

Current Good Manufacturing Practice & Drug Manufacturing Quality

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Agenda

- Introduction to CGMP
- Data Integrity Basics
- Most Frequently Cited Drug CGMP Observations
- CDER Compliance Program



Brief Introduction to CGMP

Legal Framework

- Congress says what is mandatory in the Act (FDCA or PHSA, etc.)
- Secretary (delegated to FDA) promulgates regulations that indicate details about what is required by the Act (21 CFR Parts 210 & 211, 600s, etc.)
- Guidance documents describe FDA's current thinking on a particular topic
 - Not binding on FDA or any party

What Is A Drug?

The term “**drug**” means¹ ...

- A) An article ***recognized*** in the US Pharmacopeia (USP) or Homeopathic Pharmacopeia of the US (HPUS) or National Formulary (NF).
- B) Articles ***intended*** for use in the ***diagnosis, cure, mitigation, treatment, or prevention*** of disease in man or other animal.
- C) Articles (*other than food*) ***intended*** to affect the structure or function of the body of man or other animal.
- D) Articles ***intended*** for use as ***a component*** of any article specified in **A, B, or C.**

¹ As defined in section 201(g)(1) of the [Federal Food, Drug, and Cosmetic Act \(FDCA\)](#)

Legal Bases for CGMP

Section 501(a)(2)(B):

“A *drug*... shall be deemed to be adulterated if the *methods* used in, or the *facilities* or *controls* used for, its *manufacture*, *processing*, *packing*, or *holding* do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented to possess*.”

Legal Bases for CGMP

FDASIA 2012 amendment to section 501:

CGMP “includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”

“Current” in CGMP...

- Requiring companies to use technologies and systems that are **up-to-date** in order to comply with the regulations
- Flexible to allow companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement
- **CGMPs are minimum requirements**
- Companies are encouraged to implement comprehensive, modern quality systems and risk management approaches that exceed these minimum standards



CGMP for Finished Pharmaceuticals

21 CFR Part 211

- Subpart A – General Provisions
- Subpart B – Organization and Personnel
- Subpart C – Buildings and Facilities
- Subpart D – Equipment
- Subpart E – Control of Components and Drug Product Containers and Closures
- Subpart F – Production and Process Controls
- Subpart G – Packaging and Labeling Controls
- Subpart H – Holding and Distribution
- Subpart I – Laboratory Controls
- Subpart J – Records and Reports
- Subpart K – Returned and Salvaged Drug Products

Subpart A – General Provisions

- **Minimum standards** for human and animal finished pharmaceuticals
- **Biologics** – applicable; also 21 CFR Part 600+

Subpart B – Organization and Personnel

- **Quality Unit:** Responsible for... almost everything
- Operators are to be trained and in sufficient number for the work
- Operators must not contaminate the process/product: wear [protective] clothing, refrain from activities when ill, wash their hands



Subpart C – Buildings and Facilities

- Designed to facilitate cleaning and maintenance
- Be big enough and have separation to prevent mix-ups and cross contamination
- For aseptic processes: have smooth walls and ceiling, temperature and humidity controls, HEPA filtration and under positive pressure air, environmental monitoring, cleaning and disinfection processes
- PENICILLIN will be in a separate facility with SEPARATE HVAC

Subpart C – Buildings and Facilities

- Adequate controls for air pressure, microbial, dust, humidity and temperature for manufacture, processing, packing or holding
- Recirculation – beware of risk for cross contamination
- Lights, potable water supply, drains have air break or mechanism to prevent back-siphonage
- Keep the place clean and keep it maintained

Subpart D – Equipment

- Appropriate equipment for intended use that is not reactive, additive, or absorptive so as to alter safety, identity, strength, quality or purity
- Keep it clean and sanitized appropriate to prevent contamination of the product
- Keep it maintained and identified

Subpart D – Equipment

- Electronic equipment: calibrated, inspected to ensure proper performance.
- Changes made by authorized person
- See electronic signatures in 21 CFR Part 11
 - Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf>
- Filters: not fiber releasing; no asbestos filters

