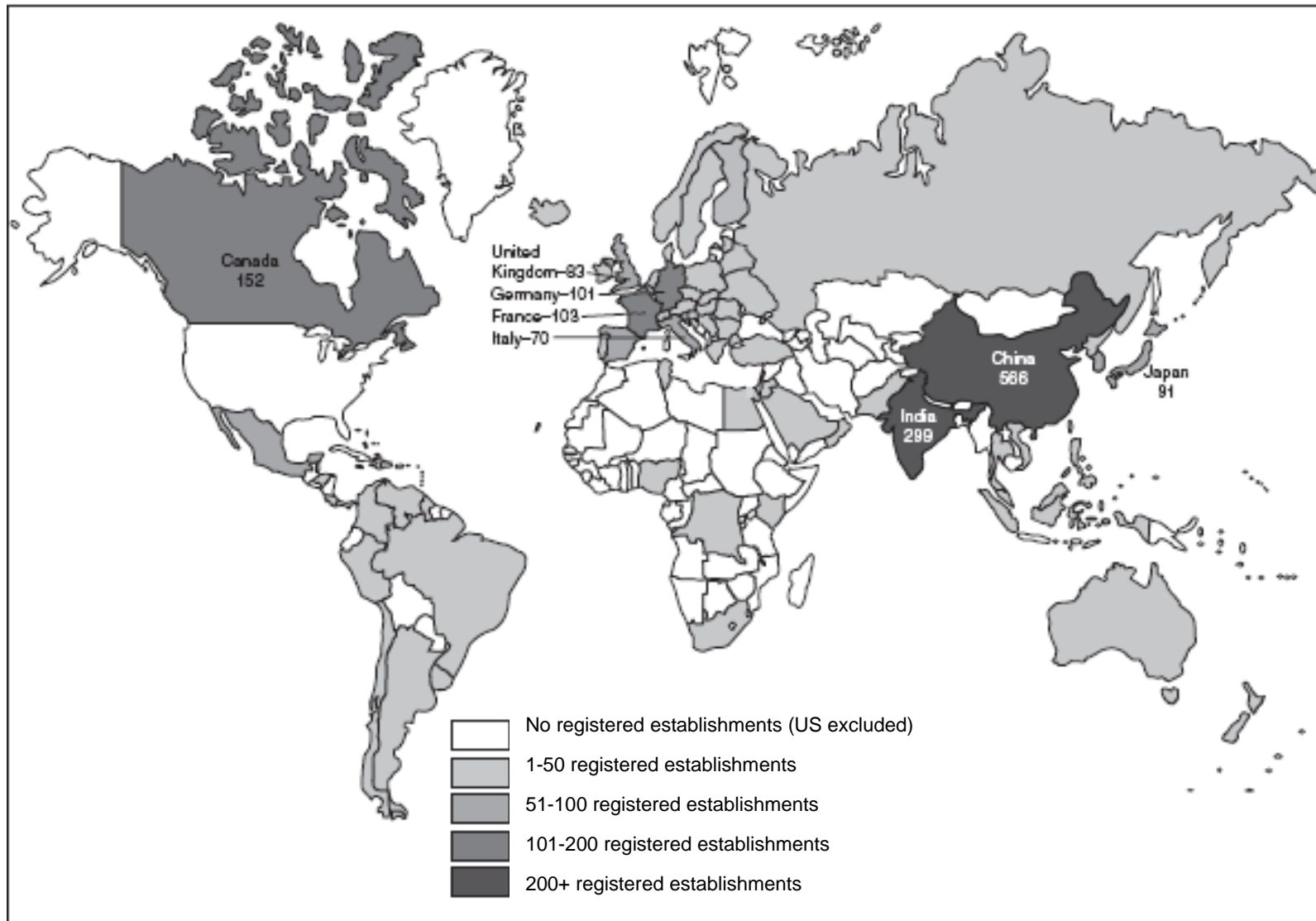
- Globalization and Supply Chain Complexity
- Current Findings (*domestic and foreign*)
  - GMP Observations by Region
- Addressing Globalization
  - International Collaboration



