CDER Update

University of Georgia GMP Conference
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Richard L. Friedman
Director, Division of Manufacturing and Product Quality
Office of Compliance
FDA/CDER

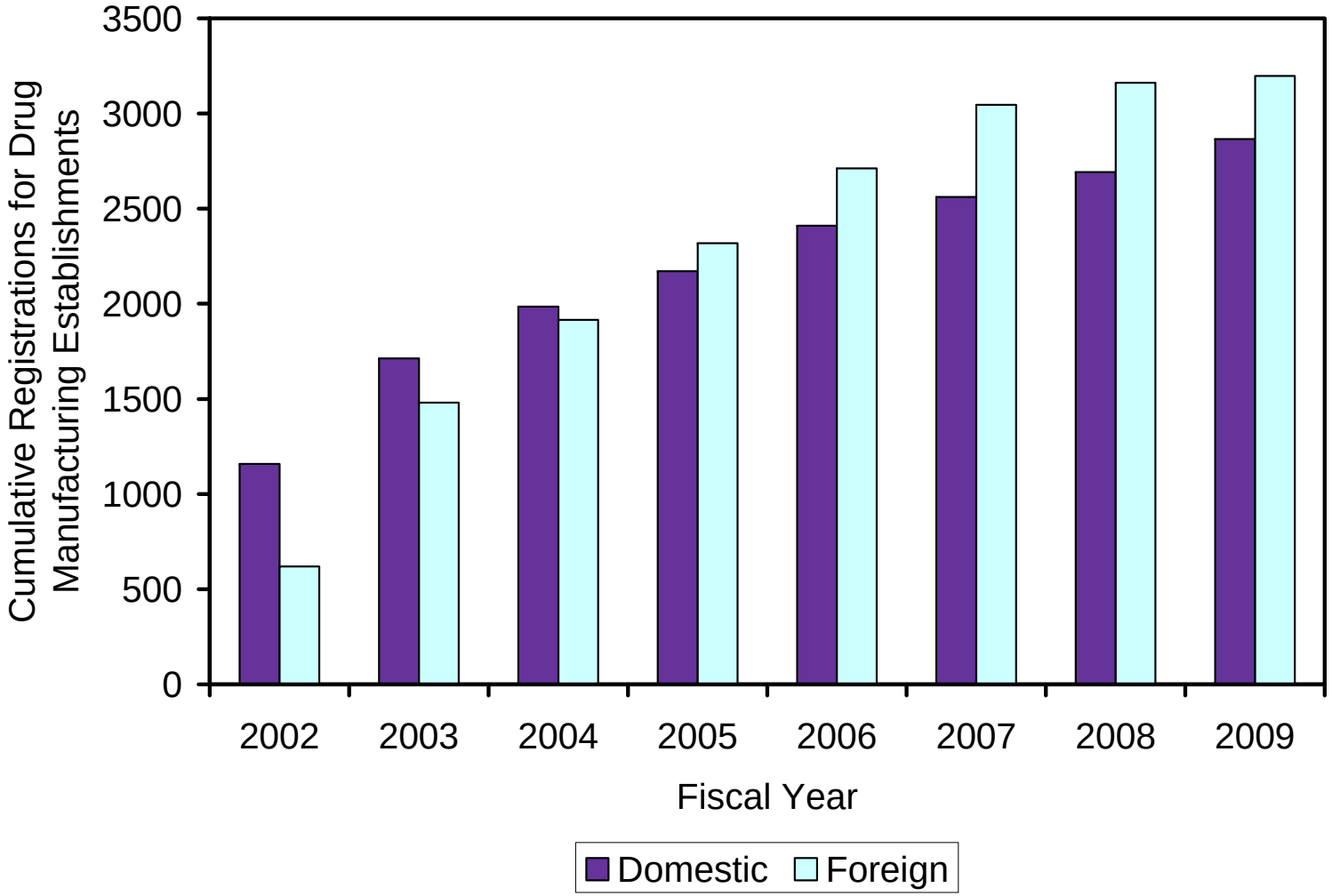
Themes

- Major Themes:
  - Globalization Statistics
  - Supply Chain
  - Contracting and Outsourcing (GXP)
  - Current Findings *(domestic and foreign)*
- Sub-themes:
  - Supplier management
  - Data Integrity
  - “State of Control”
  - Senior Management Responsibility for Quality