Subpart E – Control of Components and Drug Product Containers and Closures

- Components, containers and closures are handled to prevent contamination, stored off the floor, appropriately identified as to status (quarantined, approved, rejected)
- Examined upon receipt, stored under quarantine until released
- Each lot of component is withheld from use until sampled (a representative sample), tested and released by quality
- Sampled and examined as described

Subpart E – Control of Components and Drug Product Containers and Closures

- At least one test to determine identity
- Tested (and retest as needed) to ensure meets specifications or accepted with a CoA from a manufacturer that has been established (historic use, testing, audits) as a reliable source
- Check them for contamination of filth and for micro if there is a potential
- First-in, first-out
- Containers and closures should be appropriate to not harm the product



Subpart F – Production and Process Controls

- **Written procedures** “designed to assure” that drug products meet established specifications
- Are followed and **documented at the time of performance**; deviations justified
- Formulated to not less than 100% of labeled or established amount of active
- Components identified, examined by a 2nd person before added



Subpart F – Production and Process Controls

- Yields checked
- Equipment status identified
- In-process checks
- Hold times
- Reprocessing – allowed, but controlled and quality approved
- Prevent objectionable microorganisms (sterile or non-sterile)



Subpart G – Packaging and Labeling Controls

- Finished product examined and retains pulled
- Tamper evident packaging (for OTC products)
- **Expiration dating** – shall bear and be supported by stability
- Exemption for homeopathic, allergenic extracts, INDs, certain OTCs

Subpart H – Holding and Distribution

- Controls for
 - Proper storage (temperature and humidity) to protect: identity, strength, quality, purity.
 - Keep separated until released
- First-in, first-out
- System to facilitate recall

Subpart I – Laboratory Controls

- Establish “scientifically sound” specifications, standards, sampling plans, test procedure
- Calibrate instruments
- Test each batch of drug product with validated test methods
- Stability program
 - Exceptions: homeopathic*; allergenic extracts

Subpart I – Laboratory Controls

- Special tests
 - Sterility and pyrogen tested, if relevant
 - Ophthalmic ointments tested for foreign/abrasive particles
 - Controlled release products checked for rate of release (i.e., multipoint dissolution)
- Keep/check reserve samples
- Test non-penicillin products for penicillin when *reasonable possibility* of cross-contamination

Subpart J – Records and Reports

- Keep records for production, distribution and make available for inspection
- Conduct *at least annual review* of each drug product for changes (look at batch records, complaints, recalls and investigations)
- Tell management (in writing) if there is a problem (*e.g.*, complaints or returns)
- Keep a log for the use and cleaning of equipment
- Keep component, container, closure, and labeling records

Subpart J – Records and Reports

- Keep and control master production records (*full signature* and secondary check)
- Master record has the name strength and description, the name and weight of the active, complete list of components
- Batch production records for each batch is an accurate reproduction of the master record.
- Document significant steps in the manufacture, processing, packing, and holding
 - dates, people, equipment, weights, in-process results, inspections, yields, labeling, and investigations
 - include any changes, with appropriate justification

Subpart J – Records and Reports

- Production records to be reviewed/approved by quality control unit (before released or distributed) with all discrepancies investigated
- Laboratory data for how it was tested (**all** methods sampling, weights, calculations, and comparison to standards)
- Distribution records with lot numbers
- Complaint procedures and investigations when necessary

Subpart K – Returned and Salvaged Drug Products

- Returned goods are controlled. If in doubt, returned product shall be destroyed unless tests, examination, and investigation can prove identity, strength, quality, or purity.
- Salvage (product subject to storage extremes, humidity, fumes, pressure, age or radiation, fires, accidents) only if tests and inspection show it has identity, strength, quality, purity.