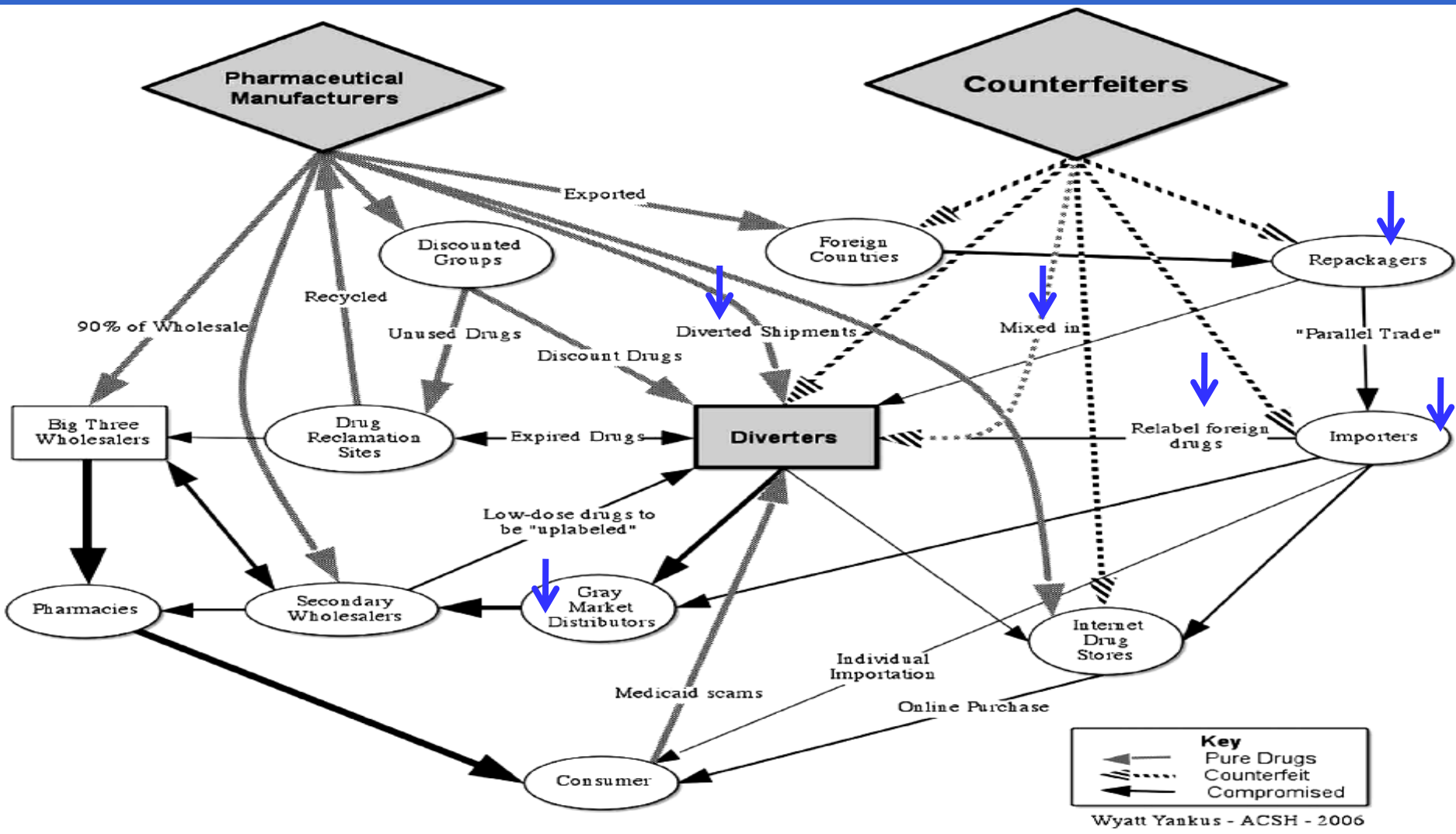
# Globalization & Supply Chain Complexity