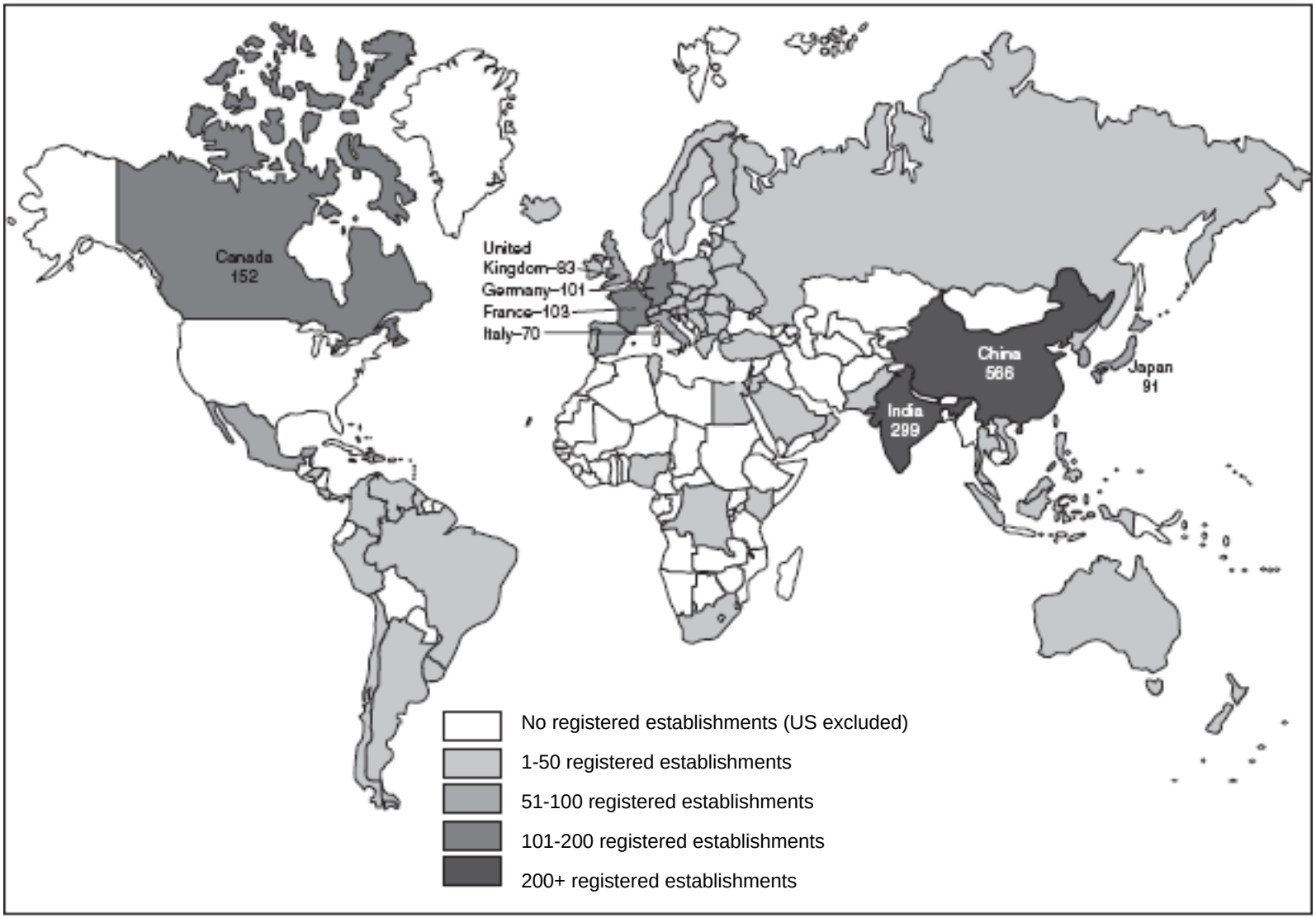
FDA Drug Shortage Program

- Shortages can have a significant impact on US patients
- Increasing shortages of Medically Necessary drugs
  - Mainly sterile injectables: 74% of 178 shortages in 2010
  - 54% of the injectable shortages were due to product quality issues (particulate, microbial contamination, etc).
- Industry's responsibility:
  - Commitment to quality: proactively identify and promptly correct issues
  - Assure that patients can rely on your firm to ensure Availability of safe, effective drugs
  - Prevent sudden lack of lifesaving medications for US consumer
  - Plan ahead by adding redundancy to manufacturing & raw material supply to prevent shortages of MN drugs (flexible regulatory approaches possible)
  - Notify FDA as soon as aware of an issue that could impact supply. Contact Drug Shortage Program at drugshortages@fda.hhs.gov