ICH Q7 and APIs

- ICH Q7 represents FDA's current thinking on CGMPs for APIs
- API and related manufacturing and testing facilities that follow ICH Q7 generally considered to comply with statutory CGMP
 - alternate approaches may be used
 - requirements of 501(a)(2)(B) can be met if approach ensures that API meets its purported or represented purity, identity, and quality characteristics
- ICH Q7 and other ICH guidance on the web at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>



Data Integrity Basics

Data Integrity

- CGMP – minimum requirements
- Data integrity underpins CGMP
- Lapses obscure other problems

Tip of iceberg



Draft Guidance

Data Integrity and Compliance with CGMP



Find the draft at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf>



FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections



When final, will provide the Agency's current thinking on the creation and handling of data in accordance with CGMP requirements

What the Draft Guidance Is and Is Not?

- It is a list of current problems and how they relate to the CGMP in 21 CFR Parts 210, 211, and 212
- Clarification of several terms in FDA's regulations
- It is **not** a comprehensive list of data controls or a "how to" guidance

What is Data Integrity?

Data integrity – requirements for complete, consistent, and accurate data

Throughout CGMP

ALCOA

Attributable

Legible

Contemporaneous

Original or true copy

Accurate






Data Integrity – ALCOA

- **A**tributable: §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10);
- **L**egible: §§ 211.180(e) and 212.110(b);
- **C**ontemporaneously recorded: §§ 211.100(b) and 211.160(a);
- **O**riginal or a true copy: §§ 211.180 and 211.194(a);
- **A**ccurate: §§ 211.22(a), 211.68, 211.188, and 212.60(g).

APIs – ICH Q7

- Computerized Systems (5.4)
 - GMP-related computerized systems should be validated.
 - Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
 - Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Other Important Concepts of Data Integrity

-  Metadata
-  Audit Trail
-  Static vs. dynamic records
-  Backup
-  Systems



Most Frequently Cited Drug CGMP Observations

Number of Registered Drug Establishments by Location

Location	FY 2013	FY 2014	FY 2015
Domestic	9,120	9,330	9,346
Foreign	3,493	3,619	3,785
Total	12,613	12,949	13,134

Types of Registered Drug Establishments

	FDP	API	Other	Total
FY 2013	4,360	1,248	7,005	12,613
FY 2014	4,383	1,495	7,071	12,949
FY 2015	4,349	1,522	7,263	13,134

