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REVIEW OF DATA INTEGRITY & CGMP VIOLATIONSFDA - PERSPECTIVE

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ABSTRACT

A review on USFDA observation and finding while inspection of Pharmaceutical the present review provide some important, Significant observation and measure of compliance. USFDA is an regulatory body governing health products which are made (in or outside INDIA) and marketed in INDIA. Significant deviation from CGMP and significant violation from CGMP for both API Facility and formulations. Strictly compliance requirements under 21 Code of federal regulations (CFR). FDA observation includes but not limited to this. If not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the Safety, Identity, Strength, Purity and Quality of drug product, violation under [21 CFR & 211]. Data integrity is main issue Raised in most FDA warning letter. Corrective action and plan. Level of control must be raised from raw material, packaging material (Accurate, Legible, Contemporaneous, Original, Attributable (ALCOA) in process, finished dosage form, Maintain log book properly. Guidelines for Out of specification (OOS) must be follow if any required.

AIM

To evaluate the number and type of warning letters issued by the US Food and Drug Administration (FDA) to pharmaceutical manufacturers for violations.

OBJECTIVE

- To collect the entire data on warning letters issued during 2013FY-2017FY.
- Compilation of data by using statistical techniques based on :

(I) Country wise

(II) Category wise

(III) Yearly wise

- Compilation of data for India and detailed investigation on it.
- Explaining the criteria of issuing the warning letters on CGMP and DATA INTEGRITY
- To determine the various ways in minimizing the issue of warning letters.
- Brief explanation on CAPA and its effectiveness.

INTRODUCTION

Pharmaceutical manufacturers communicate the drug's intended efficacy and benefits to physicians and patients through promotional claims for the particular product. The various promotional materials include print advertisements, broadcast advertisements, and visual aids which are commonly used by sales representatives around the world as part of their product promotion strategy. These claims should ideally be based on scientific evidence since they form the basis of medication prescribing by physicians, and utilization by patients. All promotional claims that are made by or on behalf of global drug manufacturers in the United States (US) are subject to regulation by the US Food and Drug Administration (FDA).The Division of Drug, Marketing, Advertising and Communications (DDMAC) is the unit within the FDA's Center for Drug Evaluation and Research (CDER), which is concerned with the regulation of prescription drug promotion and oversees all the promotional activities.

In contrast to countries that rely mainly on industry self-regulation, the US-FDA directly monitors promotion of prescription drugs. The FDA can employ a number of enforcement tools when they perceive a promotional claim violation, depending on the degree of severity of the claim violated, the previous track record of the individual company, and its past confrontation with FDA. Warning letters constitute one of the most frequently pursued advisory actions by the FDA. According to the definition given by Department of Scientific Investigation (DSI), a warning letter "is an informal advisory, to a firm or clinical investigator, communicating the Agency's position on a matter but does not commit the FDA to take enforcement action". The company receiving a warning letter is required to reply within 15 days, immediately ceasing the circulation of the material or action in violation or issue a "Dear Doctor" letter or take any corrective action as required. Past research suggests that lack of standardized FDA guidelines for reviewing warning letters may have led to use of more informal criteria while overseeing drug marketing and promotional activities.

The US Department of Health and Human Services (DHHS) and the Pharmaceutical Research and Manufacturers of America (PhRMA) implemented two policies in 2002 and

2005 respectively, pertaining to the oversight of warning letters and promotion of claims. In the light of informal criteria adopted by FDA officials for reviewing regulatory letters, the DHHS policy, implemented in January 2002, required the Office of Chief Counsel to review these letters before they were issued by the DDMAC. In 2005, the PhRMA issued guidance effective January 2006, which required pharmaceutical companies to submit all new Direct to Consumer (DTC) television drug advertisements to the FDA prior to broadcasting them. Therefore, the objective of the current study was to evaluate the number and type of warning letters issued by the FDA.

The **Food and Drug Administration** (**FDA** or **USFDA**) is a United Statesgovernment agency that protects and promotes public health, by regulating food safety, tobacco, prescription drugs, over-the-counter drugs, vaccines, and cosmetics. The FDA enforces federal laws along with other agencies, such as the DEA. The agency was made in 1906, and is led by the Commissioner of Food and Drugs, currently Scott Gottlieb.

FDA Mission

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.

FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of

medical products to respond to deliberate and naturally emerging public health threats.

What does FDA regulate?

The scope of FDA's regulatory authority is very broad. FDA's responsibilities are closely related to those of several other government agencies. Often frustrating and confusing for consumers is determining the appropriate regulatory agency to contact. The following is a list of traditionally-recognized product categories that fall under FDA's regulatory jurisdiction; however, this is not an exhaustive list.

In general, FDA regulates:

Foods, including

- Dietary supplements
- Bottled water
- Food additives
- Infant formulas
- Other food products (although the U.S. Department of Agriculture plays a lead role in regulating aspects of some meat, poultry, and egg products)

Drugs, including

- Prescription drugs (both brand-name and generic)
- Non-prescription (over-the-counter) drugs

Biologics, including

- vaccines
- blood and blood products
- cellular and gene therapy products
- tissue and tissue products
- allergenics

Medical Devices, including

- simple items like tongue depressors and bedpans
- complex technologies such as heart pacemakers
- dental devices
- surgical implants and prosthetics

Electronic Products that give off radiation, including

- microwave ovens
- x-ray equipment
- laser products
- ultrasonic therapy equipment
- mercury vapor lamps
- sunlamps

Cosmetics, including

- color additives found in makeup and other personal care products
- skin moisturizers and cleansers
- nail polish and perfume

Veterinary Products, including

- livestock feeds
- pet foods
- veterinary drugs and devices

Tobacco Products, including

- cigarettes
- cigarette tobacco
- roll-your-own tobacco
- smokeless tobacco

The following contact information is for government agencies that have functions related to that of FDA. (Contact information is given for agency headquarters offices, which are located in the Washington, D.C., area. Local offices, listed in the phone book under U.S. Government, may be available to provide assistance as well).

Advertising

The Federal Trade Commission is a federal agency that regulates many types of advertising. The FTC protects consumers by stopping unfair, deceptive or fraudulent practices in the marketplace. Consumers may write to FTC at 6th St. and Pennsylvania Ave., N.W., Washington, DC 20580; telephone (202) 326-2222.

Alcohol

The Department of the Treasury's Alcohol and Tobacco Tax and Trade Bureau (TTB) regulates aspects of alcohol production, importation, wholesale distribution, labeling, and advertising. Consumers may write to TTB at 1310 G St. N.W., Box 12, Washington, DC 20005; telephone (202) 453-2000 or see the TTB Contact page.

Consumer Products

The Consumer Product Safety Commission (CPSC) works to ensure the safety of consumer products such as toys, cribs, power tools, cigarette lighters, household chemicals, and other products that pose a fire, electrical, chemical or mechanical hazard. Consumers may send written inquiries to CPSC, Washington, DC 20207. CPSC operates a toll-free hot line at (800) 638-2772 or TTY (800) 638-8270 for consumers to report unsafe products or to obtain information regarding products and recalls.

Drugs of Abuse

The Department of Justice's Drug Enforcement Administration (DEA) works to enforce the controlled substances laws and regulations of the United States, including as they pertain to the manufacture, distribution, and dispensing of legally produced controlled substances. Inquiries regarding DEA activities may be sent to the Drug Enforcement Administration, Office of Diversion Control 8701 Morrissette Drive Springfield, VA 22152; telephone (202) 307-1000.

Meat and Poultry

The U.S. Department of Agriculture's Food Safety and Inspection Serviceregulates aspects of the safety and labeling of traditional (non-game) meats, poultry, and certain egg products. Consumers with questions regarding meat or poultry, including safe handling and storage practices, should write or call the Food Safety Inspection Service's Meat and Poultry Hotline, Room 2925S, Washington, DC 20250; telephone (800) 535-4555.

Pesticides

The Environmental Protection Agency (EPA) regulates many aspects of pesticides. EPA sets limits on how much of a pesticide may be used on food during growing and processing, and how much can remain on the food you buy. Public inquiries regarding EPA should be mailed to U.S. Environmental Protection Agency, Office of Pesticide Programs Public Docket (7506C), 3404, 401M St., Washington, DC 20460; telephone (202) 260-2080.

Vaccines for Animal Diseases

The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics, regulates aspects of veterinary vaccines and other types of veterinary biologics. Public inquiries regarding APHIS's Center for Veterinary Biologics should be mailed to Center for Veterinary Biologics, 1920 Dayton Ave, P.O. Box 844, Ames, Iowa, 50010; telephone (515) 337-6100 or see the APHIS Contact page.

Water

The Environmental Protection Agency (EPA) regulates aspects of drinking water. EPA develops national standards for drinking water from municipal water supplies (tap water) to limit the levels of impurities.

Laws Enforced by FDA

The Food and Drugs Act of 1906 was the first of more than 200 laws that constitute one of the world's most comprehensive and effective networks of public health and consumer protections. Here are a few of the congressional milestones:

- The Federal Food, Drug, and Cosmetic Act of 1938 was passed after a legally marketed toxic elixir killed 107 people, including many children. The FD&C Act completely overhauled the public health system. Among other provisions, the law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.
- The Kefauver-Harris Amendments of 1962, which were inspired by the thalidomide tragedy in Europe (and the FDA's vigilance that prevented the drug's marketing in the United States), strengthened the rules for drug safety and required manufacturers to prove their drugs' effectiveness.
- The Medical Device Amendments of 1976 followed a U.S. Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness safeguards to new devices.

Today, the FDA regulates $1 trillion worth of products a year. It ensures the safety of all food except for meat, poultry and some egg products; ensures the safety and effectiveness of all drugs, biological products (including blood, vaccines and tissues for transplantation), medical devices, and animal drugs and feed; and makes sure that cosmetics and medical and consumer products that emit radiation do no harm.

A regulatory letter represents the FDA's first official notification to a pharmaceutical company that the FDA has discovered a product or activity in violation of the FDCA. A regulatory letter can result from awareness of a FDCA violation from an inspection or other sources. Regulatory letters serve as communication channels that express the FDA's assessment of compliance with the law without obligating the agency to initiate enforcement action. They also serve as one of the principal means to achieve prompt voluntary compliance with the FDCA before the FDA resorts to more severe enforcement actions. There are two types of regulatory letters: warning letters and untitled letters. Untitled letters are also known as notices of violation. Warning letters are issued to alert pharmaceutical companies of significant regulatory violations. Failure to adequately and promptly achieve correction may lead to enforcement action. Notices of violation are untitled letters that describe violations that do not meet the regulatory significance threshold for warning letters. Both types of regulatory letters describe the violation observed and provide a citation of the statutory provision and, if applicable, the regulation violated. A warning letter requires correction of violation and a written response within 15 days of receipt of letter; otherwise, enforcement action may ensue. Enforcement procedures also mandate that the FDA follow up to evaluate whether the violations have been corrected and the company's adequacy in response. A notice of violation letter requests (rather than requires) ceasing the inappropriate activities and a written response from the company. And it does not include a warning statement that failure to take prompt correction may result in enforcement action.

Regulatory letters may be issued by either the FDA centers or district offices. Generally, district offices issue regulatory letters to domestic pharmaceutical companies based on inspections, whereas FDA headquarter centers issue regulatory letters for advertising and promotional violations or to foreign companies marketing products in the US. Except for in a few defined circumstances, the FDA is not legally bound to warn pharmaceutical companies of their violations to the law preceding any enforcement action taken.

The variability in the number of regulatory letters released by the FDA was previously described in public sector reports. The Office of Inspector General (OIG) released a report in 1999 that cited the following reasons: a more cooperative relationship fostered by the FDA with the pharmaceutical industry; changes in the scope and type of inspections; and pharmaceutical companies becoming more familiar with the regulation and less likely to unintentionally commit regulatory violations.

Changes in policy also affected the regulatory letters released by FDA. Beginning November 2001 and formally in January 2002, the Department of Health and Human Services directed the FDA to forward all drafts of regulatory letters to the FDA's Office of Chief Counsel (OCC) for review and approval before the letter could be issued. The FDA stated that the objective behind this policy was to ensure that all draft letters were reassessed for "legal sufficiency and consistency with agency policy". The new policy of reviewing drafts of regulatory letters resulted in a reduction in the number and types (i.e. warning letters and notices of violation) of regulatory letters issued.

A 2006 Committee on Government Reform (CGR) evaluated the declining trend in regulatory letters released during the Bush administrations. According to the CGR report, increased compliance by manufacturers did not account for this decline, because the number of violations observed by the FDA inspectors remained stable. The CGR report cited several factors that could explain the reduction in regulatory letters released, including: failure to take enforcement actions recommended by field investigators; pursuing of actions less severe than recommended by investigators; choosing to meet with firm representatives to discuss violations and potential corrective measures instead of taking formal action as recommended by field investigators; suspending recommendations with no official action subsequently taken; and delaying acting on recommendations for an extended period of time. The FDA argued that merely counting the number of regulatory letters released did not accurately reflect a shift in enforcement strategy that sought to pursue fewer but legally solid cases.

The GAO released a second report in 2006 highlighting the need for improvements in FDA oversight of DTC advertising. This second GAO report found that the FDA received considerably more final and draft advertising materials submitted by pharmaceutical companies than could possibly be reviewed due to limitations in staff, and therefore, only a small percentage was actually reviewed.

In August 2009, the FDA announced a new policy initiative to improve the effectiveness of the FDA enforcement system. This initiative included the following changes related to regulatory letters: to accelerate the warning letter issuance process by limiting FDA OCC review to only draft letters of significant legal issues; to prioritize enforcement follow-up on warning letters to assess companies' reported compliance; to consider enforcement action even prior to issuance of warning letter to address significant public health concerns and violations if necessary; and to develop "close-out" process for warning letters issued to

confirm that all violations have been appropriately rectified and to provide incentive for companies to comply with regulations . The new policy initiative modified the November 2001 policy requiring OCC review of all regulatory letters. Under the new policy, OCC reviews selected regulatory letters including novel, controversial, or sensitive legal issues; drug misbranding charges; and violations of the general current good manufacturing practice (CGMP) regulations.

Although previous studies and reports have examined the FDA warning letters and notices of violation to pharmaceutical companies during a limited time period or in regards to specific contexts, like direct-to-consumer advertising or quality-of-life claims, no studies have conducted a comprehensive evaluation of the number and type of regulatory letters issued by the different offices of the FDA over a comprehensive period of time covering several federal administrations. Therefore, the objectives of this study were two-fold: 1) to assess trends in the number of pharmaceutical-related warning letters and notices of violation released by the FDA between 1997 and 2011; and 2) to evaluate differences in the type of regulatory letters released during the last four federal administrations by type of regulatory letter and releasing office.

What is a Warning Letter?

When FDA finds that a manufacturer has significantly violated FDA regulations, FDA notifies the manufacturer. This notification is often in the form of a Warning Letter.

The Warning Letter identifies the violation, such as poor manufacturing practices, problems with claims for what a product can do, or incorrect directions for use. The letter also makes clear that the company must correct the problem and provides directions and a timeframe for the company to inform FDA of its plans for correction. FDA then checks to ensure that the company's corrections are adequate.