(Looking at the numbers)

## Challenges of Globalization: Many U.S. Drugs Are Produced Abroad



# Drug Supply Chain: Complexity & Hazards



Ref.: The American Council on Science and Health, August 2006, Counterfeit Drugs

[http://www.acsh.org/docLib/20060825\\_CDmgW\\_condensed.pdf](http://www.acsh.org/docLib/20060825_CDmgW_condensed.pdf) <http://acsh.org>



# Recent GMP Inspectional Findings *(paraphrased)*

# Warning Letter

## *API Manufacturer*

- The **vendor qualification program** should establish that your upstream material supplier (crude drug) can **consistently** provide reliable and **safe** materials. Suppliers should be regularly scrutinized to assure **ongoing reliability**.
- Insufficient impurity testing of each batch
- Failure to establish an adequate impurity profile

# Warning Letter

## *API Manufacturer*

- A complaint identified potential contamination with Over-sulfated Chondroitin Sulfate (OSCS) in Heparin Sodium, USP, lot \*\*\*\*\* in October, 2008. Your firm did not initiate formal investigation until September, 2009.
  - Failed to investigate complaints about OSCS and extend the investigations to other lots that used the same crude lot.
- Firm used a **contract lab** to perform testing of another API. This lab **reported passing values to your firm.** However, FDA inspection of this lab revealed failing test results. The firm failed to conduct an audit that could have possibly caught the problem **before data was submitted as part of an application.**

# Warning Letter

## *Clinical Supply Manufacturing Facility*

- Inspection of your clinical supply manufacturing facility (parenterals), identified significant violations of Current Good Manufacturing Practice regulations:
  - Failed to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair
  - **Mold observed during the inspection**
    - On wall in component preparation room, which was adjacent to the Aseptic Filling Room. Mold was identified as *Penicillium, sp., Chaemotomium sp.,* and *Allewia sp.*
  - Failed to thoroughly investigate the cause of **repeated leaks of heat transfer fluid in your lyophilizer** and its impact on product.
  - Routinely failed to adequately investigate & identify root causes when environmental monitoring data exceeds the action limit.

# Warning Letter

## *OTC Manufacturer*

- Firm's management, including the Quality Control Unit, was not **responsive to adverse trend** of customer complaints.
- Failure of your Quality Control Unit to ensure a thorough investigation with conclusions and follow up accomplished (two deviations, both **211.192 and 211.198**)
- Failure to submit NDA-Field Alert Reports (**FARs**) within three (3) working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other changes or deterioration in the distributed drug products as required by 314.81(b)
- **Senior management (includes corporate in this case) is responsible for ensuring the quality, safety, and integrity of your firm's drug products.**

# Warning Letter

## *Contract Manufacturer*

- Your firm failed to assure adequate process design and control of three emulsion injection products to prevent objectionable particulate contamination (primarily stainless steel).
- “We note that the CGMP violations listed in this letter include a similar violation (failure to identify actions needed to correct and prevent the recurrence of defective product) to the violation cited in the 2009 Warning Letter to your company’s facility located at another location. It is apparent that your company’s attempts to implement global corrective actions after past notifications by the FDA have been inadequate. Be advised that corporate management has the responsibility to ensure the quality, safety, and integrity of its drug products and devices.

## PAI Withhold

### *Computer Validation*

- FDA Inspectional Findings
  - Inspection found that NMR testing **files could be deleted.**
  - **Also, no audit trail for the spectra** acquired by the NMR.
- Specifics:
  - No audit trail for computer system running heparin purity test
  - **Electronic data is the original raw data.** Firm stated that they had used the hardcopy data as official information and it was archived. Investigator audited electronic files, and found multiple electronic spectra with no corresponding **spectra in the hardcopy archive.**
  - NMR instrument also not qualified (no IQ, OQ, or PQ).

## Warning Letter *API Manufacturer*

Your Quality Unit failed to discover, document and investigate the data altering practices and poor documentation practices at your facility. Specifically, the practice of scraping off or erasing original data from production batch records is pervasive throughout your facility.