Challenges of Globalization: Registered Drug Manufacturing Firms

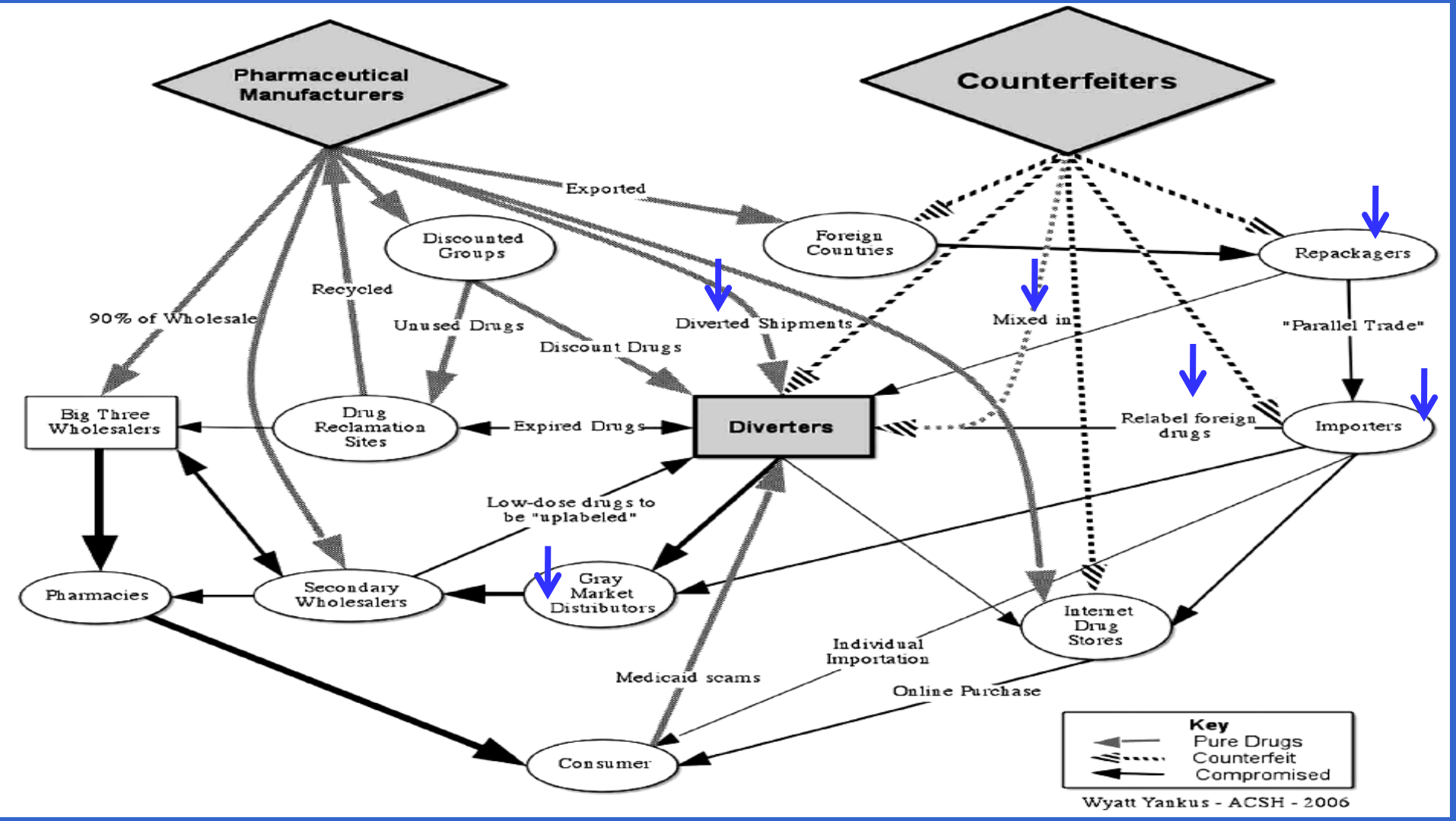


Challenges of Globalization: Many U.S. Drugs Are Produced Abroad



(Source: GAO Report 08-224T on Drug Safety. **Foreign** firms registered to manufacture drugs for the U.S., FY2007)

Drug Supply Chain: Complexity & Hazards



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