Why issued

An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts. FDA investigators are trained to ensure that each observation noted on the FDA Form 483 is clear, specific and significant. Observations are made when in the investigator's judgment, conditions or practices observed would indicate that any food, drug, device or cosmetic has been adulterated or is being

prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health.

Q: What is the purpose of an FDA Form 483?

The FDA Form 483 notifies the company's management of objectionable conditions. At the conclusion of an inspection, the FDA Form 483 is presented and discussed with the company's senior management. Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.

Q: Is the FDA Form 483 intended to be an all-inclusive list of every possible deviation from law and regulation?

A: No, it's not. The FDA Form 483 is a report which does not include observations of questionable or unknown significance at the time of the inspection. There may be other objectionable conditions that exist at the firm that are not cited on the FDA Form 483. FDA investigators are instructed to note only what they saw during the course of the inspection. Companies are responsible to take corrective action to address the cited objectionable conditions and any related non-cited objectionable conditions that might exist.

Q: How is the FDA Form 483 shared with the company?

A: FDA Form 483s are discussed with a company's management at the conclusion of the inspection. Each observation is read and discussed so that there is a full understanding of what the observations are and what they mean.

Q: What are the implications of the FDA Form 483 for agency enforcement and what happens next?

A: The FDA Form 483 does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations. The FDA Form 483 is considered, along with a written report called an Establishment Inspection Report, all evidence or documentation collected on-site, and any responses made by the company. The Agency considers all of this information and then determines what further action, if any, is appropriate to protect public health.

CHAPTER I--FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER A--GENERAL

CFR: PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A--General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically expected by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

(f) This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(g) This part does not apply to electronic signatures obtained under 101.11(d) of this chapter.

(h) This part does not apply to electronic signatures obtained under 101.8(d) of this chapter.

(i) This part does not apply to records required to be established or maintained by part 117 of this chapter. Records that satisfy the requirements of part 117 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(j) This part does not apply to records required to be established or maintained by part 507 of this chapter. Records that satisfy the requirements of part 507 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(k) This part does not apply to records required to be established or maintained by part 112 of this chapter. Records that satisfy the requirements of part 112 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(l) This part does not apply to records required to be established or maintained by subpart L of part 1 of this chapter. Records that satisfy the requirements of subpart L of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(m) This part does not apply to records required to be established or maintained by subpart M of part 1 of this chapter. Records that satisfy the requirements of subpart M of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(n) This part does not apply to records required to be established or maintained by subpart O of part 1 of this chapter. Records that satisfy the requirements of subpart O of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(o) This part does not apply to records required to be established or maintained by part 121 of this chapter. Records that satisfy the requirements of part 121 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

[62 FR 13464, Mar. 20, 1997, as amended at 69 FR 71655, Dec. 9, 2004; 79 FR 71253, 71291, Dec. 1, 2014; 80 FR 71253, June 19, 2015; 80 FR 56144, 56336, Sept. 17, 2015; 80 FR 74352, 74547, 74667, Nov. 27, 2015; 81 FR 20170, Apr. 6, 2016; 81 FR 34218, May 27, 2016]

Sec. 11.2 Implementation

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

(1) The requirements of this part are met; and

(2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

(2) Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-903 (21 U.S.C. 321-393)).

(3) Agency means the Food and Drug Administration.

(4) Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

(5) Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

(6) Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

(7) Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(8) Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(9) Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(10) Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.

Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Subpart B--Electronic Records

Sec. 11.10 Controls for closed systems

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in 11.10, as appropriate, and additional measures such as document encryption and use of appropriate

digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Sec. 11.50 Signature manifestations

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Sec. 11.70 Signature/record linking

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.

Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Subpart C--Electronic Signatures

Sec. 11.100 General requirements

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.

(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls

(a) Electronic signatures that are not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.

(2) Be used only by their genuine owners; and

(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.

Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Data Integrity and Compliance with CGMP Guidance for Industry

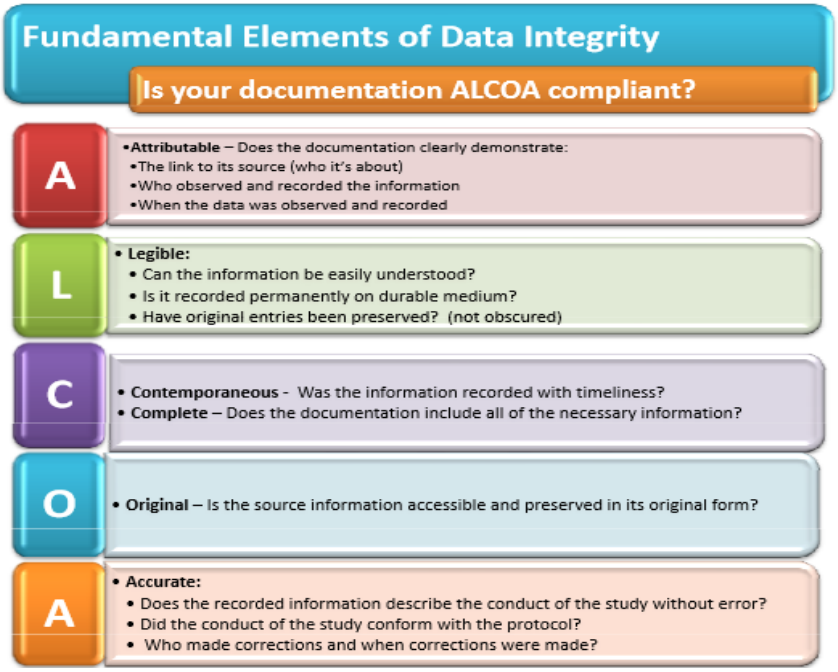
INTRODUCTION The purpose of this guidance is to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required in 21 CFR parts 210, 211, and 212. Part 210 covers Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; part 211 covers Current Good Manufacturing Practice for Finished Pharmaceuticals; and part 212 covers Current Good Manufacturing Practice for Positron Emission Tomography Drugs. This guidance provides the Agency's current thinking on the creation and handling of data in accordance with CGMP requirements. FDA expects that data be reliable and accurate (see the "Background" section). CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based upon their process understanding and knowledge management of technologies and business models .In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health. These data integrity-related CGMP violations have led tounderlying premise in §§ 210.1 and 212.2 is that CGMP sets forth minimum requirements to assure that drugs meet the standards of the Federal Food, Drug,

and Cosmetic Act (FD&C Act) regarding safety, identity, strength, quality, and purity. Requirements with respect to data integrity in parts 211 and 212 include, among other things: § 211.68 (requiring that "backup data are exact and complete," and "secure from 48 alteration, inadvertent erasures, or loss");§ 212.110(b) (requiring that data be "stored to prevent deterioration or loss"); §§ 211.100 and 211.160 (requiring that certain activities be "documented at the time of performance" and that laboratory controls be "scientifically sound");§ 211.180 (requiring that records be retained as "originalrecords," "true copies," or other "accurate reproductions of the original records"); and §§ 211.188, 211.194, and 212.60(g) (requiring "complete information," "complete data derived from all tests," "complete record of all data," and "complete records of 56 all tests performed"). Electronic signature and record-keeping requirements are laid out in 21 CFR part 11 and apply to certain records subject to records requirements set forth in Agency regulations, including parts 210, 211, and 212. For more information, see guidance for industry Part 11, Electronic Records; Electronic Signatures — Scope and Application. The guidance outlines FDA's current thinking regarding the narrow scope and application of part 11 pending FDA's reexamination of part 11 as it applies to all FDA-regulated products

What is "data integrity"?

For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).



What is "metadata"?

Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. For example, the number "23" is meaningless without metadata, such as an indication of the unit "mg." Among other things, metadata for a particular piece of data could include a date/time stamp for when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, audit trails, etc.Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194). The relationships between data and their metadata should be preserved in a secure and traceable manner.

What is an "audit trail"?

For purposes of this guidance, audit trail means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. An audit trail is a chronology of the "who, what, when, and why" of a record. For example, the audit trail for a high performance liquid chromatography (HPLC) run could include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any, including change justification for the reprocessing. Electronic audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file). CGMP-compliant record-keeping practices prevent data from being lost or obscured (see §§ 211.160(a), 211.194, and 212.110(b)). Electronic record-keeping systems, which include audit trails, can fulfill these CGMP requirement.

How does FDA use the terms "static" and "dynamic" as they relate to record formats?

For the purposes of this guidance, static is used to indicate a fixed-data document such as a paper record or an electronic image, and dynamic means that the record format allows interaction between the user and the record content. For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger. It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as

calculated yield.

How does FDA use the term "backup" in § 211.68(b)?

FDA uses the term backup in § 211.68(b) to refer to a true copy of the original data that is maintained securely throughout the records retention period (for example, § 211.180). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format. This should not be confused with backup copies that may be created during normal computer use and temporarily maintained for disaster recovery (e.g., in case of a computer crash or other interruption). Such temporary backup copies would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

What are the "systems" in "computer or related systems" in § 211.68?

The American National Standards Institute (ANSI) defines systems as people, machines, and methods organized to accomplish a set of specific functions. Computer or related systems can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

When is it permissible to exclude CGMP data from decision making?

Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180). Electronic data generated to fulfill CGMP requirements should include relevant metadata. To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion (see the guidance for industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, and §§ 211.188, 211.192, and 212.71(b)). The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.

Does each workflow on our computer system need to be validated?

Yes, a workflow, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation (see 160 §§ 211.63, 211.68(b), and 211.110(a)). If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly. For example, qualifying the Manufacturing Execution System (MES) platform, a computer

system, ensures that it meets specifications; however, it does not demonstrate that a given MPCR generated by the MES contains the correct calculations. In this example, validating the workflow ensures that the intended steps, specifications, and calculations in the MPCR are accurate. This is similar to reviewing a paper MPCR and ensuring all supporting procedures are in place before the MPCR is implemented in production (see §§ 211.100, 211.186, and 212.50(b), and the guidance for industry PET Drugs — Current Good Manufacturing Practice (CGMP)). FDA recommends you implement appropriate controls to manage risks associated with each element of the system. Controls that are appropriately designed to validate a system for its intended use address software, hardware, personnel, and documentation.

How should access to CGMP computer systems be restricted?

You must exercise appropriate controls to assure that changes to computerized MPCRs, or other records, or input of laboratory data into computerized records, can be made only by authorized personnel (§ 211.68(b)). FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data). FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content. To assist in controlling access, FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use. If these independent security role assignments are not practical for small operations or facilities with few employees, such as PET or medical gas facilities, FDA recommends alternate control strategies be implemented. For example, in the rare instance that the same person is required to hold the system administrator role and to be responsible for the content of the records, FDA suggests having a second person review settings and content. If second-person review is not possible, the Agency recommends that the person recheck settings and his or her own work**.**

Why is FDA concerned with the use of shared login accounts for computer systems?

You must exercise appropriate controls to assure that only authorized personnel make changes to computerized MPCRs, or other records, or input laboratory data into computerized records, and you must implement documentation controls that ensure actions are attributable to a specific individual (see §§ 211.68(b), 211.188(b)(11), 203 211.194(a)(7) and (8), and 212.50(c)(10)). When login credentials are shared, a unique individual cannot be identified

through the login and the system would thus not conform to the CGMP requirements in parts 211 and 212. FDA requires that systems controls, including documentation controls, be designed to follow CGMP to assure product quality (for example, §§ 211.100 and 212.50).

How should blank forms be controlled?

There must be document controls in place to assure product quality (see §§ 211.100, 212 211.160(a), 211.186, 212.20(d), and 212.60(g)). FDA recommends that, if used, blank forms (including, but not limited to, worksheets, laboratory notebooks, and MPCRs) be controlled by the quality unit or by another document control method. For example, numbered sets of blank forms may be issued as appropriate and should be reconciled upon completion of all issued forms. Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement (for example, see §§ 211.192, 211.194, 212.50(a), and 212.70(f)(1)(vi)). Similarly, bound paginated notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages.

How often should audit trails be reviewed?

FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record. Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters. FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use. See audit trail definition 1.c. above for further information on audit trails.

Who should review audit trails?

Audit trails are considered part of the associated records. Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data associated with the record as they review the rest of the record (for example, §§ 241 211.22(a), 211.101(c), 211.194(a)(8), and 212.20(d)). For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit (§ 211.192). This is similar to the expectation that cross-outs on paper be assessed when reviewing data.

Can electronic copies be used as accurate reproductions of paper or 247 electronic records?

Yes. Electronic copies can be used as true copies of paper or electronic records, provided the copies preserve the content and meaning of the original data, which include associated metadata and the static or dynamic nature of the original records. True copies of dynamic electronic records may be made and maintained in the format of the original records or in a compatible format, provided that the content and meaning of the original records are preserved and that a suitable reader and copying equipment (for 256 example, software and hardware, including media readers) are readily available (§§ 257 211.180(d) and 212.110).

Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

A paper printout or static record may satisfy retention requirements if it is a complete copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). For example, pH meters and balances may create a paper printout or static image during data acquisition as the original record. In this case, the paper printout or static image created during acquisition, or a true copy, should be retained (§ 211.180). However, electronic records from certain types of laboratory instruments are dynamic records, and a printout or a static record does not preserve the dynamic format which is part of the complete original record. For example, the spectral file created by FT-IR (Fourier transform infrared spectroscopy) can be reprocessed, but a static record or printout is fixed, which would not satisfy CGMP requirements to retain original records or true copies (§ 211.180(d)). Also, if the full spectrum is not displayed, contaminants may be excluded. Control strategies must ensure that original laboratory records, including paper and electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain that all test results are appropriately reported. For PET drugs, see the guidance for industry PET Drugs — Current Good Manufacturing Practice (CGMP) for discussion of equipment and laboratory controls, including regulatory requirements for records.

Can electronic signatures be used instead of handwritten signatures for master production and control records?

Yes, electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record. While § 211.186(a) specifies a "full

signature, handwritten," as explained in the Federal Register on September 29, 1978 (43 FR 45069), part of the intent of the full signature requirement is to be able to clearly identify the individual responsible for signing the record. An electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement. This comports with part 11, which establishes criteria for when electronic signatures are considered the legally binding equivalent of handwritten signatures. Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically. There is no requirement for a handwritten signature for the MPCR in the PET CGMP regulations (21 CFR part 212).

When does electronic data become a CGMP record?

When generated to satisfy a CGMP requirement, all data become a CGMP record. You must document, or save, the data at the time of performance to create a record in compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and 211.160(a). FDA expects processes to be designed so that quality data required to be created and maintained cannot be modified. For example, chromatograms should be sent to long-term storage (archiving or a permanent record) upon run completion instead of at the end of a day's runs. It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook (see §§ 211.100(b), 211.160(a), and 211.180(d)). Similarly, it is not acceptable to store data electronically in temporary memory, in a manner that allows for manipulation, before creating a permanent record. Electronic data that are automatically saved into temporary memory do not meet CGMP documentation or retention requirements. You may employ a combination of technical and procedural controls to meet CGMP documentation practices for electronic systems. For example, a computer system, such as a Laboratory Information Management System (LIMS) or an Electronic Batch Record (EBR) system, can be designed to automatically save after each separate entry. This would be similar to recording each entry contemporaneously on a paper batch record to satisfy CGMP requirements. The computer system could be combined with a procedure requiring data be entered immediately when generated.

Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result (e.g., testing different samples until the desired passing

result is obtained). This practice, also referred to as testing into compliance, is not consistent with CGMP (see the guidance for industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production). In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance. We would consider it a violative practice to use an actual sample in test, .prep, or equilibration runs as a means of disguising testing into compliance. According to the United States Pharmacopeia (USP), system suitability tests should include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied (see USP General Chapter <621>Chromatography). System suitability tests, including the identity of the preparation to be injected and the rationale for its selection, should be performed according to the firm's established written procedures and the approved application or applicable compendial monograph (§§ 211.160 and 212.60). If an actual sample is to be used for system suitability testing, it should be a properly characterized secondary standard, written procedures should be established and followed, and the sample should be from a different batch than the sample(s) being tested (§§ 211.160, 211.165, and 212.60). All data should be included in the record that is retained and subject to review unless there is documented scientific justification for its exclusion. For more information, see also the ICH guidance for industry Q2 (R1) Validation of Analytical Procedures: Text and Methodology**.**

Is it acceptable to only save the final results from reprocessed laboratory chromatography?

No. Analytical methods should be capable and stable. For most lab analyses, reprocessing data should not be regularly needed. If chromatography is reprocessed, written procedures must be established and followed and each result retained for review (see §§ 211.160(a), 211.160(b), 211.165(c), 211.194(a)(4), and 212.60(a)). FDA requires complete data in laboratory records, which includes raw data, graphs, charts, and spectra from laboratory instruments (§§ 211.194(a) and 212.60(g)(3)).

Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?

No. Suspected or known falsification or alteration of records required under parts 210, 211, and 212 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken (see §§ 211.22(a), 211.125(c),

211.192, 211.198, 211.204, and 212.100). FDA invites individuals to report suspected data integrity issues that may affect thesafety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. "CGMP data integrity" should be included in the subject line of the email. See also Application IntegrityPolicy, available at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm.

Should personnel be trained in detecting data integrity issues as part of a 388 routine CGMP training program?

Yes. Training personnel to detect data integrity issues is consistent with the personnel requirements under §§ 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

Is the FDA investigator allowed to look at my electronic records?

Yes. All records required under CGMP are subject to FDA inspection. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§§ 211.180(c) and 212.110(a) and (b)). See also section of the FD&C 400 Act.

How does FDA recommend data integrity problems identified during 403 inspections, in warning letters, or in other regulatory actions be addressed?

FDA encourages you to demonstrate that you have effectively remedied your problems by: hiring a third party auditor, determining the scope of the problem, implementing a corrective action plan (globally), and removing at all levels individuals responsible for problems from CGMP positions. FDA may conduct an inspection to decide whether CGMP violations involving data integrity have been remedied. These expectations mirror those developed for the Application Integrity Policy. For more detailed guidance, see the "Points to Consider for Internal Reviews and Corrective Action Operating Plans" public document available on the FDA Web site, accessible at. http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744

Guidelines for Writing Warning Letters

1. State the reason(s) for the discipline, such as unsatisfactory performance, failure to maintain regular and satisfactory attendance, inappropriate conduct, etc. and quote the rule(s) of conduct violated.

For example: "You are being issued this written warning for tardiness. This is in violation of

The Staff Handbook, which states, “Employees are expected to be punctual and functioning in their positions consistent with their scheduled work hours.”

2. State the facts, giving specific examples, listing witnesses, dates, etc., that verify the substandard performance/behavior. Explain the impact that this has had on operations.
For example: "I am giving you this written warning because you have failed to follow the department call in procedures on two occasions in the last month on [dates]. You also had unexcused absences on [dates]. As a result of your conduct, there was insufficient staffing and our service to students was not up to the desired standard.

3. Describe any previous discussions or corrective actions such as verbal warnings, coaching/counseling, etc., that are relevant to the current problem or similar in nature to the current problem.
For example: "On [date], you received a verbal warning regarding your attendance."

4. Describe future consequences if similar behavior continues.
For example: “Further instances of unscheduled absences will result in additional disciplinary action, up to and including a possible recommendation for the termination of your employment.”

5. Include signature line for employee to show that s/he has received the letter. State clearly that the employee’s signature does not imply agreement with the letter but simply acknowledges receipt of it.

Rules For Responding To FDA 483s And Warning Letters

t happens again and again in the industry, from brand-new technologies to established product lines, from startups to the most recognized and respected medical device companies: an FDA compliance action. Quality units are routinely slapped with significant 483 observations or, even worse, a warning letter, whenever FDA has concerns about product quality, organizational control, complaint handling, or management oversight.

The unfortunate reality is that FDA’s view of a company’s performance may differ from a firm’s self-assessment. Sometimes, the cause is a drift over time in quality oversight. Other times, it's a lack of resources. Whatever the cause, FDA has a way of finding vulnerabilities, and the company is left with a new reality where remediation is a mandate, along with running the actual business.

In this article, we'll discuss how to respond when your organization receives one of these formal declarations of FDA concern. These practices are based on our years of experience, including guiding clients through the journey from citation to successful remediation.

Let's begin by setting the context. The cost of quality and compliance grows exponentially the further you are in the development of your product, and a 483 observation is like an IRS notice: It doesn't go away. So, if one comes along, commit to a thorough response with actionable follow-ups that the FDA can measure. That can avoid escalation to a warning letter.

Remember: the sky is not falling, but it may be a bit cloudy for a while. A quality remediation project can last from a few months to over a year, pulling resources from development or ongoing business operations. Like any business obstacle, a response requires dedicated, focused efforts to resolve the problem and, ultimately, leave your company with a competitive advantage.

To that end, here are the six essential best practices to navigate a 483 or warning letter response**:**

1. Immediately secure executive leadership support and the right expertise

While your head of RA/QA is tasked with leading the response, he or she cannot do it alone. Executive management should be brought on right away to enable and support the response, marshal resources, prioritize company attention, and run external interference. Their support will be key to closing your 483s and warning letters.

Remember, this is an extremely labor-intensive effort and timelines are short, so make sure you have the right in-house resources and expertise and, if not, consider outside help. Regulatory legal advisors and expert regulatory consultants are great at shaping the overall message — both the content and the delivery — in a way that protects your business. For example, they will know how to set the right tone, when to include company executives on correspondence, and how often to correspond with FDA.

Identify leaders within each function area that pertains to the 483; typically, these would be regulatory, quality, compliance, and clinical. This team will be responsible for overseeing the response and the daily (or every-other-day) briefings that will keep executives apprised of progress and prevent meddling.

2. Set the emotional tone: calm and supportive

Remain calm. Once people understand management is committed and in control, they're likely to stick around and contribute to remediation.

It is also important to acknowledge the severity and significance of the situation. Some portion of the staff will have an "I told you so" attitude, while others will be dazed by the sudden change they are facing. Listen, engage, and respond to concerns and comments, as your staff may offer useful information for your response to FDA.

Your staff and other stakeholders will realize that the response to FDA is like a new full-time job on top of their regular job. Acknowledge this new reality and show that the company is committed to easing the burden — either by providing more resources or temporarily removing some responsibilities**.** One of our most successful response teams for a client was composed of 12 dedicated resources, assigned just for the response. The CEO stood in front of his entire team and said, *"We do not have to do this alone. The cavalry is here to help us. And if we need more help, we will get it!"*

3. Organize: Open the communication channels and keep them open

Writing a response to FDA can be a little like coming across an automobile crash on a busy highway. It's human nature to want to rush in and get involved. It is important to harness this enthusiasm and create parallel work streams. Assign teams to work on responses to each observation. This can also free up time for RA and QA to guide or lead efforts to collect and analyze data.

Inform the members of the teams about needs to be done, who is going to do what, how everyone will be kept on the same page, and what the timeline is. This is an ideal time to have your executive support on display, committed to getting resources and acknowledging what lies ahead.

It is critical to hold a regular team meeting — typically weekly, in the beginning — to provide status updates on how observation responses are coming together. Inquire if executive management wants to participate. This structure allows staff to stay connected, holds workstream leads accountable, and provides a non-threatening environment for executive involvement in the response. Use one of the first status meetings to craft a communication plan that helps maintain broad stakeholder alignment.

An often-overlooked element of compiling a response is basic logistics. A response to FDA can be a hefty document — many are in paper form — with hundreds of attachments. It may seem mundane, but make sure you have the right tools to carry out this labor intensive, paper-laden, organizationally demanding project**.** For example, printing 8 to 10 copies of a two- to three-volume response can take an entire day on a standard speed printer.

4. Write a thorough, proactive response

Issuing the initial response to a 483 is one of the most critical regulatory responses you will ever have to provide to FDA. A well-done, thorough response can change the tenor of the interaction with FDA and establish your company's commitment to quality. Conversely, a misguided or antagonistic response can be a key reason for escalation to an enforcement action.

A well-constructed cover letter that emphasizes your company's (and its executive team's) commitment to quality and compliance sets a positive stage for responding to any FDA findings. Like all good scientific writing, a good cover letter should state up-front what you are going to tell the agency. A message of "we hear you" and "commitment to patient safety is paramount" should be reiterated throughout the response. In cases where the 483 is complex or resources are limited, it may be wise to state up front that expert consultant(s) have been engaged to assist in remediation, showing the company's commitment to thorough remediation.

The more comprehensive the response, the more FDA will be assured that your company takes its concerns seriously. We were recently engaged by a client who received a warning letter following three inspections over three years, each with 483 observations Every response to FDA contained rationales as to why the inspectors missed key data or were just plain wrong. While in some cases the assertions may have been accurate, three years of observations, by different teams and with no evidence of real evaluation and change by the company, had the predictable outcome of a warning letter. The takeaway lesson is the importance of a proactive response.

Although it can be difficult to distinguish between them, 483 observations can be divided into "one-off" or systemic observations. However, a good root cause analysis will help determine if, for example, a complaint that was not closed on time was due to sub-par operator performance or poor processing flow of that complaint.

Every observation should have a thorough root cause analysis performed and, if necessary, one or more corrective and preventive actions (CAPAs) identified, along with a CAPA reference. (Next month's article will discuss why you should embrace your CAPAs.) In the case of "one-off" observations, adequate responses are often based on surveillance and training. A systemic observation usually requires fundamental or broad process changes, which must be described in the response.

The final element of a successful response is the description of a set of actions or programs to correct and prevent recurrence of FDA observations. Instill confidence in the remediation plan with realistic due dates, competent people to lead them, and specific outcomes that can be measured and documented. This is where the proverbial rubber hits the road: Failure to demonstrate proof of corrections could lead to more compliance risk, escalating a 483 to a warning letter or a warning letter to a consent decree.

A note about timelines: FDA would rather see viable due dates that correct the root cause with a sustainable solution than quick, superficial corrections that could result in further FDA inquiry. As with most projects, it's better to set up a realistic timeline and come in early than to explain a delay.

5. Engage a range of internal and external stakeholders to thoroughly review the response

As this massively important document comes together and the reply deadline is fast approaching, who should review and comment? Internal reviewers typically include executive management, key functional heads, regulatory/quality, legal, and compliance. Many times, marketing and R&D also weigh in, depending on the observation. These are important voices and represent the teams that will have to implement any follow-up actions committed to by the company.

External reviewers can provide a second or third opinion to identify gaps in the response or tweak key messages. Regulatory advisors or consultants experienced with FDA communication should review the response. We often recommend more than one review — for example, a review on day one or two to hone the theme, and another once the draft is compiled, to fine-tune specific messages.

6. Timing is everything.

Remediation should start the day after receiving a notice of 483 or a warning letter. FDA requires a response to most compliance notices within 15 business days. Although FDA doesn't have to confirm your response, it is a good idea to contact the agency and confirm receipt.

In your written response to FDA and in any phone/email correspondence, voluntarily establish a follow-up plan. Set a schedule for providing regular updates following the response. Monthly updates often make sense, but for warning letters or field actions, bi-monthly is recommended. Whatever schedule you choose, it is important to demonstrate your company's commitment by sticking to the schedule.

Take and maintain control to achieve a successful response

Although responding to a 483 can be a complicated process, it can be reduced to several key components: Acknowledge the observation at the executive level, quickly ascertain the root cause, react with commitment and urgency, acknowledge when you need outside expertise, and show progress. Follow these steps and you're well on your way to a successful response.

One way that the Food and Drug Administration (FDA) protects public health and ensures compliance with the Food, Drug and Cosmetic Act is by conducting inspections of clinical trial investigators, clinical trial sponsors, Institutional Review Boards (IRB) and facilities that manufacture, process or pack FDA-regulated products. At the conclusion of an investigation, a site may be issued a Form 483 or a Warning Letter. Read on to learn the differences and similarities of these forms of communication provided by the FDA to the inspection site.

What is a Form 483?

- A list of observations made during the inspection that is communicated at the conclusion of the inspection.
- The observations are listed in descending order of importance
- The list is a snap-shot of observations noted, not an all inclusive list

What to do at the conclusion of an inspection and after when issued a Form 483:

- *Take time with the inspector at the conclusion of the inspection to review the Form 483*
  - Gain an understanding of observations noted and assure their accuracy
  - Understand the broader message the agency is sending

- Identify and discuss any errors in observations
- Ask questions!
- Demonstrate awareness of applicable regulations
- Consult with legal counsel as necessary

- *Respond formally in writing*
- Not required, but demonstrates good practice
- Address to the District Director with a courtesy copy to the lead investigator
- Respond within 15 days or the agency does not have to consider the response in their decisions for subsequent actions

Taking the opportunity to ask questions and understand the observations noted in the 483 prior to the inspector leaving the site will help formulate a future response and implement corrective action plans. Challenges or questions to the observations noted are not uncommon, as long as the focus is on the issues and not the inspector personally. If convincing information is provided regarding an observation, it may be deleted from the 483.

What is a Warning Letter?

After a Form 483 is issued and the inspector completes the Establishment Inspection Report, the agency may issue a Warning Letter. A Warning Letter indicates that higher FDA officials have reviewed the observations and that a serious violation may exist. This formal notification allows for voluntary and prompt correction action. *A Warning Letter:*

- Includes evidence collected to support observations and provides further explanation
- Establishes a background of warnings should further action be required by the FDA
- Might be hand-delivered or the agency may invite top corporate management to a meeting at the District Office or Center
- The site must reply, in writing, within a time line as prescribed (usually 15 days) or request an extension and provide justification for request

Form 483s and warning letters are public information. Form 483s are difficult to obtain quickly and one has to know that it exists to request it. Adversely, Warning Letters are published upon issuance and promptly posted on http://www.fda.gov.

