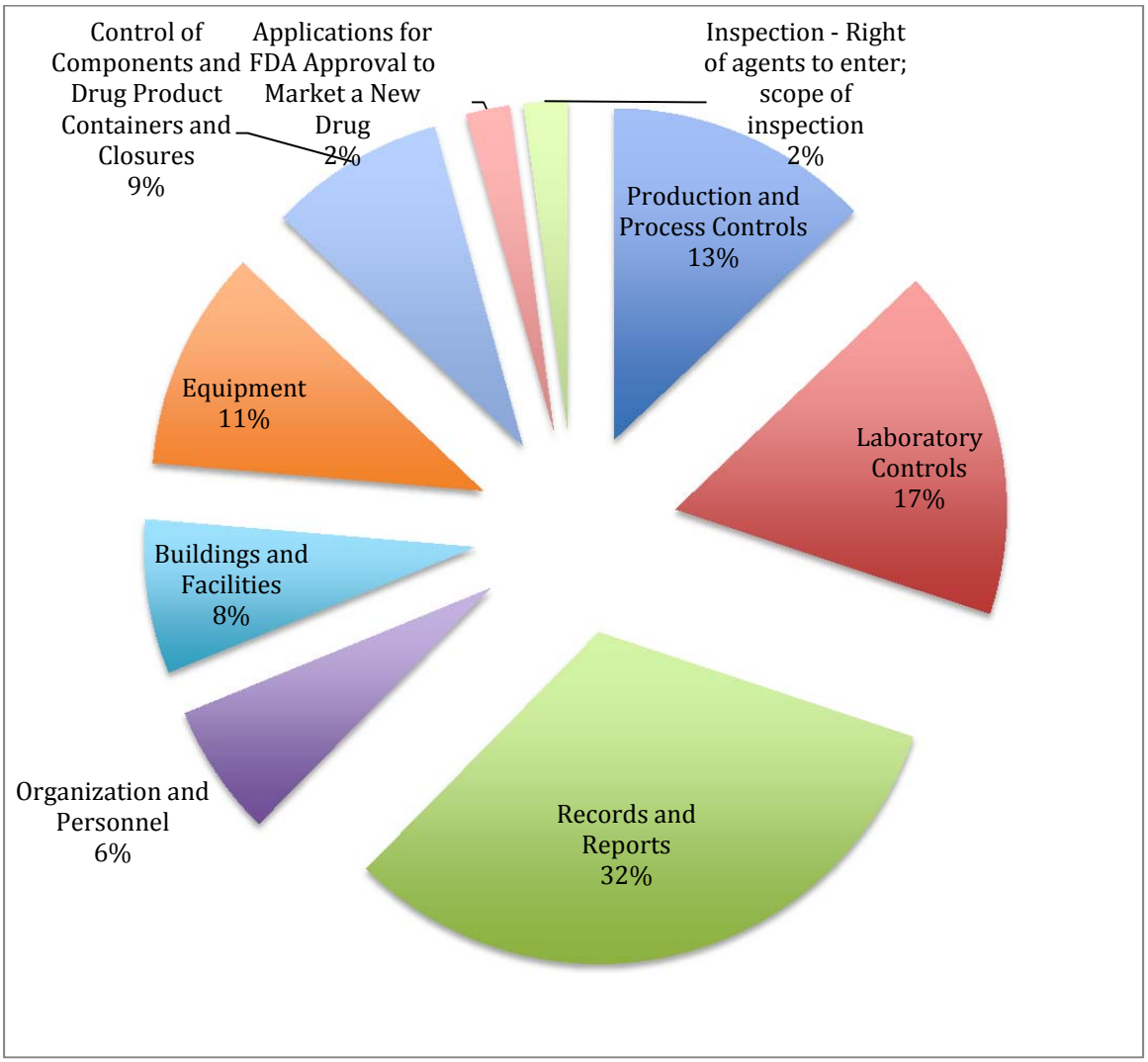
FDA inspections continue to focus on CGMP violations related to basic GMP controls. A survey of Warning Letters issued in 2013 on CMC (Chemistry / Manufacturing / Controls) violations reveals an emphasis on production, laboratory, and records systems.

Also, to date all CMC Warning Letters issued in 2013 for drug substance (API) and drug product manufacturers, whether domestic or foreign, involved manufacturing facilities outside of the US. Leading violations included production and process controls (12%), laboratory controls (16%), records and reports (30%), and equipment (10%).

Less frequently observed were organization and personnel controls related to the quality control unit or training (6%), buildings and facilities controls especially those related to environmental controls (7%), and control of components especially raw materials testing and release (8%). Rounding out 2013 Warning Letter observations for these manufacturers were non-GMP violations including marketing of non-approved drugs (2%) and deliberate obstruction of inspections (2%). See Figure 1.

Figure 1



Observations in production and process largely involved batch control records that were absent or deficient. Within records and reports, 17% of violations cited involved failure to properly investigate out-of-specification (OOS) results and/or use of materials that failed specification. Equipment violations usually involved failure to properly qualify and/or secure computerized systems.