http://www.acsh.org/docLib/20060825_CDrugW_condensed.pdf http://acsh.org

There Are *192* Foreign Facilities Currently Requiring a Pre-approval Inspection (PAI), but There Are *62* Foreign PAIs in the FY2011 Work Plan

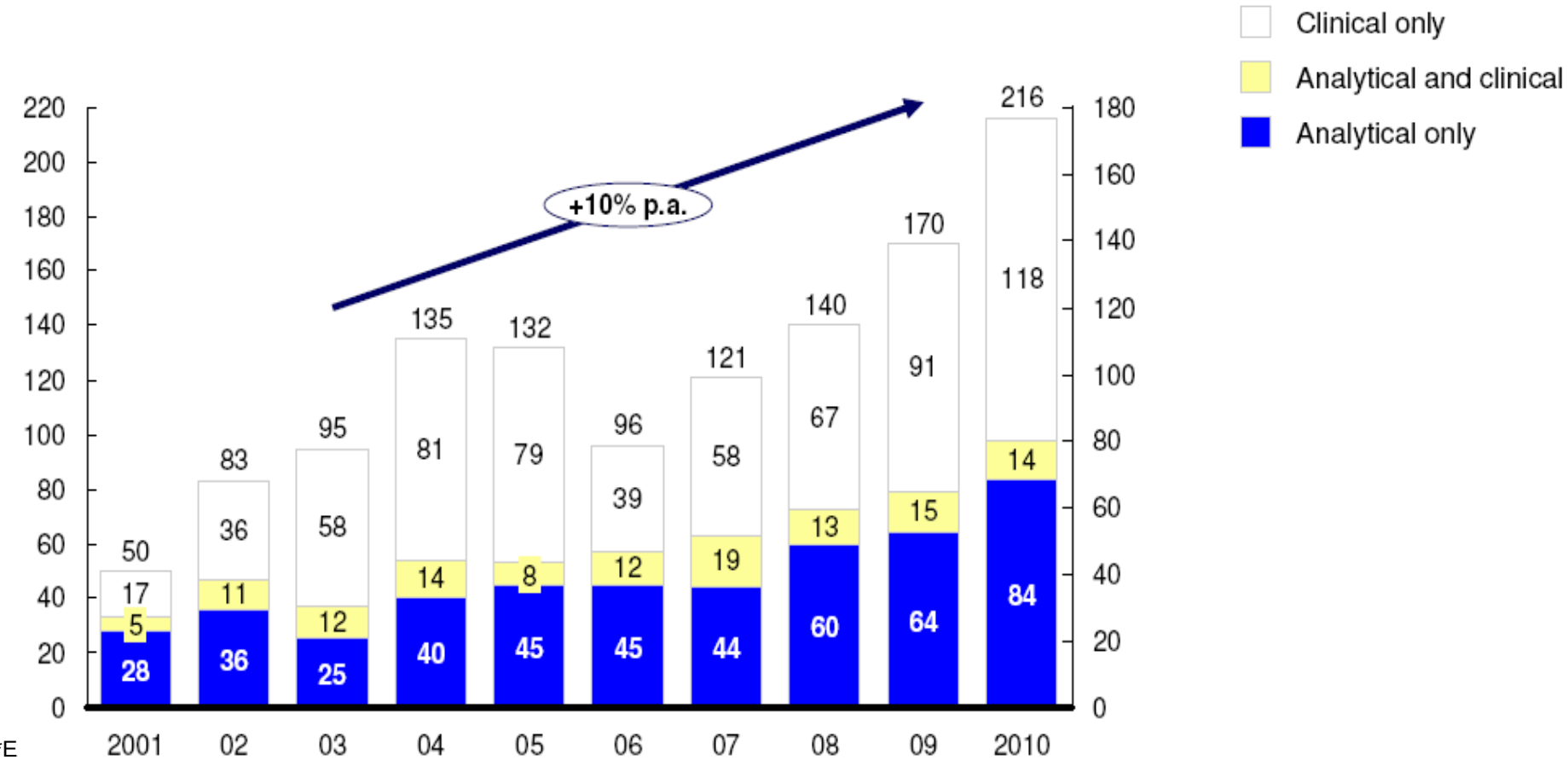
	Number of PAIs Allotted in the FY 2011 Workplan	*Facilities Pending PAI as of 25-JAN-2011*
Domestic	47	39
Foreign	62	**192**