General violations in CGMP

CGMP Deviation regulations of finished pharmaceutical Title 21 CFR, Part 210 and 211

This violation cause drug product to be adulterated with the meaning of section 501 (a) (2)

(B) of the federal food, drugs and cosmetics Act (21 U.S.C & 351 (a) (2) (B)) is that the method used in or the facilities or control used for, their manufacturer, processing, packing or holding do not conform to ,or are not operated or administered in conformity with CGMP.
In addition, drug product are unapproved new drug violation of section 505 (a) of the Act [21 U.S.C & 355 (a)], these unapproved new drugs are also misbranded in violation of 502(f) (1) of the Act

If not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the Safety, Identity, Strength, Purity and Quality of drug product (SISPQ), violation under [21 CFR & 211.67 (a)]

Example

Not validated cleaning methods or not adequate scientific justification

- If laboratory records fails to include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 CFR & 211.194]

Example

Failure to take readings and raw data or incomplete data

- If not established or followed appropriate written procedure designed to prevent microbiological contamination of drug product purporting to be sterile [21 CFR & 211.113 (B) violation)

Example

A) Environment monitoring is inadequate in relation to personnel monitoring
B) Technician performing air sampling at HEPA Filter in wrong way or not as per SOP

- If failed to have facilities used in the manufacture, process, packaging and holding of drug products of appropriate construction to facilitate cleaning, maintenance and proper operation. If not then violation of this (21 CFR, 211.42(a)).

Example

Floor titles in specific area (production, sterile or manufacture having filth or hole or cracked or inadequately repair with more gap.

- Firm has not thoroughly investigated the failure of a batch or any of its components to meet its specification whether or not the batch has already released or distributed. If not then violation of this (21 CFR, 211.192).

- If failed to follow and document at the time of performance required laboratory control mechanism. (21 CFR, 211.160(a)).

Example

1. Laboratory Analyst did not document balance weight at the time of sample weighing.
2. Weigh print after chromatographic run.
3. Backdated print out of sample.

Data integrity is main issue Raised in most FDA warning letter.

Laboratory record

FDA observed deletion of data peak

HPLC – No Injection Deletion

GC – observed deletion of data

Compliance can be made by no addition or no deletion of data and all trails must be justified and if training is given to staff then no addition or no deletion and log book must state that training schedule for trails run.

Audit trail must be enable and reviewed periodically.

Corrective action and plan

- Original data
- Risk assessment
- Management quality policy
- Strictly follow cGMP Norms
- Action to prevent the recurrence of cGMP deviation
- Establishment of stability study program
- Voluntary recall if the error or critical deviation at industry level after marketing or during post marketing surveillance
- Follow good documentation practices
- Follow good laboratory practices
- Medicine and pharmaceutical must also follow with specific good distribution practices
- Level of control must be raised from raw material, packaging material (Accurate, Legible, Contemporaneous, Original, Attributable(ALCOA)) in process, finished dosage form. Maintain log book properly

- Guidelines for Out of specification(OOS) and out of trends(OOT) must be follow if any required

FDA Warning letter Format

Department of Health and Human Services
Warning Letter
Acknowledgement receipt Requested
Date format (Month Date, Year)
Address of unit (Pharmaceutical)
Dear (Director/ VP or Management)
During our **DATE OF INSPECTION** inspection of your active pharmaceutical ingredient (API) and finished pharmaceutical manufacturing facility, **NAME OF INDUSTRY** , investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) for the manufacture of APIs and the CGMP regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your APIs and drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated DATE OF COMPLIANCE COMMENT RECVIED and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence (If Any).

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following

API
CGMP,VIOLATIONS
FINISHED PRODUCT: CGMP VIOLATIONS
Response to this letter, please inform this office of the actions your firm will take to prevent recurrence of this situation. Also, provide a retrospective evaluation of all lots currently in the stability program and assess whether an OOS was obtained at any testing interval.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

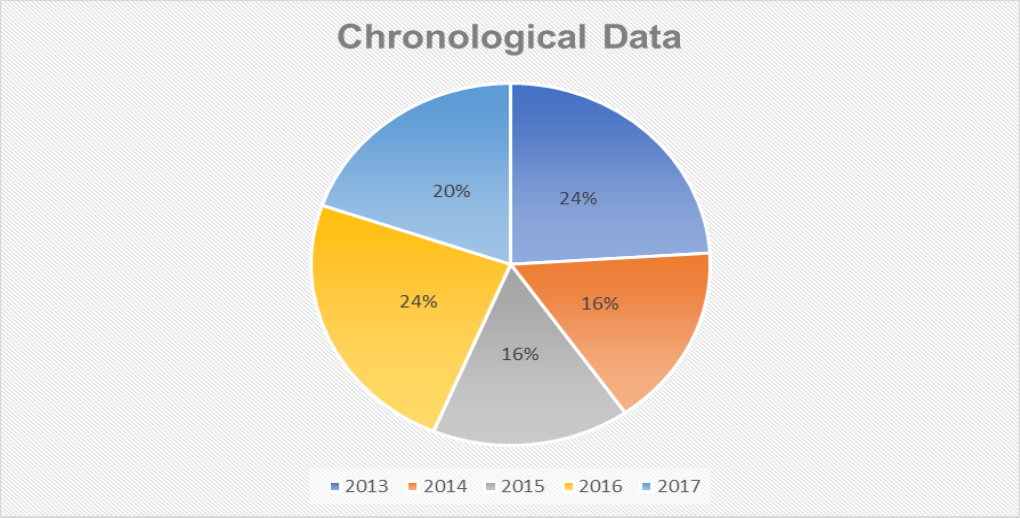
If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of

patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at manufacturing site (inspected) into the United States. The articles are subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Reply Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI (UNIQUE CODE)

Please send your reply to the following address
ComplianceOfficer
FDA/CDER/OC/OMPQ/DIDQ
10903NewHampshireAve.
WhiteOakBuilding 51,
Room4237
Silver Spring, MD 20993
Sincerely,
Director
Office of Manufacturing and Product Quality
Office of Compliance Center for Drug Evaluation and Research



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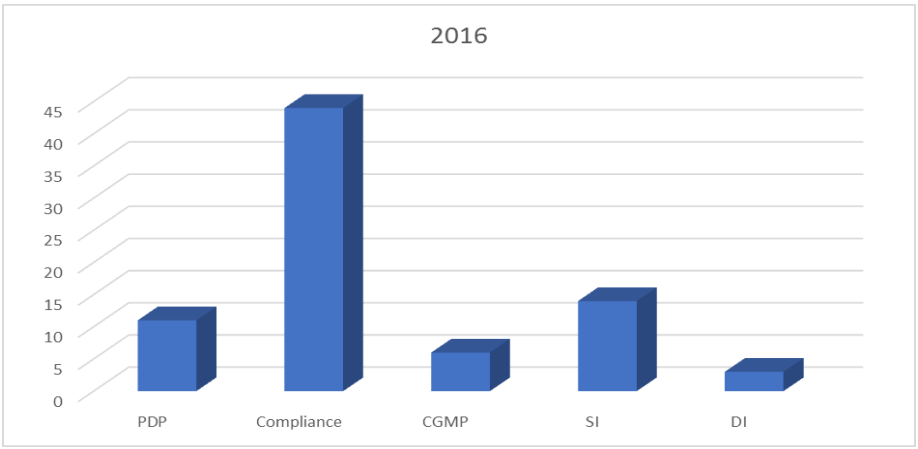
The above diagram represents the data of warning letters issued during 2017FY in all categories.



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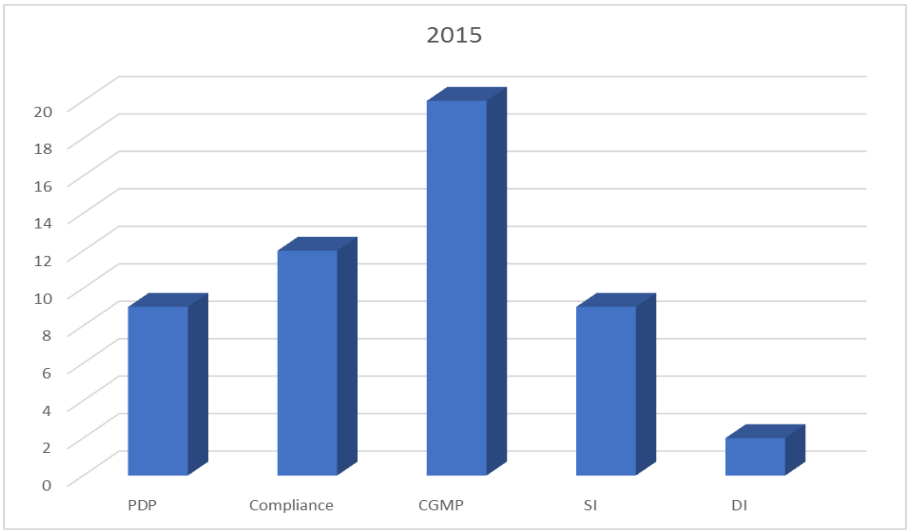

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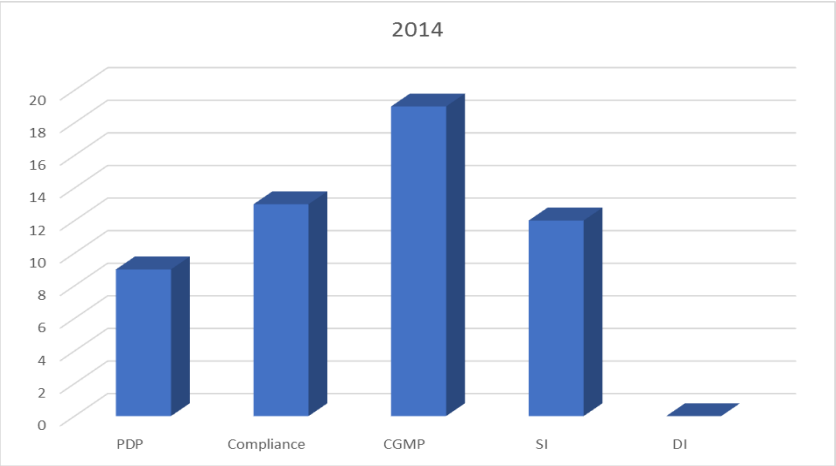

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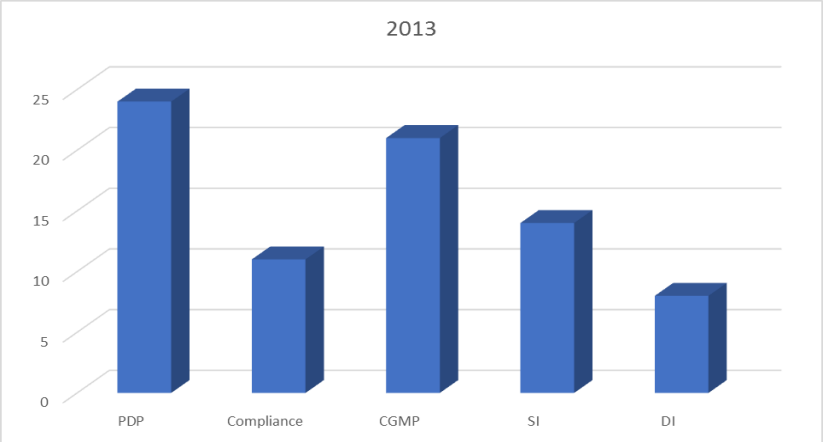
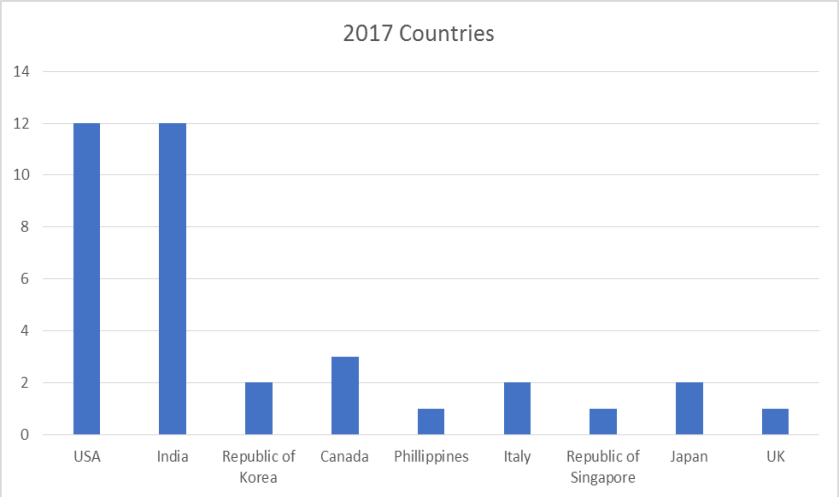
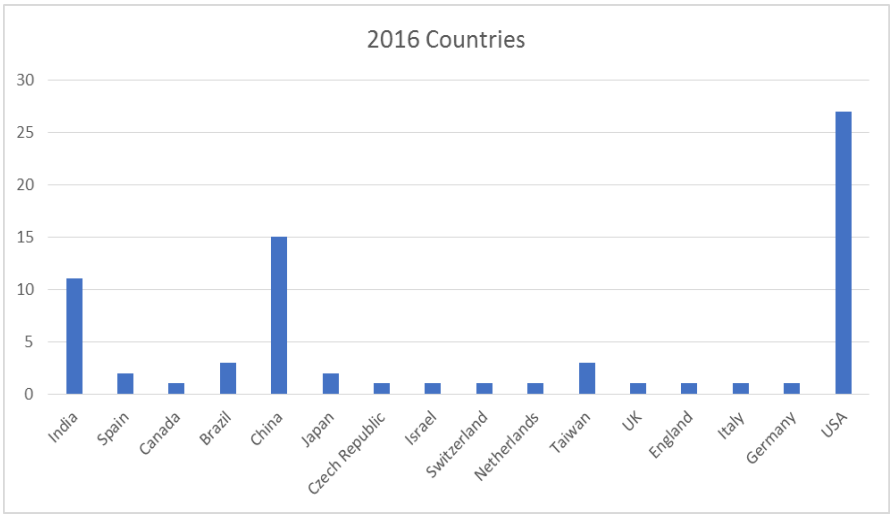


The above diagram represents the data of warning letters issued during 2013FY in all categories

Data arranged based on countries received warning letters



The above diagram represents the data of different countries received warning letters in 2017



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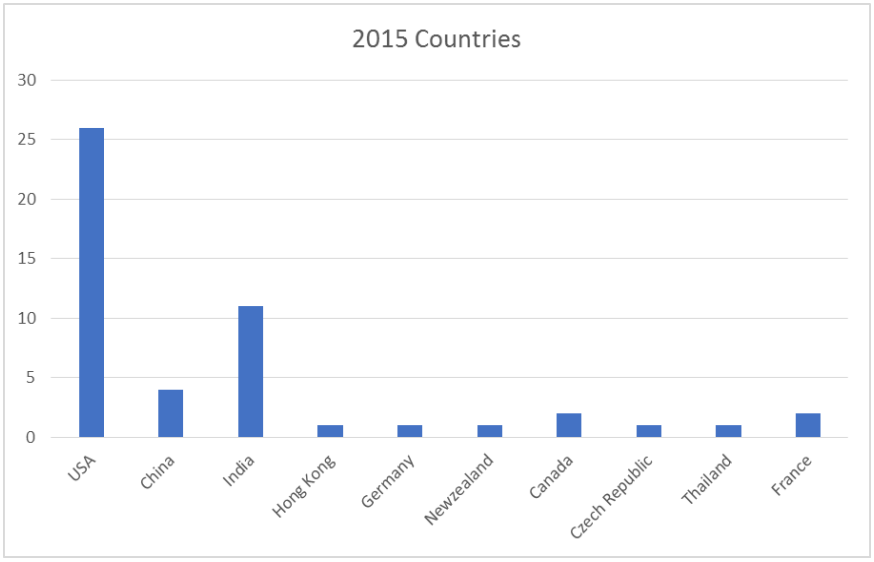