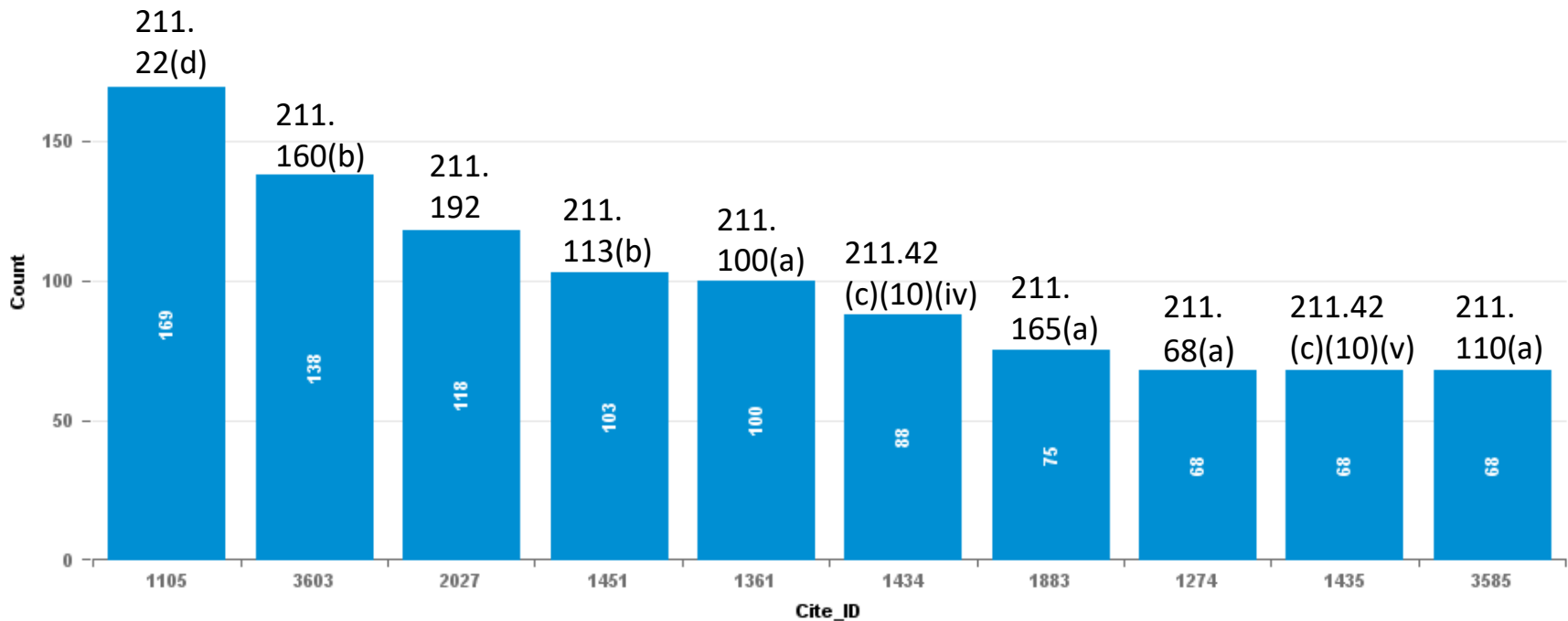


CGMP Inspections of Registered Domestic & Foreign Drug and Device Establishments

Location	FY 2013	FY 2014	FY 2015
Domestic	4,858	4,175	4,055
Foreign	1,138	1,379	1,560
Total	5,996	5,554	5,651

Most Frequently Cited 211s

January 1, 2015 – January 1, 2016



Trend Analysis

- 211.22(d): The responsibilities and procedures applicable to the quality control unit are not in writing or fully followed
- 211.160(b): Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures
- 211.192: Failure to thoroughly review any unexplained discrepancy or 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.

Trend Analysis

- 211.113(b): Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written or followed.
- 211.100(a): 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.
- 211.42(c)(10)(iv): Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Trend Analysis

- 211.68(a): Routine calibration, inspection and checking of automatic, mechanical and/or electronic equipment is not performed according to a written program designed to assure proper performance.
- 211.42(c)(10)(v): Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