Our investigators documented over **30 production batch records (approximately 80% of the records reviewed)** that contained evidence of original data such as dates, signatures and temperature, test results, weights, volumes and time being removed, and new data entered. The data alteration was done without an explanation of why the data was changed.....

# Shadow/Show Factory

- The inspection revealed that the facility was **not** manufacturing, and did not appear to have ever manufactured, XXXXXX for the U.S. market.
- The investigators also determined that, **contrary** to your firm's claims, manufacturing of XXXXX was conducted at facilities **other than the one identified in your DMF**.
- FDA inspections of both your facility and of **subcontractor** XXXXXX, along with additional information, uncovered untrue statements and information submitted by your firm to the agency with respect to the actual manufacturer (s) of XXXXX.
- Our inspection found **that two other facilities have performed manufacturing and testing of XXX in place of your facility since 2001**.
- Your firm lacked laboratory testing records for the XXXXX released from your facility to the U.S. to demonstrate that each batch met specifications.

## Contract Manufacturer

### *Large Volume Parenterals (IV Bags)*

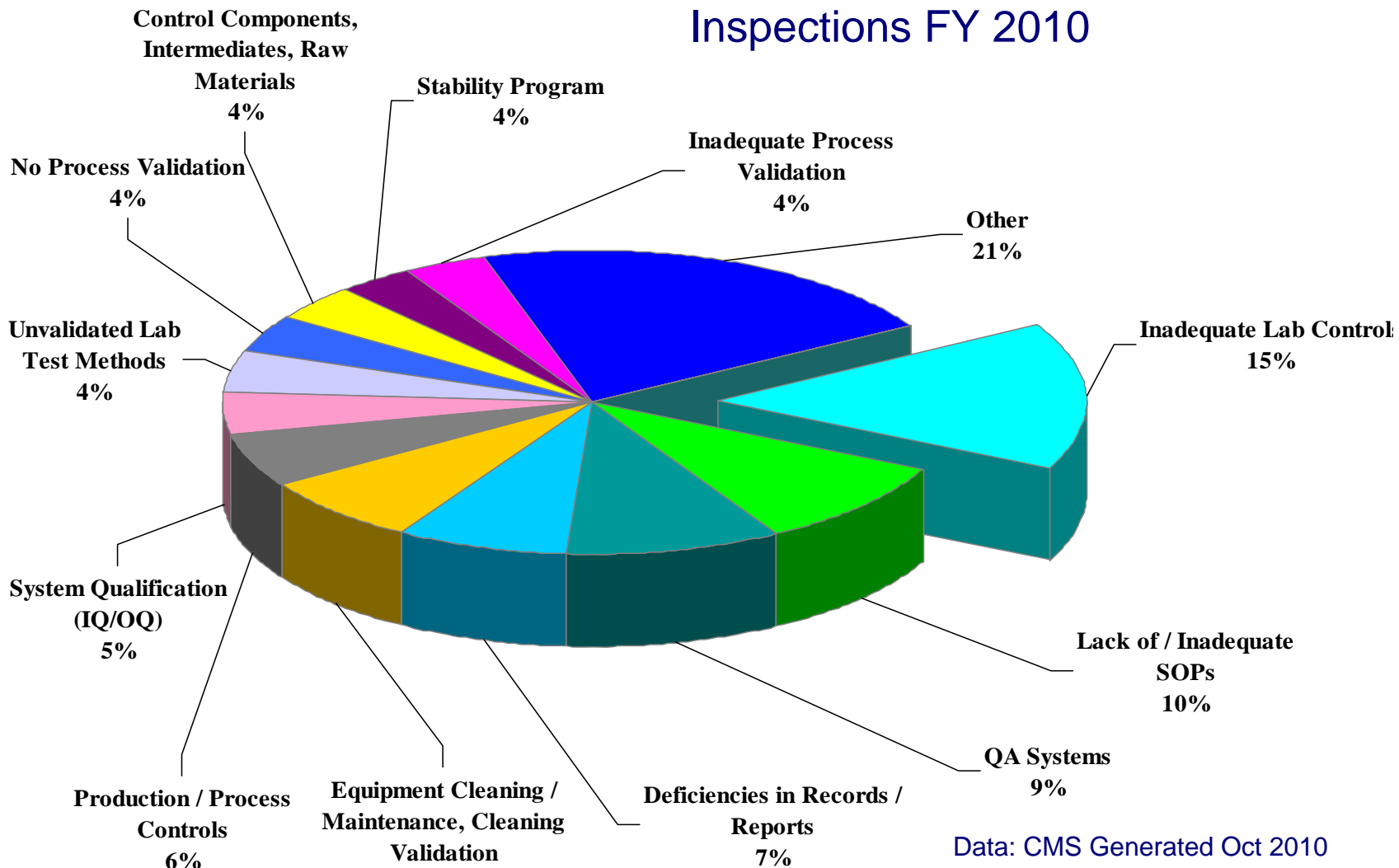
- FDA notified of contaminated intravenous bags in distribution chain. Visible microbiological contamination in the IV bags
- Found by the end user (hospitals/clinicians)
- Customers found swirling mass of fungi (e.g., *Cladosporium, sp. and Mucor, sp.*) and bacteria
- All product on market was recalled (Class I). Three US Customers.
- Contamination attributed to sharp edges on equipment making micro-holes in the IV bags during the printing operation. Leakers resulted.
- Risk can be eliminated through use of a non-implosion printer. 100% leak testing (non-destructive) also can be done.
- FDA quickly placed firm under Import Alert for all sterile products. Warning Letter issued for GMP, FAR, ADE's, and Unapproved New Drugs violations.