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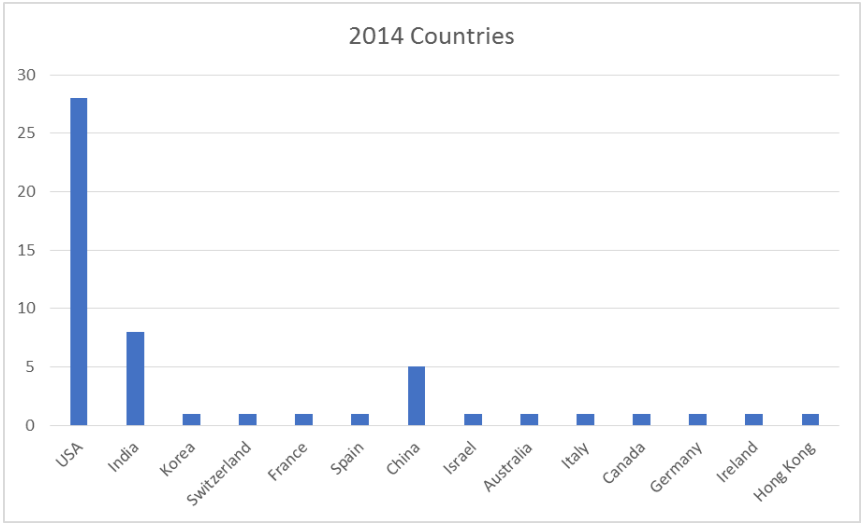

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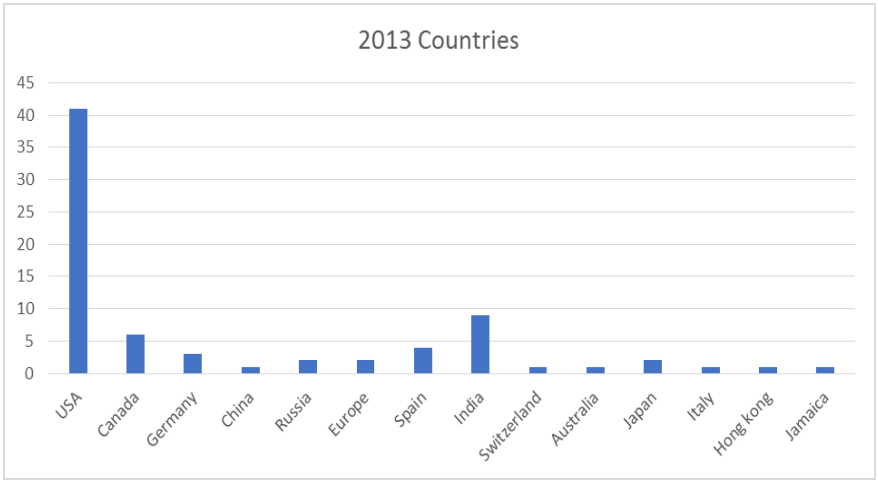
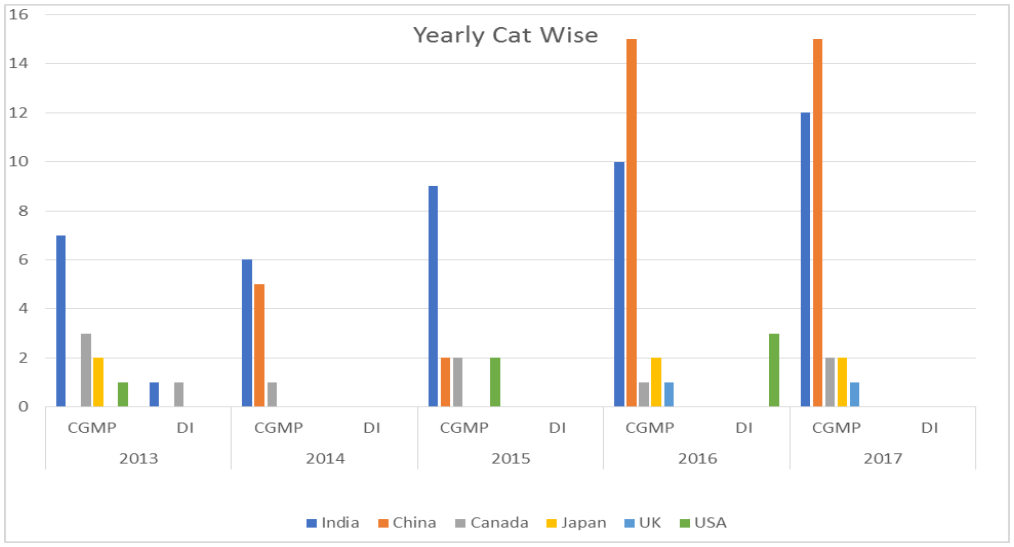
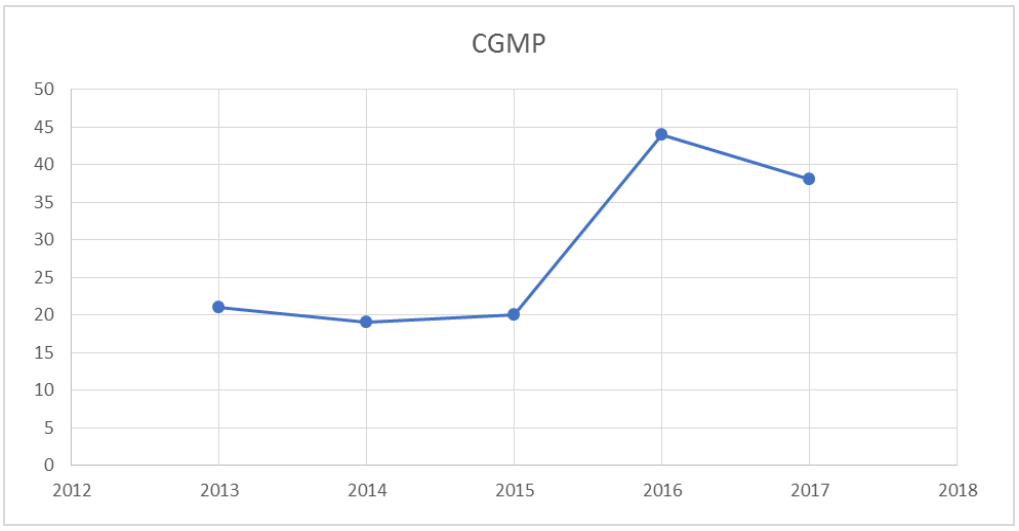


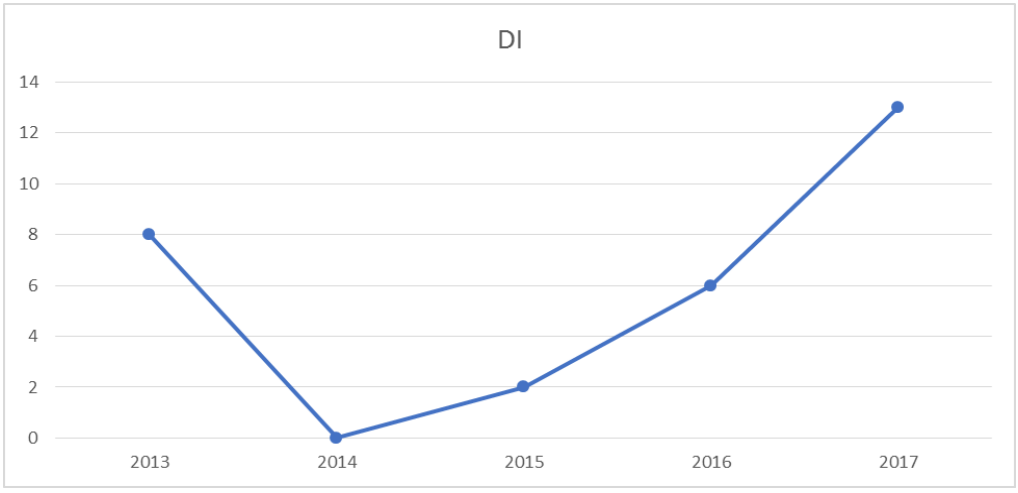
The above diagram represents the data of different countries received warning letters in 2013

The following diagram represents the data on CGMP and DI for the following countries during 2013-2017



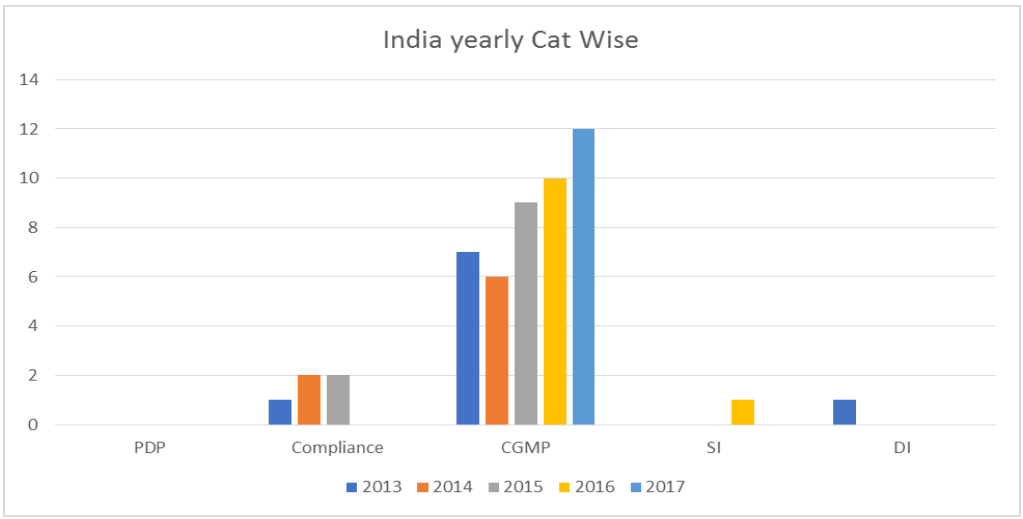


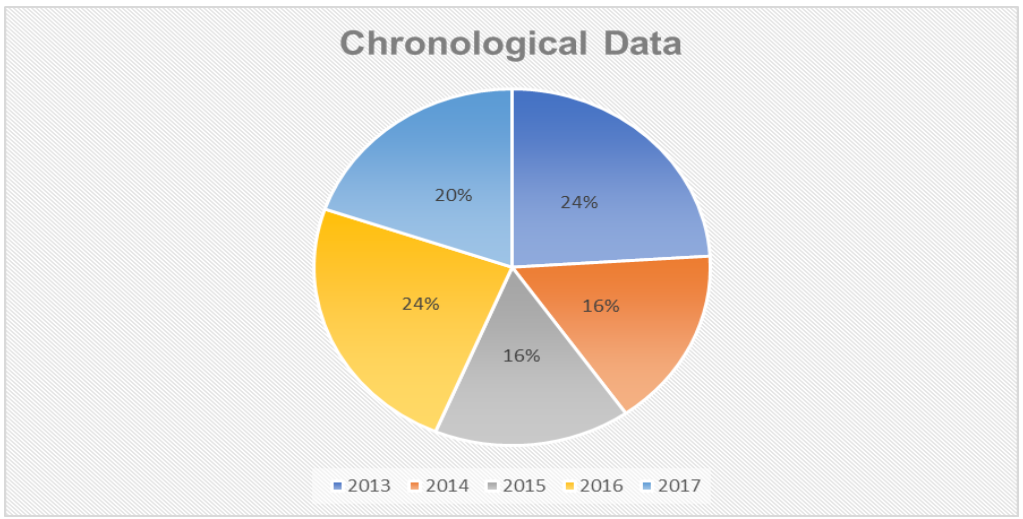
The above diagram represents no of CGMP letters issued during 2013-2017



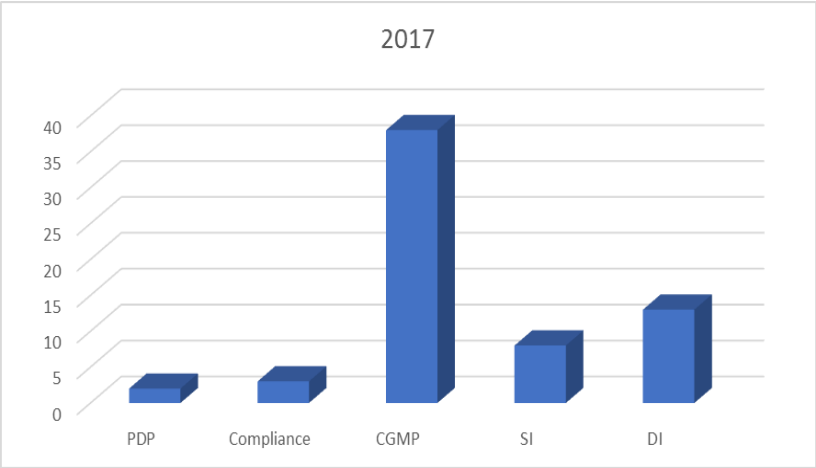
The above diagram represents no of DI letters issued during 2013-2017

THE BELOW DIAGRAM REPRESENTS THE TOTAL NUMBER OF WARNING LETTERS ISSUED IN INDIA FROM 2013 -2017

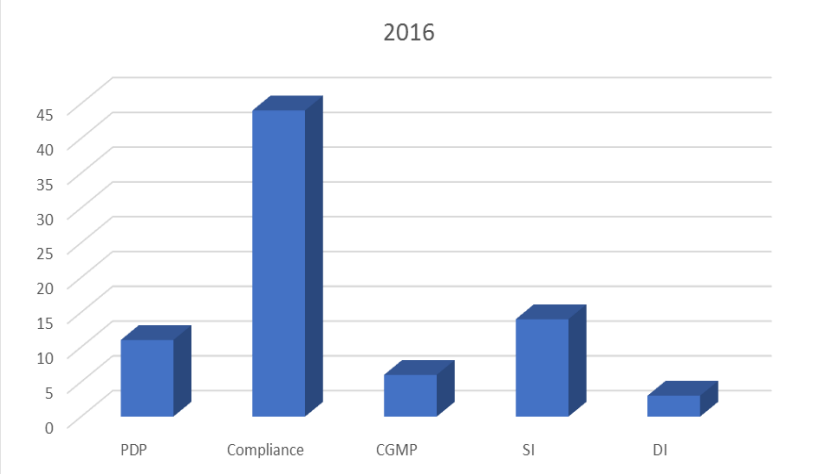




The above diagram represents the chronological data of the warning letters issued during the financial years from 2013 to 2017.