- The **192 foreign facilities** requiring pre-approval inspection affect ***354 ANDA submissions***
- The **39 domestic facilities** requiring pre-approval inspection affect ***61 ANDA submissions***

(Data Generated: 25-JAN-2011; Data Source: EES)

Total Number of BE Site Inspection Requests has Grown Through the Last Decade, Including Rapid Growth of Clinical Only Inspections in Recent Years

Site inspection requests*
Number per fiscal year



*E

Source: BE database; team analysis.

Reporting Information Regarding Falsification of Data

- Proposed rule published February 19, 2010
  - http://edocket.access.gpo.gov/2010/pdf/2010-3123.pdf
- Requires sponsors to promptly report information to FDA about known or suspected falsification of data in the course of:
  - Reporting study results or
  - Proposing, designing, performing, recording, supervising, or reviewing studies
- Applies to studies with human or animal subjects, whether
  - conducted by or
  - on behalf of a sponsor or
  - relied on by a sponsor

GMP Inspection 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 Oversulfated 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

Failure of your quality unit to ensure that materials are appropriately tested and the results are reported. For example, your firm used the infrared spectra for Lot #----, to support the release of two subsequent incoming lots, # --- and # ---. Laboratory analyst modified printed raw data related to the IR Spectra test results.

Your firm used this single IR spectra for one lot to release two different subsequent incoming lots. This practice is unacceptable and raises serious concerns regarding the integrity and reliability of the laboratory analyses conducted by your firm.

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
- Severe risk detected by the customer (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 of stereos used in printing operation. Caused microholes in IV bags. Leakers ➔ non-sterility
- Cause can be eliminated by using Non-impression printer. Today's technology also provides for non-destructive 100% leak testing of all IV bags.
- FDA quickly placed firm under Import Alert for all sterile products. Warning Letter issued for GMP, FAR, ADE, and Unapproved New Drugs violations.

Warning Letter

Contract Giver…

We are concerned about your understanding of the regulatory expectations, including the quality unit role, for a firm that enters into agreements with contract manufacturers to manufacture all drug products. Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), you are ultimately responsible for the quality of your products. Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the Act and its associated regulations.