# Warning Letter

## *Contract Manufacturer*

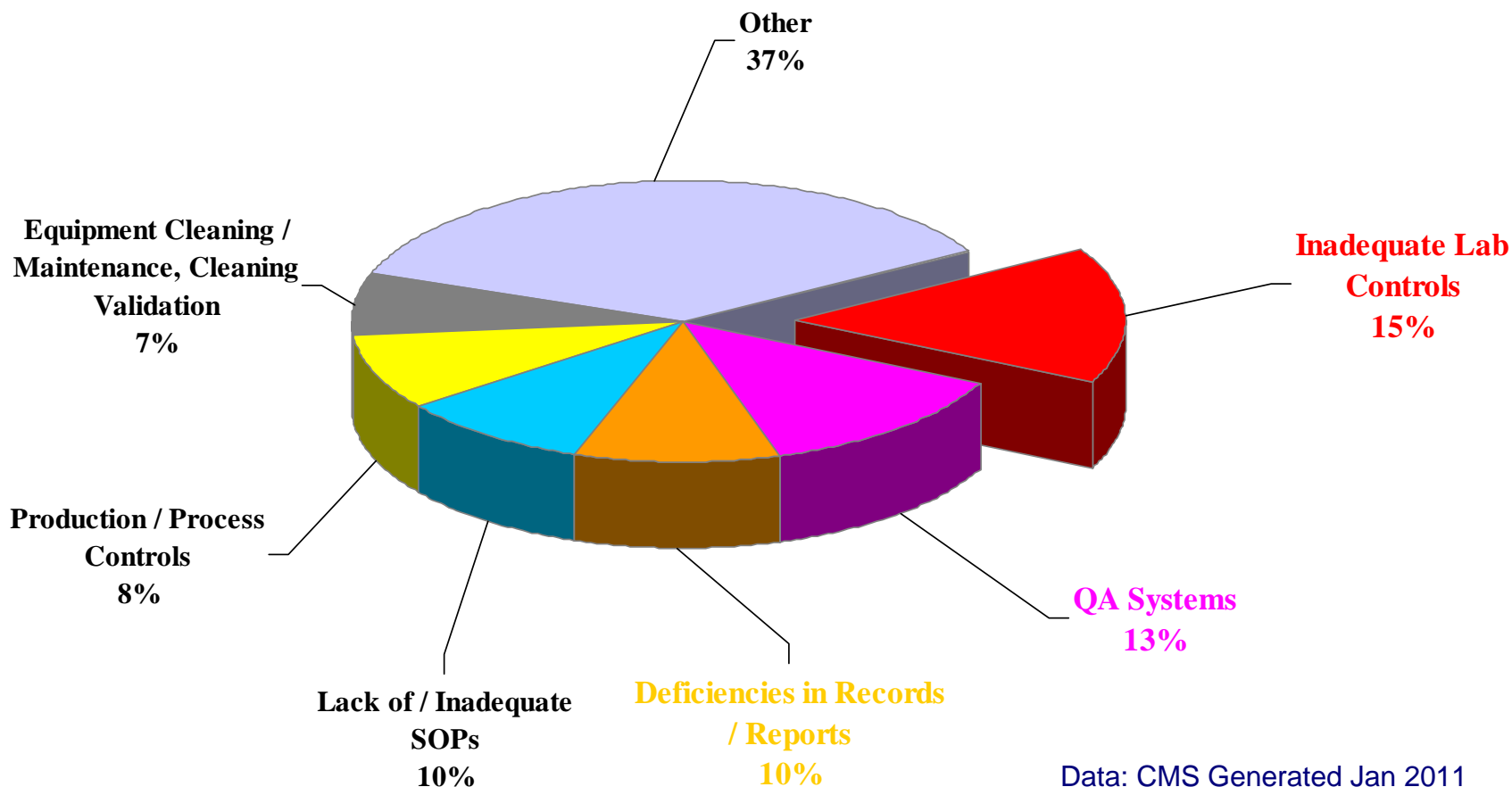
In 2009, multiple batches of ---- powder for suspension failed either the **assay or dissolution** tests prior to release. Your OOS investigation reported that there were no errors in analysis and that the OOS results were **confirmed**. However, your firm did not report the OOS as the final result, as required by your OOS investigation procedure, but instead invalidated the failing results after obtaining results from a re-sample of the batches. These batches were released for distribution.