The above diagram represents the data of warning letters issued during 2017FY in all categories.



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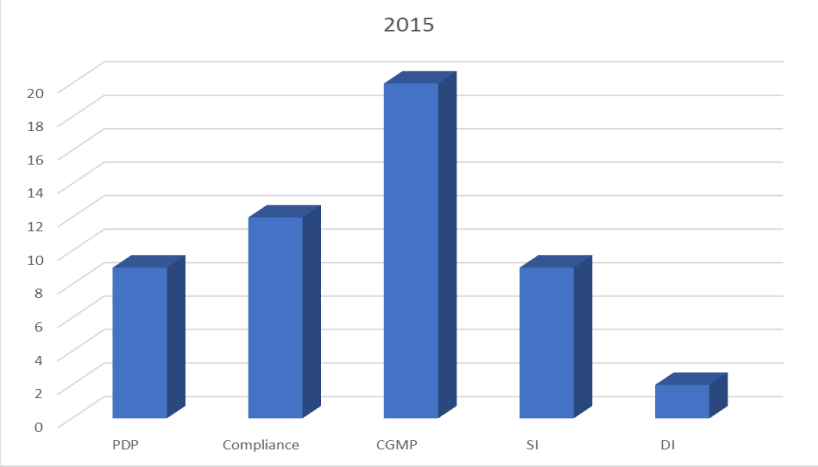

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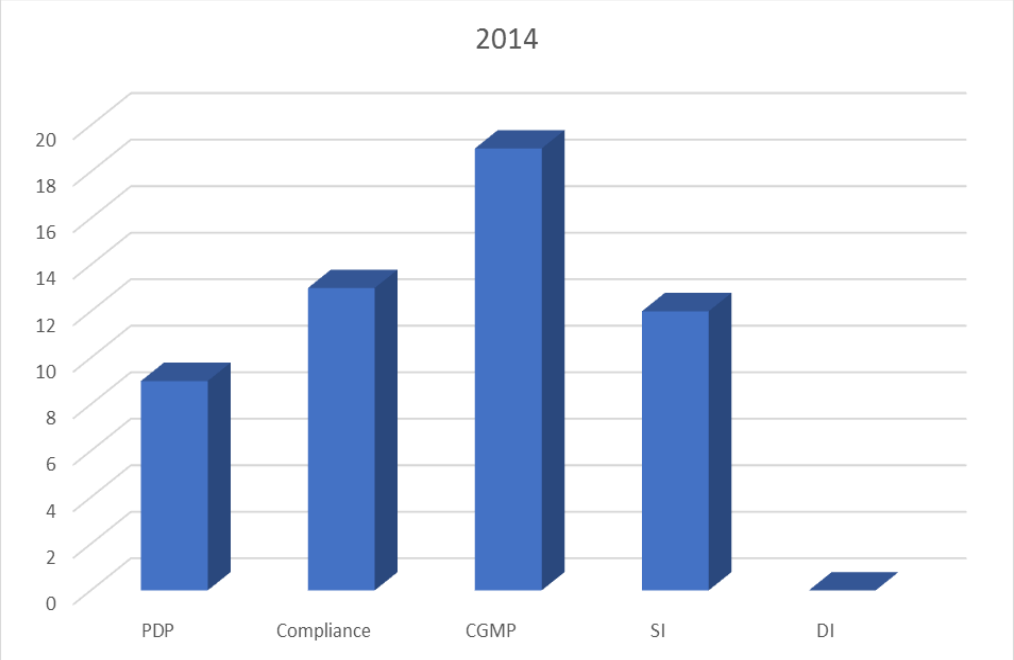

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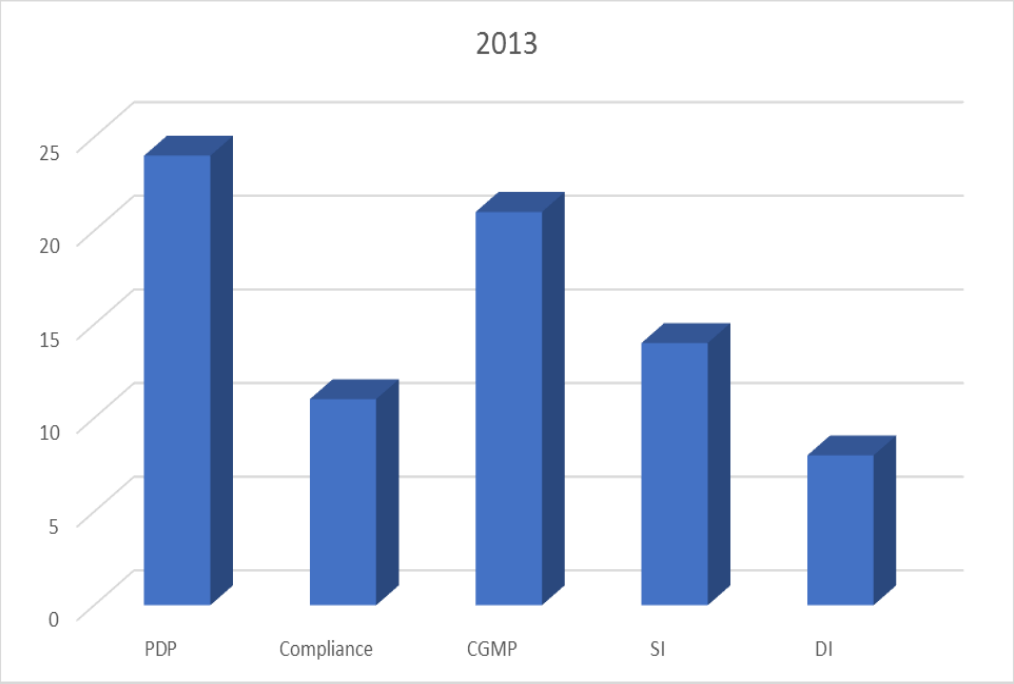

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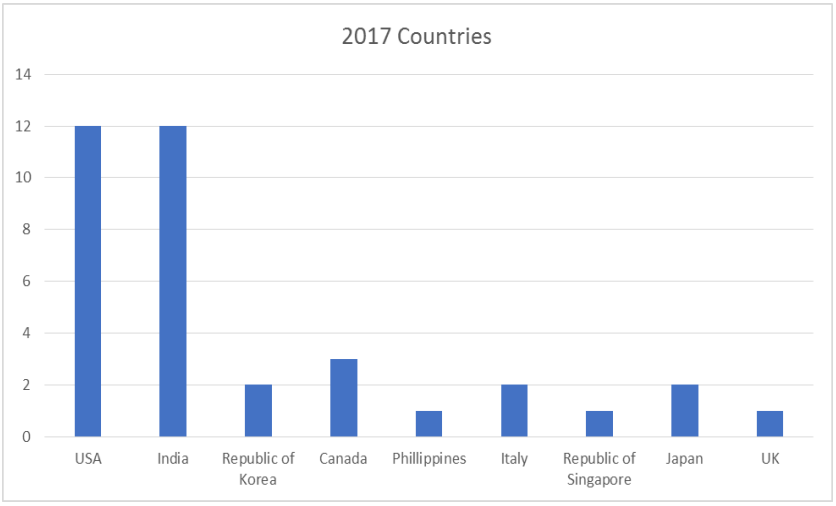
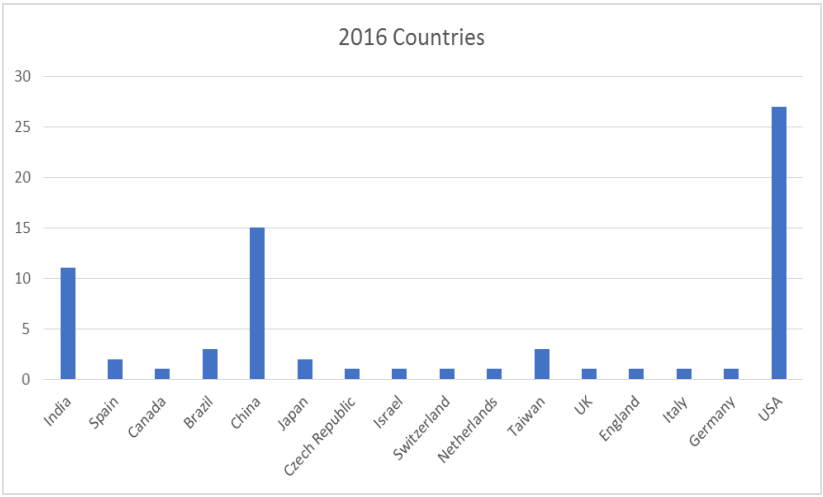
Data arranged based on countries received warning letters



The above diagram represents the data of different countries received warning letters in 2017



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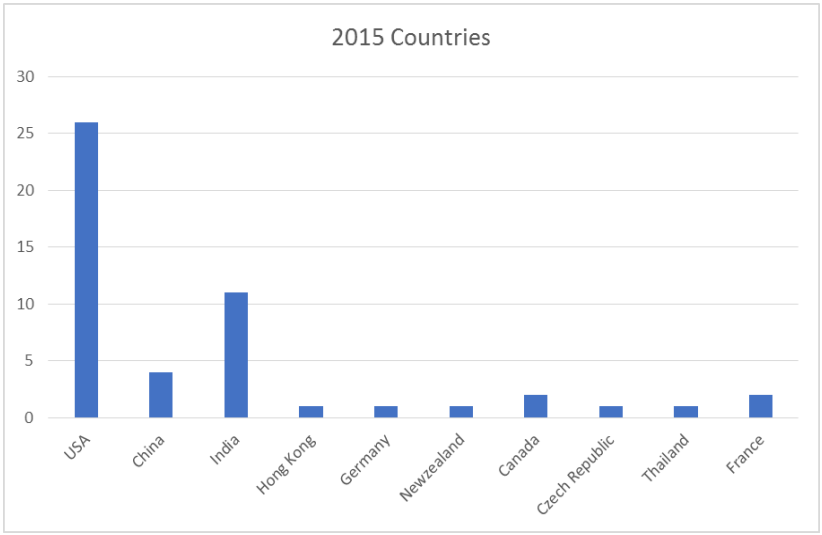

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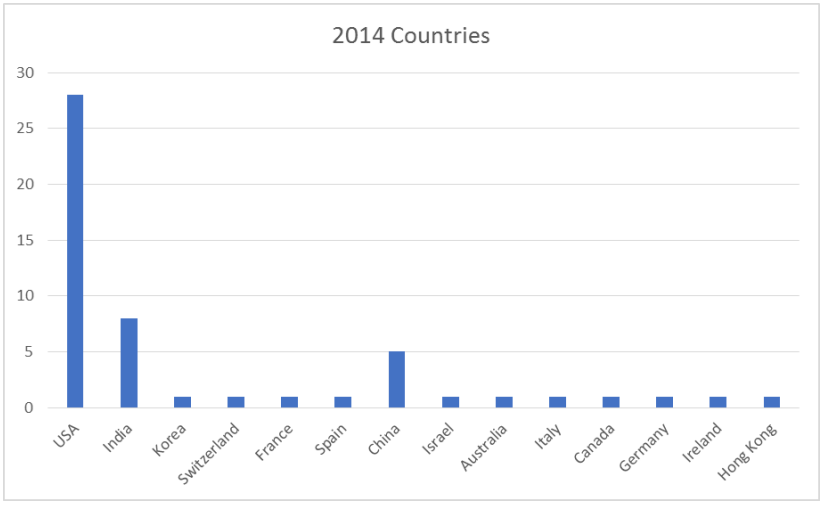

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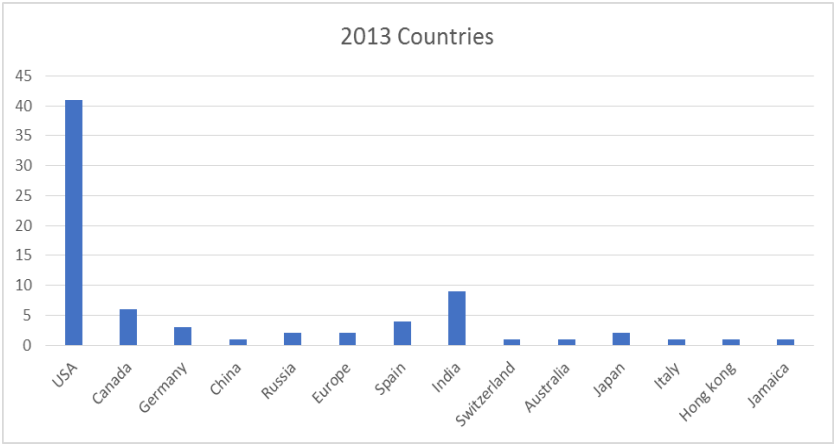