Actual observations by regulation included the following:

Subpart B – Organization and Personnel, 21 CFR 211.22 Responsibilities of the quality control unit.

- failure of the quality control unit to provide organizational structure, procedures, processes, and activities to ensure quality, purity, safety, identity, and effectiveness

Subpart B – Organization and Personnel, 21 CFR 211.25 Personnel qualifications.

- failure to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions

Subpart C – Buildings and Facilities, 21 CFR 211.42 Design and construction features.

- failure to establish an adequate system for monitoring environmental conditions in aseptic processing
- failure to have facilities used in the manufacture, process, packaging and holding of a drug product of appropriate construction to facilitate cleaning, maintenance, and proper operations
- failure to perform operations within specifically defined areas of adequate size and to have separate or defined areas of such other control systems necessary to prevent contamination or mixups

Subpart C – Buildings and Facilities, 21 CFR 211.46 Ventilation, air filtration, air heating and cooling.

- failure to provide equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature when appropriate for the manufacture, packing, or holding of a drug product

Subpart C – Buildings and Facilities, 21 CFR 211.52 Washing and toilet facilities.

- failure to provide adequate washing and toilet facilities to working areas

Subpart C – Buildings and Facilities, 21 CFR 211.56 Sanitation.

- failure to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition

Subpart D – Equipment, 21 CFR 211.67 Equipment cleaning and maintenance.

- failure to establish and follow adequate written procedures for cleaning and maintenance of equipment

Subpart D – Equipment, 21 CFR 211.68 Automatic, mechanical, and electronic equipment.

- failure to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product
- failure to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records
- failure to implement access controls and audit trails for laboratory computer systems

Subpart E – Control of Components and Drug Product Containers and Closures, 21 CFR 211.80 General requirements.

- failure to establish written procedures that describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval, rejection of components, drug product containers, and closures
- failure to establish written procedures pertaining to handling of raw materials used in API production, and failure to establish specifications for finished API release

Subpart E – Control of Components and Drug Product Containers and Closures, 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures.

- failure to ensure that test procedures are scientifically sound and appropriate to ensure that key starting materials and intermediate(s) conform to established standards of quality and/or purity
- failure to withhold from use each lot of components, drug product containers, and closures until the lot had been sampled, tested, or examined, as appropriate, and released for use by the quality control unit
- failure to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality
- failure to conduct at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals

Subpart F – Production and Process Controls, 21 CFR 211.100 Written procedures; deviations.

- failure to establish adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and/or purity they purport or are represented to possess
- failure to record all quality activities at the time they are performed

Subpart F – Production and Process Controls, 21 CFR 211.111 Time limitations on production.

- failure to establish time limits for the completion of each phase of production to assure the quality of the drug product

Subpart F – Production and Process Controls, 21 CFR 211.113 Control of microbiological contamination.

- failure to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile
- failure to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes

Subpart I – Laboratory Controls, 21 CFR 211.160 General requirements.

- failure to establish specification, standards, sampling plans, test procedures, laboratory control mechanisms including any changes thereto
- failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality, and purity

Subpart I – Laboratory Controls, 21 CFR 211.165 Testing and release for distribution.

- failure to have appropriate laboratory determinations of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release
- failure to establish acceptance criteria for the sampling and testing conducted by the quality control unit that are adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release

Subpart I – Laboratory Controls, 21 CFR 211.166 Stability testing.

- failure to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expirations dates

Subpart J – Records and Reports, 21 CFR 211.186 Master production and control records.

- failure to establish and follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch

Subpart J – Records and Reports, 21 CFR 211.188 Batch production and control records.

- failure to prepare batch production and control records for each batch of drug product that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch

Subpart J – Records and Reports, 21 CFR 211.192 Production record review.

- failure to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed

Subpart J – Records and Reports, 21 CFR 211.194 Laboratory records.

- failure to maintain laboratory control records with complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays

Subpart J – Records and Reports, 21 CFR 211.198 Complaint files.

- failure to investigate all quality-related complaints

The leading categories observed -- production and process controls (12%), laboratory controls (16%), records and reports (30%), and equipment (10%) – generally involved failures to document, investigate, test, or otherwise control production and testing areas. Quality oversight, facilities controls, and failures to control raw materials were less often observed.

In May 2013 FDA published "Guidance for Industry – Contract Manufacturing Arrangements for Drugs: Quality Agreements". The Agency cited ICH Q7 ("Good

Manufacturing Practice Guidance for Active Pharmaceutical Ingredients"), ICH Q9 ("Quality Risk Management"), and ICH Q10 ("Pharmaceutical Quality Systems") to emphasize the sponsor's role in assuring that their contractors adhere to CGMPs, and their ultimate responsibility in assuring the quality, purity, safety, identity, and effectiveness of drugs manufactured using CMOs.

FDA officials have stated in recent industry conferences that the Agency plans to perform more overseas inspections, pointing to strong quality agreements between sponsors and foreign contractors as a mainstay in ensuring product quality.