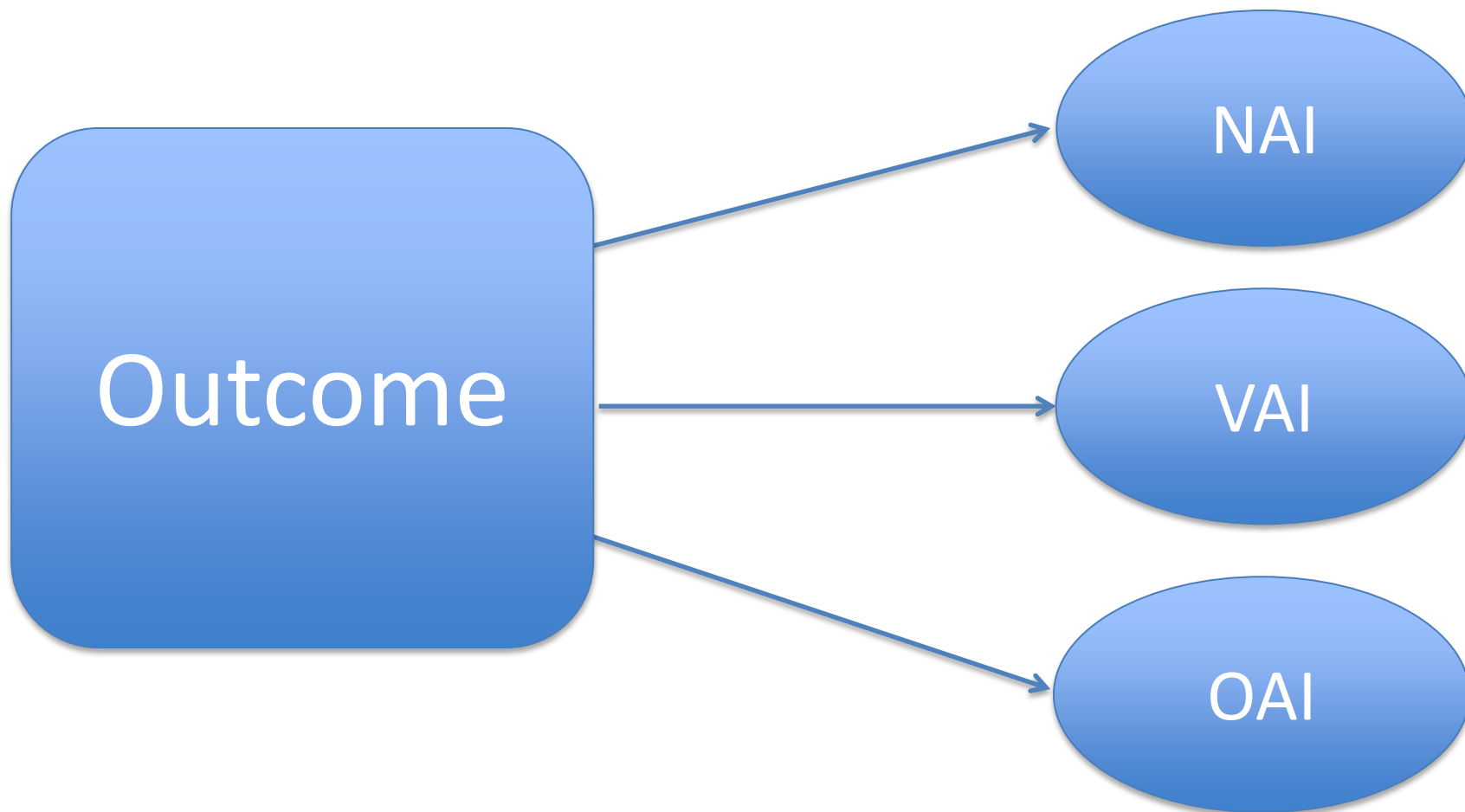


Drug Manufacturing Compliance Evaluation and Enforcement


Enforcement Process



Inspection Outcome



Primary Considerations for CGMP Enforcement

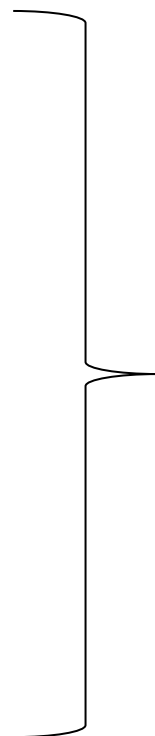
- Is the drug “adulterated”?
 - Food, Drug & Cosmetic Act
 - FDA regulations at 21 CFR Parts 210 & 211
 - For API, standards are set forth in ICH Q7
- Most important – patient risk
 - High risk  FDA takes quick action
 - Sub or super-potent
 - Contamination
 - Sterility concerns
 - Other defects

“OAI” Outcomes

- Regulatory Meeting
- Warning Letter
 - Official letter stating violations and giving notice of consequences if problems are not fixed
- Import Alert
 - Notice to Customs and Border Protection to stop imports
 - If “such article is adulterated, misbranded, or in violation of section 355... then such article shall be refused admission”
- Seizure/Injunction
 - Legal action in the U.S. federal court system
 - Can stop goods from entering commerce, prohibit or compel action

Compliance and Enforcement Actions

- Consent decrees
- Import alerts
- Seizures/Injunctions
- Warning letters
- Clinical investigator disqualifications
- Criminal indictments/convictions