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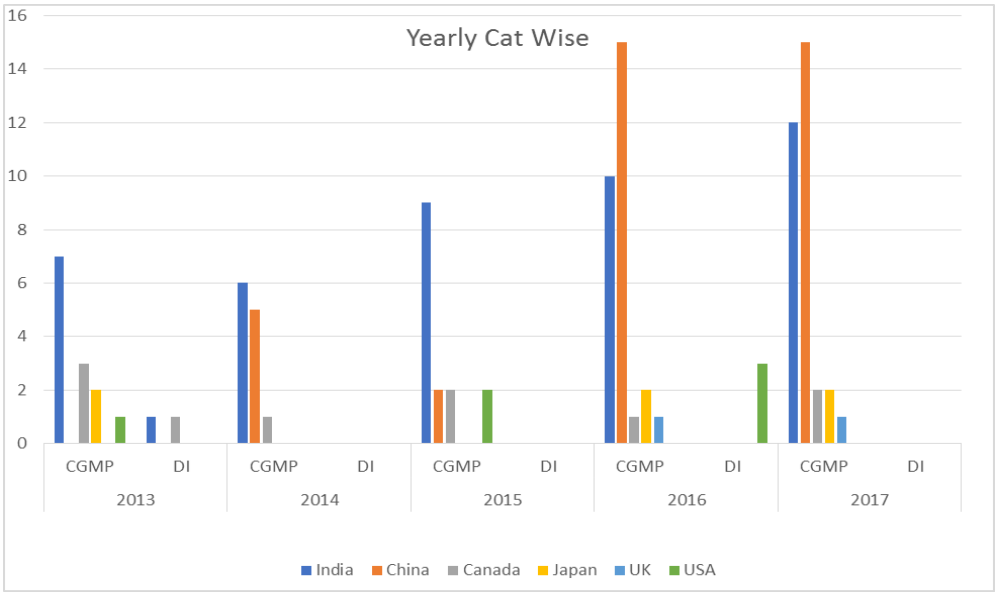
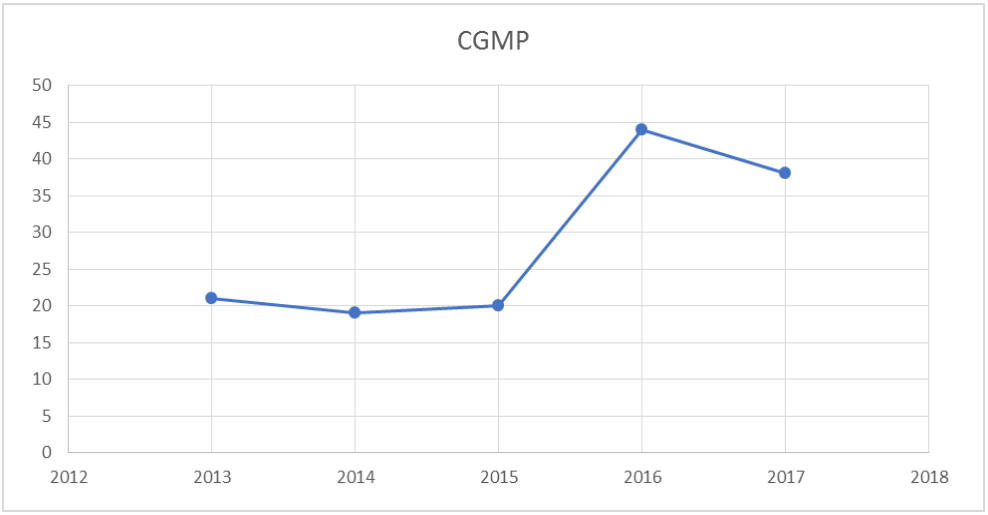
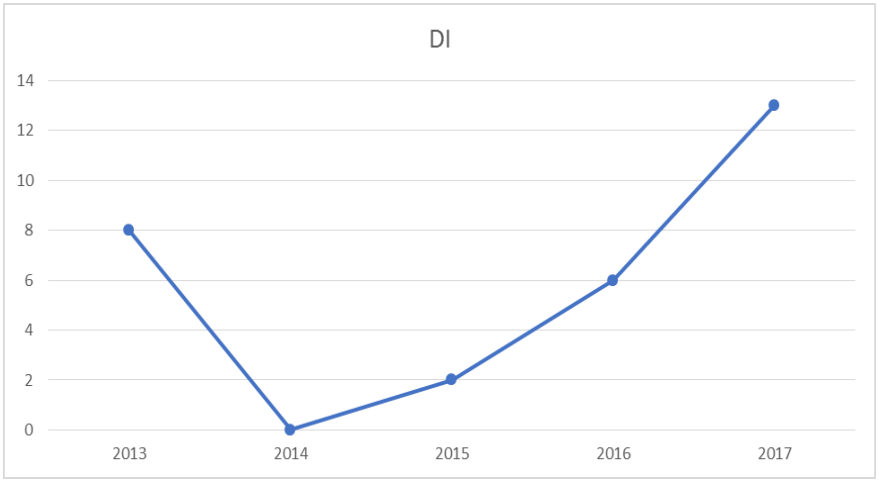




The above diagram represents no of CGMP letters issued during 2013-2017



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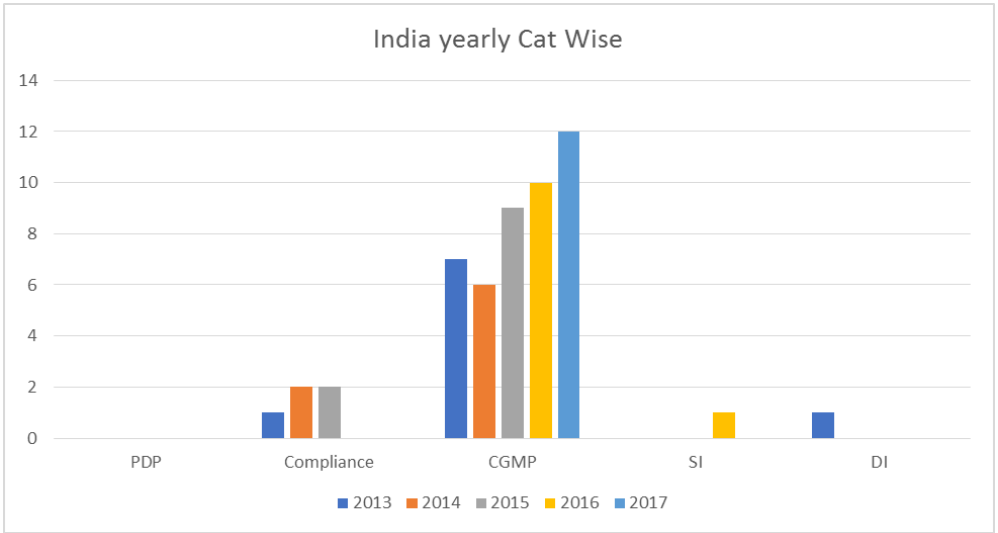

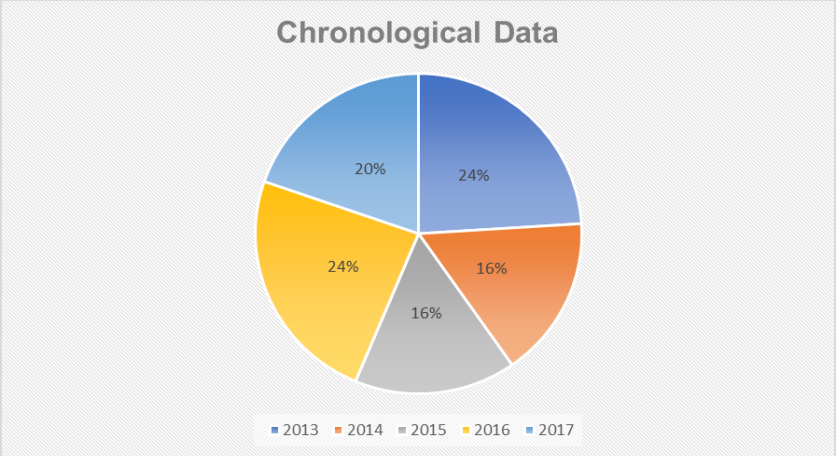

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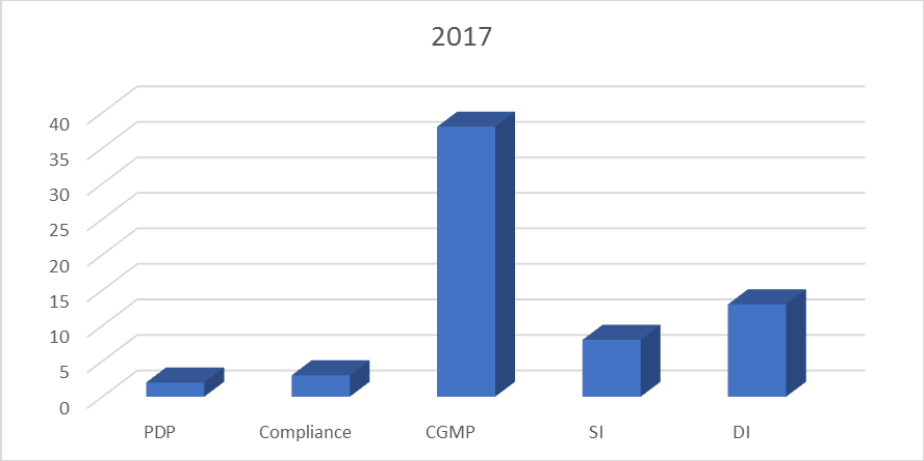

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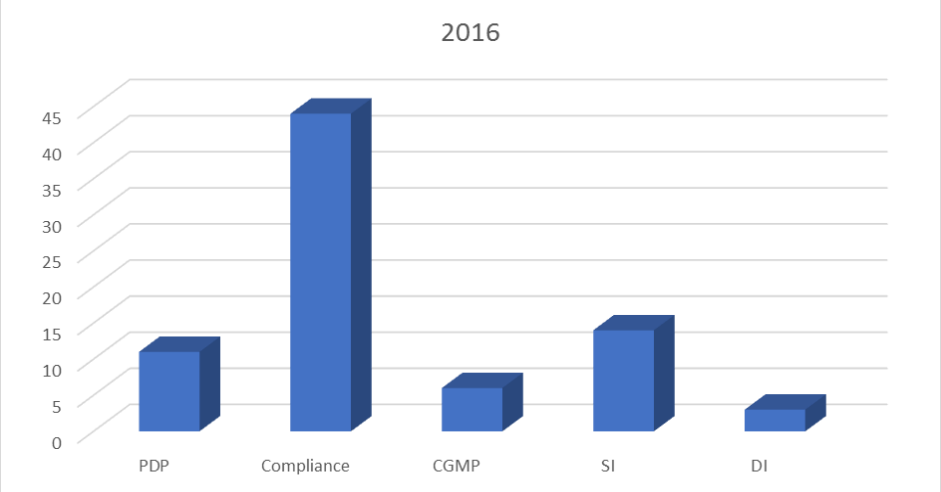

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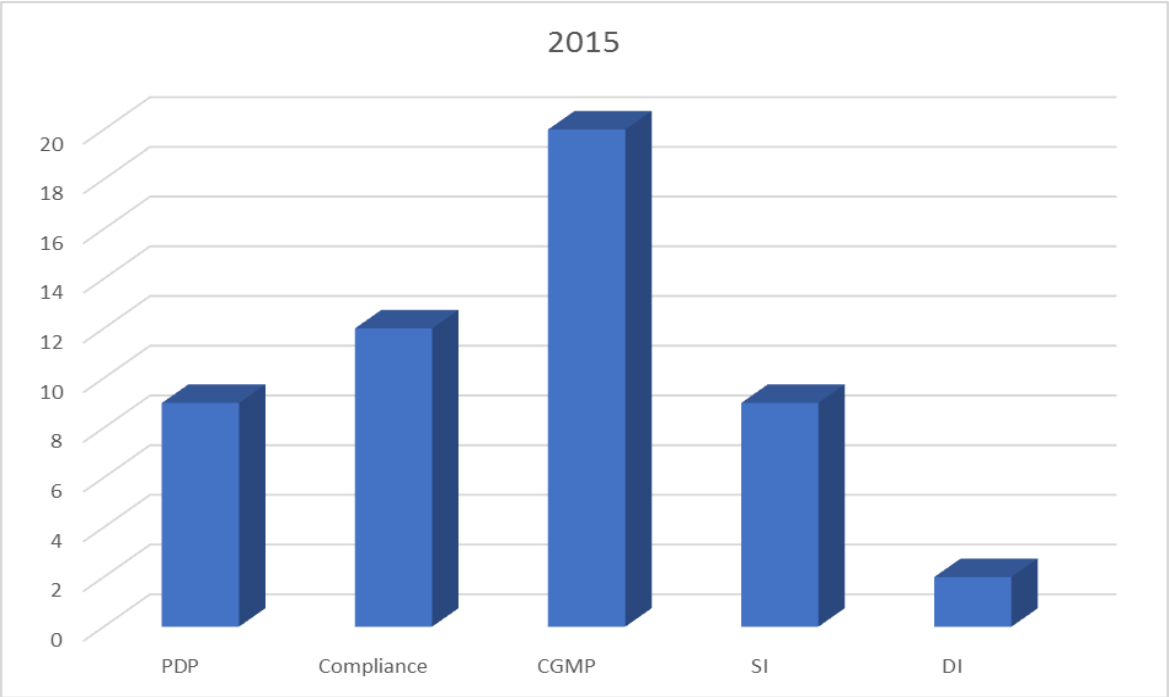

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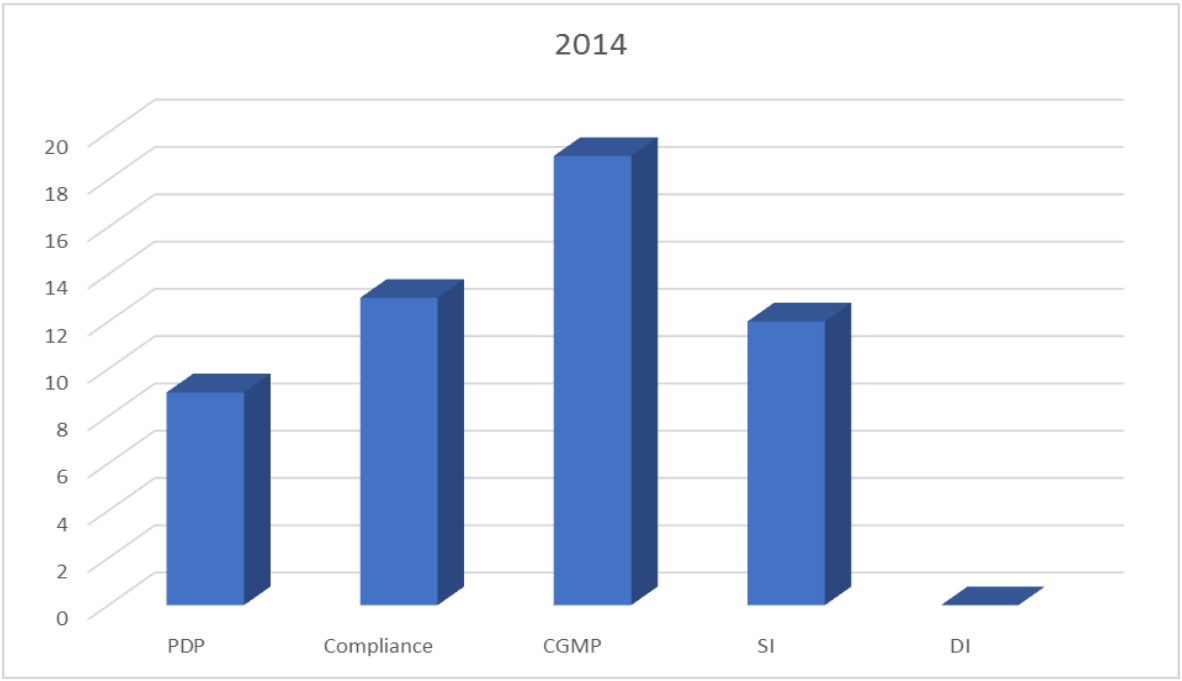