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.

Process Validation Guidance Finalized

Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

Final PV Guidance

For purposes of this guidance, ***process validation*** **is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.**

Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

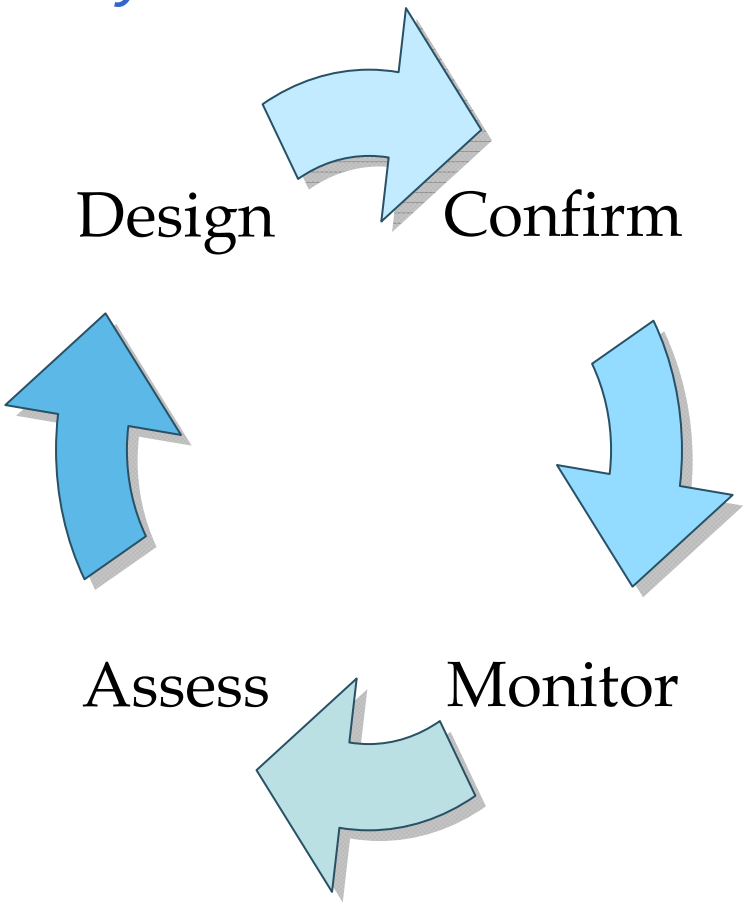
- Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a **state of control.**

This guidance describes activities typical in each stage, but in practice, some activities in different stages might overlap.

Building Knowledge

Process Validation Lifecycle

- Replication at full scale provides initial assurance of commercial process reliability. (Stage 2)
- Validation includes lifecycle monitoring (Stage 3). **Post-market information gathering, promotes maintenance of a stable process** and identifies areas for continual improvement and **adaptation**.
- Our Compliance Policy Guide on Process Validation, and the new Process Validation Guidance, recognize the value of **advanced engineering principles and control technologies**.



Stage 3 - Continued Process Verification (maintaining “state of control")

CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, **will allow detection of undesired process variability.** Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).

Key CGMPs for Process Validaton

211.100(a)

211.42

211.160(b)

211.110(a)

211.63

211.165(c)

211.110(b)

211.68

211.165(d)

211.84

211.180(e)

Process Validation: Lifecycle Stages

Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and *scale-up* studies to establish process based on knowledge	Functional understanding between parameters (material and process) and quality attributes
Stage 2: Process Qualification	
▪ Facility, utilities and equipment ▪ Performance Qualification (*evaluate* commercial process design)	Scientific measurable evidence that ▪ product meets specifications consistently ▪ process performance reproducibly meets appropriate limits and standards
Stage 3: Continued Process Verification	
▪ Monitor, collect information, assess during commercialization ▪ **Maintenance, continuous verification, process improvement**	▪ ***prompt* actions to maintain or improve control** ▪ reduce product and process variability

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