## CGMP Deficiencies Cited During International Inspections FY 2010

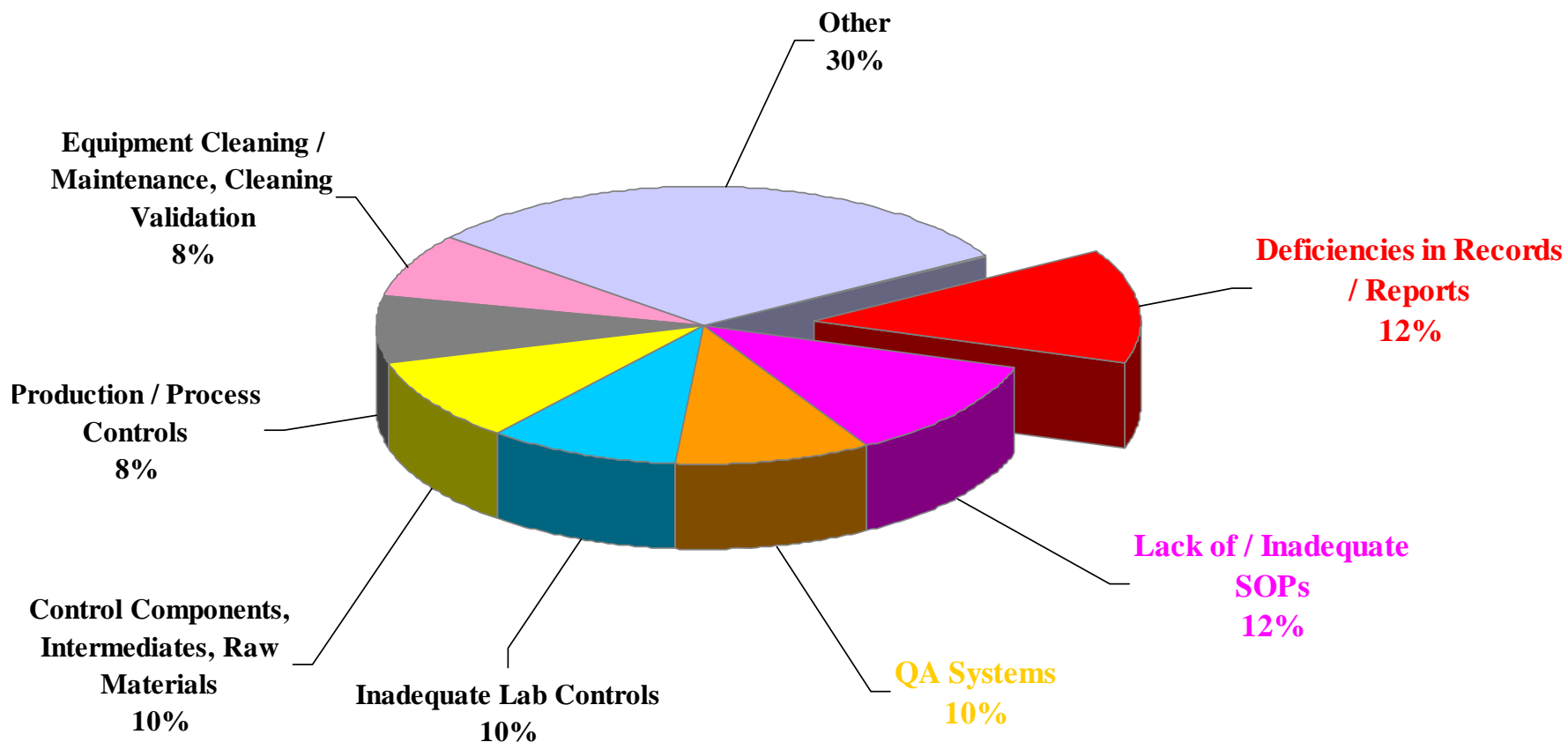


Data: CMS Generated Oct 2010

## CGMP Deficiencies Cited During Inspections in Europe, CY 2010

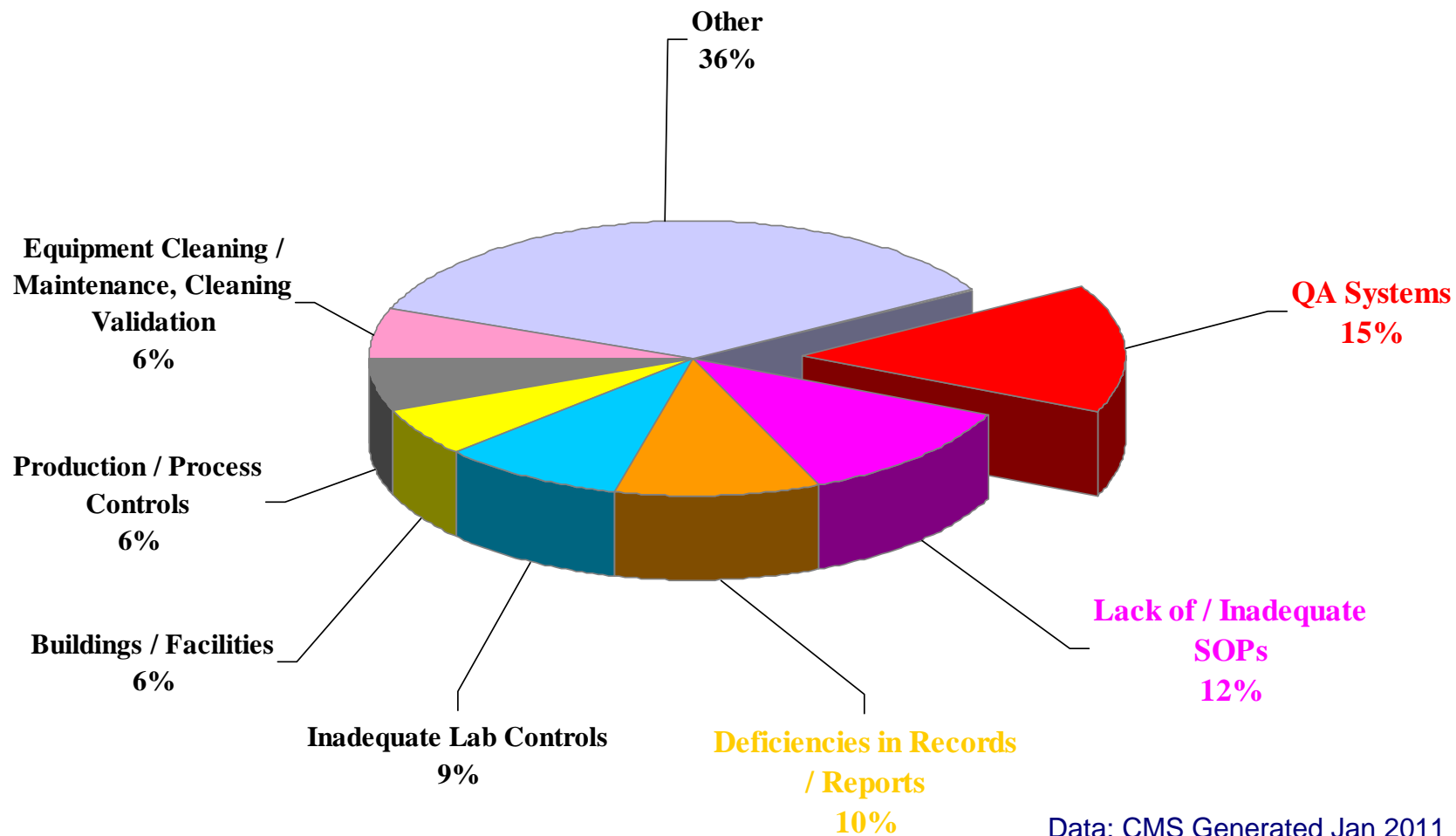


## CGMP Deficiencies Cited During Inspections in China, CY 2010



Data: CMS Generated Jan 2011

## CGMP Deficiencies Cited During Inspections in India, CY 2010



# Comparison

- Common Top Deficiencies
  - Documentation Issues
    - Deficient Records and Reports
    - Lack of or Inadequate Procedures
  - Lack of or Inadequate Procedures
  - QA Systems
  - Inadequate Lab Controls
- Differences
  - China: Control of Components, Intermediates & RM
  - India: Buildings & Facilities and Equipment Cleaning & Maintenance
  - Europe: Production & Process Controls