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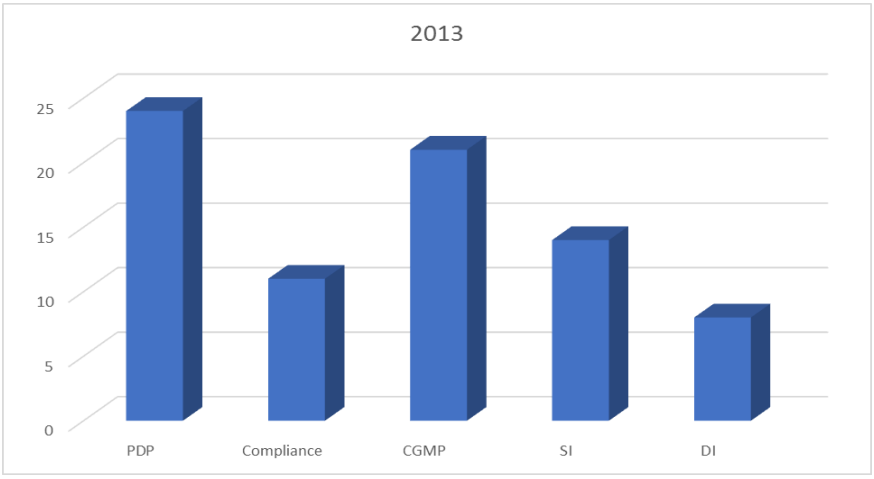
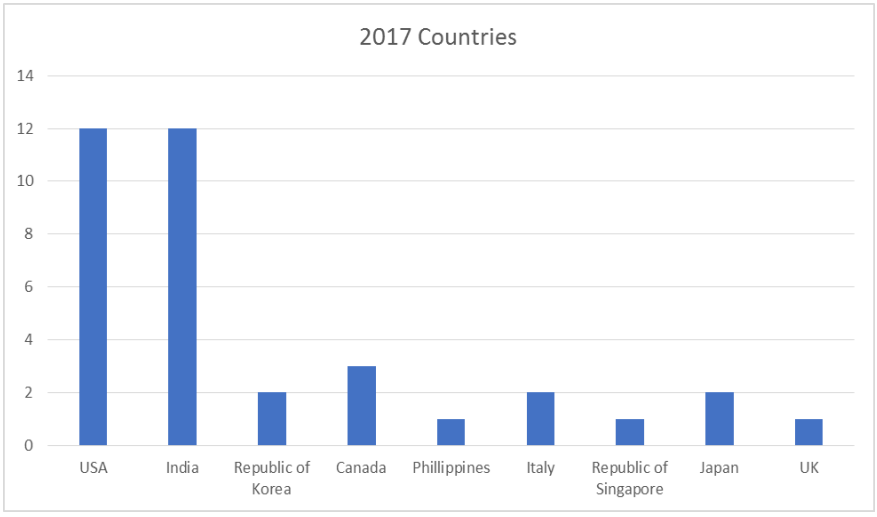
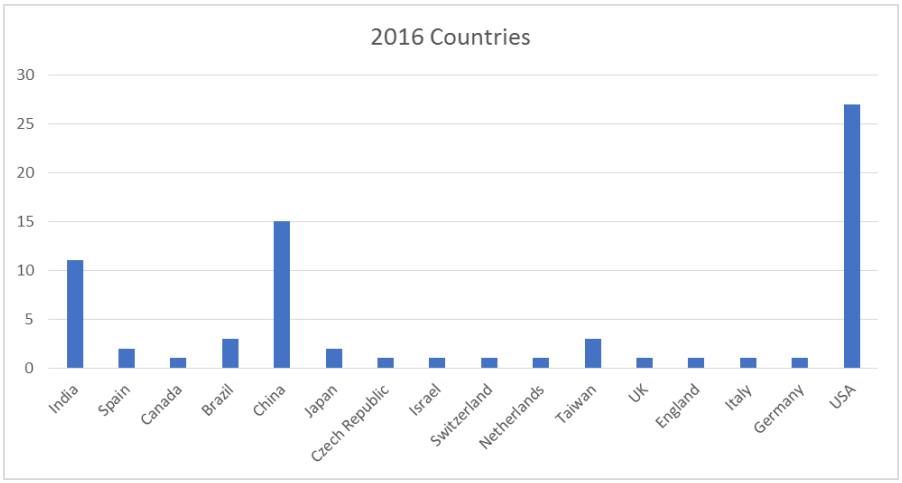


The above diagram represents the data of warning letters issued during 2013FY in all categories

Data arranged based on countries received warning letters



The above diagram represents the data of different countries received warning letters in 2017



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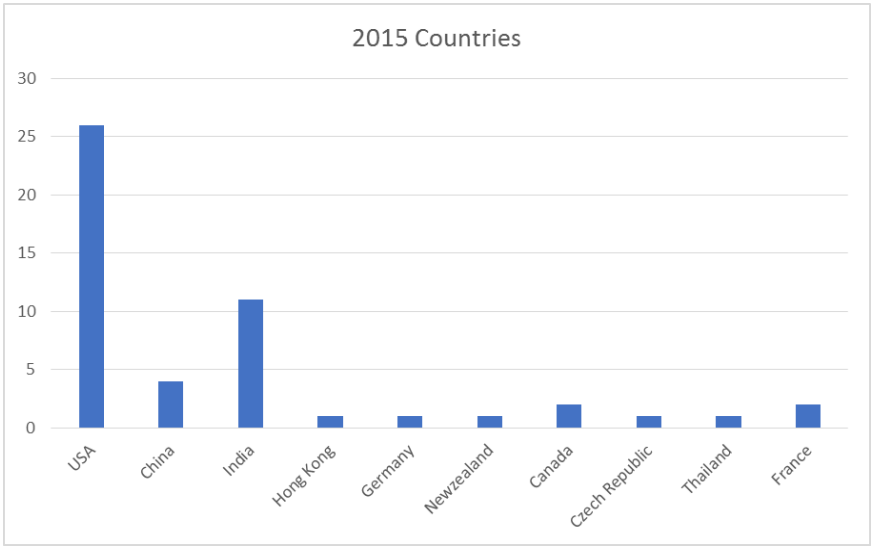

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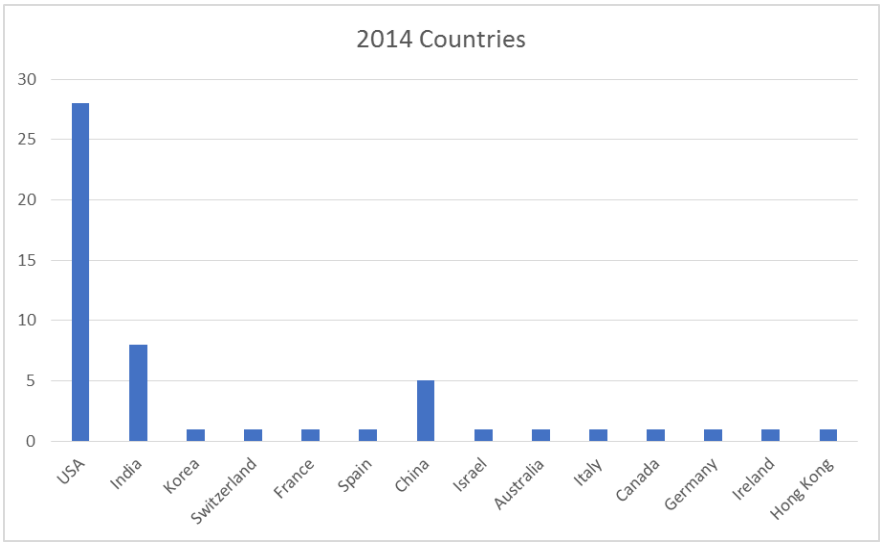
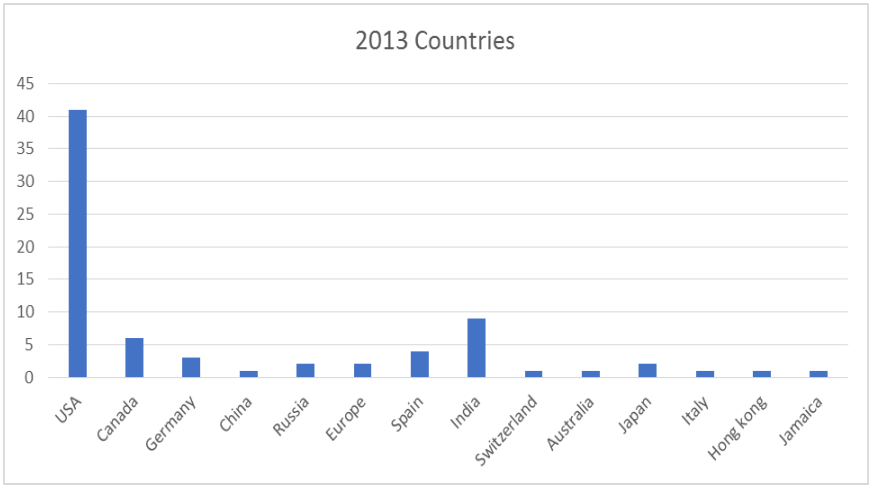
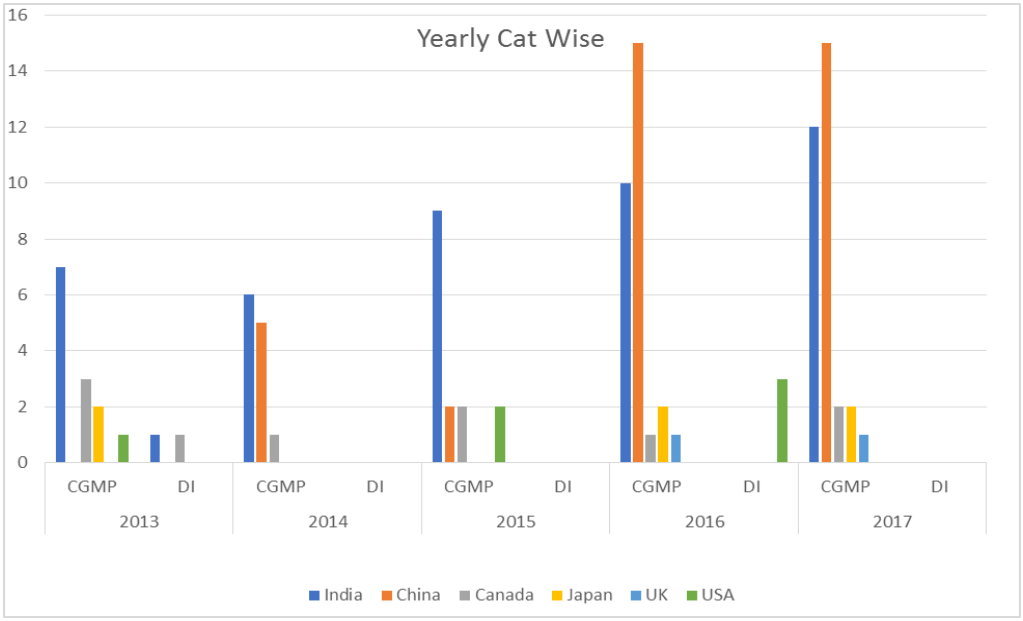


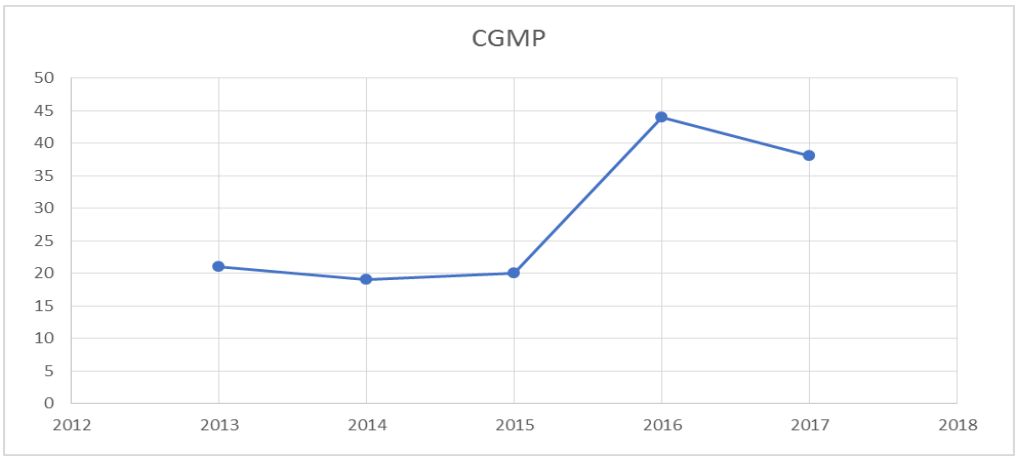
The above diagram represents the data of different countries received warning letters in 2014



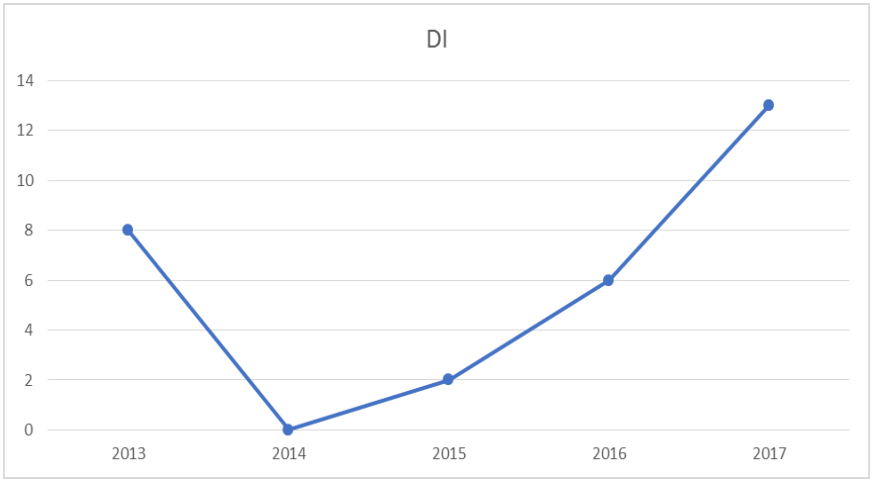
The above diagram represents the data of different countries received warning letters in 2013

The following diagram represents the data on CGMP and DI for the following countries during 2013-2017



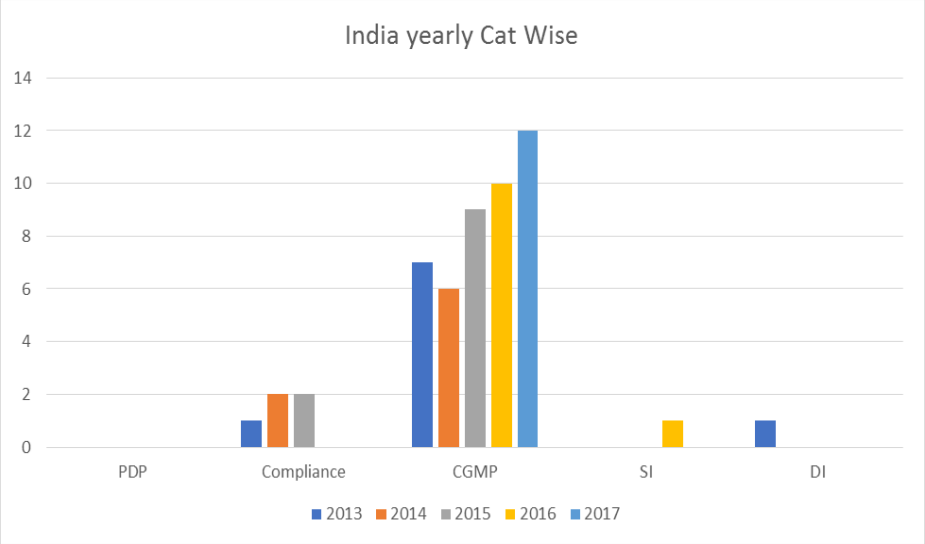


The above diagram represents no of CGMP letters issued during 2013-2017



The above diagram represents no of DI letters issued during 2013-2017

THE BELOW DIAGRAM REPRESENTS THE TOTAL NUMBER OF WARNING LETTERS ISSUED IN INDIA FROM 2013 -2017



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