Unapproved drugs

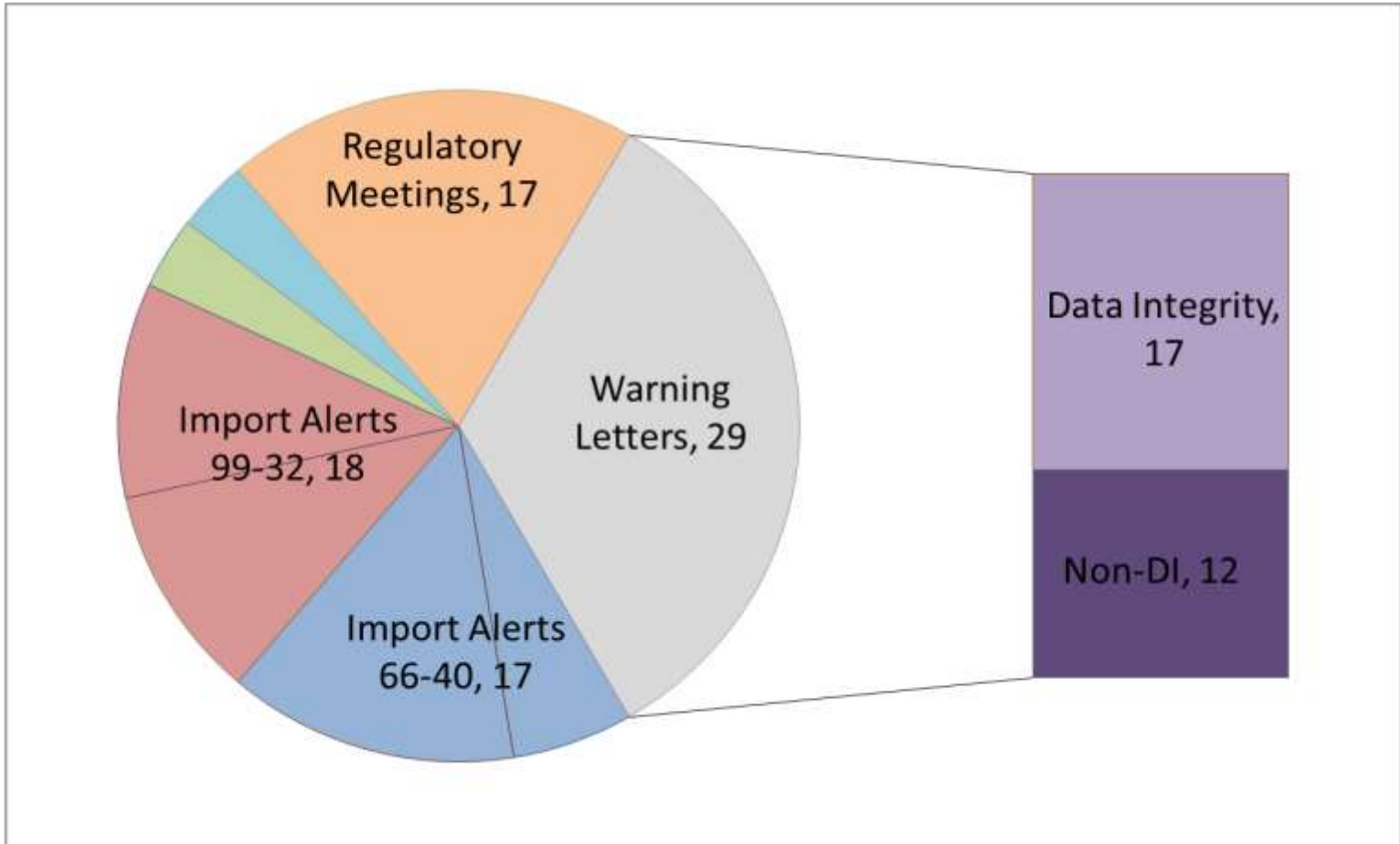
Health fraud

Data integrity

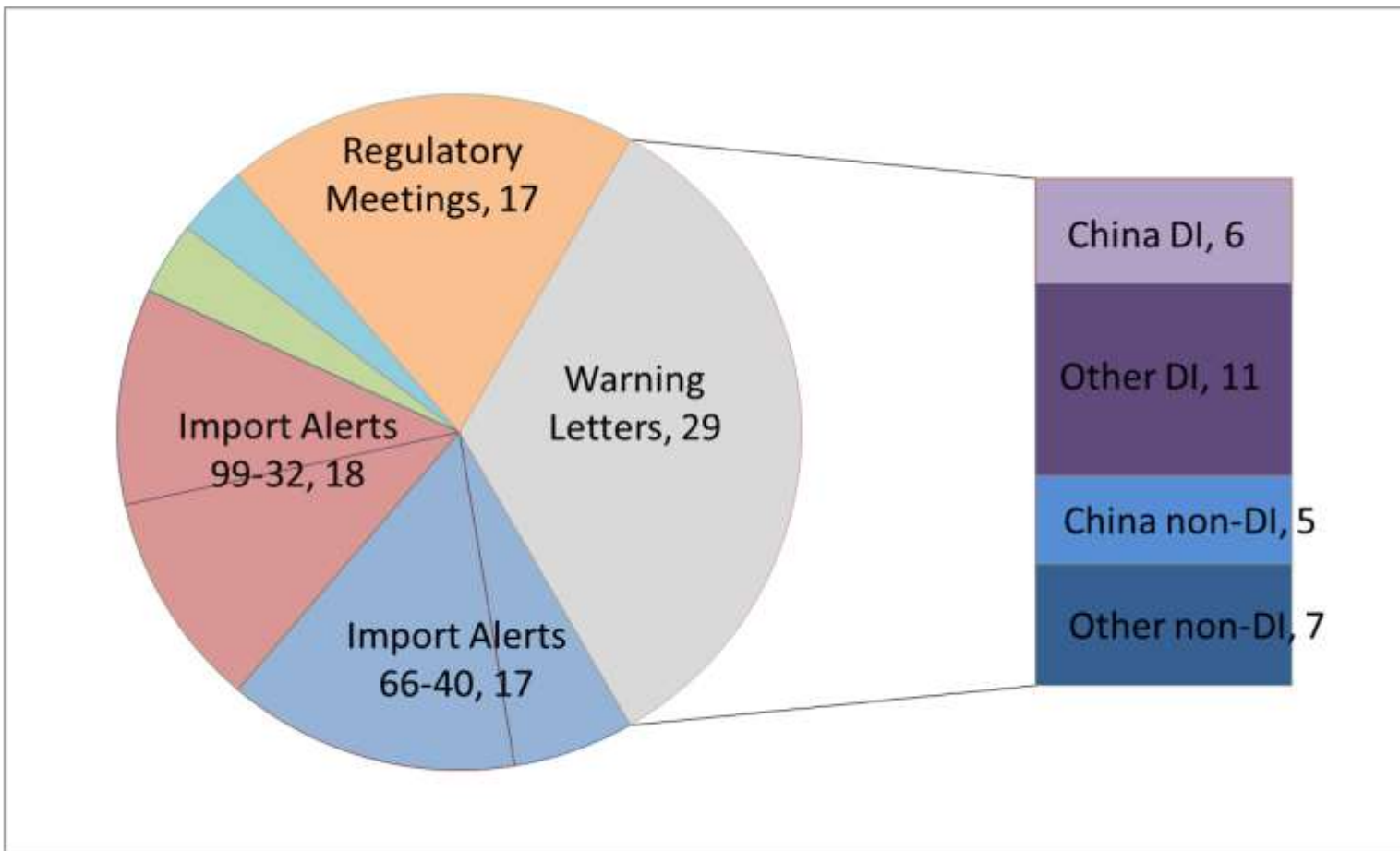
CGMP violations

GCP violations

Compliance/OMQ Actions January to August 31, 2016



Compliance/OMQ Actions January to August 31, 2016



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