# How does this help?

- Benefits:
  - Scheduling/Sending appropriate staff
  - Collaboration efforts with foreign regulatory authorities
  - Center support of In-Country Staff
  - Focused trainings



# Efforts to Ensure Global Coverage

## (International Collaboration)

# International Collaboration

- API Program
  - EMA / TGA
  - Focused on information sharing, Inspection Report exchange
  - Limited Joint inspections
  - Focused on countries outside of the US and EU
  - Pilot ended Dec 2010, Final Report to be Issued
  - Post Pilot: Regular business practice

# International Collaboration

- Finished Drug Pilot
  - EMA
  - Focused on Joint Inspections
  - Focused on US and EU firms/facilities
  - Currently a pilot, following the success of the API Pilot
  - Continued Inspection Report exchange

# FDA's In-Country Offices/Staff

Office of International Programs (OIP) has established In-Country offices to:

- Educate and collaborate with local regulatory authorities
- Out-Reach to pharmaceutical industry
- Ability to conduct expedited inspections for ORA or CDER

China and India offices have Drug specific staff

# In-Country Staff and ICB

- Regularly Scheduled teleconferences
  - Recent global or local emergencies affecting the region
  - For Cause assignments / Informants
  - Active Case Review
  - Training Assistance, based on Industry or Local Authority needs
  - Coordinate Communication

# Acknowledgements

- Rick Friedman
- Carmelo Rosa
- Raphael Brykman
- Beth Philpy
- Brian Hasselbalch
- Deb Autor
- Leslie Ball
- Teddi Lopez
- Grace McNally



# Thank You. Any Questions?

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