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Medical Device Warning Letters: Trend Analysis from 2011 to 2016

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ABSTRACT
The medical device industry is one of the most dynamic fields of medical progress with thousands of new products marketed every year among other revolutionized technologies. The USFDA's Center for Devices and Radiological Health (USFDA/CDRH) governs the Regulatory oversight of the medical devices. This article presents a summary of the Warning Letters issued for medical devices by USFDA from 2011 to 2016 and a trend analysis and statistics were made, which demonstrates a clear picture of the number of Warning Letters issued for 10 categories of Medical Devices. This was done to highlight the special issues that were observed. By comparing this data to that of the recent fiscal years, Pharmaceutical and Medical Devices manufacturing firms can gain a fair picture of the FDA enforcement trends and their probable impact on both Business and industry. The study found that the implementation of quality improvement strategies such as Six sigma, Quality by Design (QbD), Total Quality Management (TQM) can minimize the number of deviations and defects which leads to reduction in 483 observations and FDA Warning Letters.: It was found that739 Warning Letters for medical devices were issued by USFDA for FYs 2011 to 2016, wherein the FY 2012 (171) issuance was more and least in 2016 (43). Adulteration and failure to implement CAPA were the major deficiencies for which the Warning Letters were issued and the number has declined by 2016.

Introduction

The term "device" means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is –

(1) Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;

(2) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (1).

Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. In addition, medical devices include in vitro diagnostic products, such as general-purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. Certain electronic radiation emitting productswith medical application and claims meet the definition of medical device. Examples include diagnostic ultrasound products, x-ray machines and medical lasers.

The Food and Drug Administration (FDA) has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

Device Classification and Regulatory Controls: Based on risk (2)

1. Class I Medical Devices

Devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness. Class I devices typically require no FDA premarket review prior to being marketed.

E.g.: General Manual Orthopedic Surgical Instruments
Adhesive Bandages
Manual Wheel Chairs
Crutches

2. Class II Medical Devices

The General controls are insufficient to provide reasonable assurance of safety and effectiveness of such device and they need to establish special controls to provide such assurance.

Class II devices typically require Premarket Notification to FDA i.e., a 510(K) prior to being marketed

E.g.: Intervertebral fusion devices
Resorbable Bone Void fillers
Powered Wheel Chairs
Powered Muscle Stimulators

FDA issued a special controls guidance to mitigate risks to health.

- Biocompatibility testing
- Material Characterization
- Mechanical testing

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- Sterility
- Labelling, Warning, Precautions, Adverse Drug Events

These special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. Companies must provide evidence in their 510(k) submissions of how the special controls were addressed.

3. Class III Medical Devices

These are of higher risk among 3 classes

These devices are

- life sustaining and/or life supporting or
- of substantial importance in preventing impairmentof human health
- presents potential unreasonable risk of illness orinjury

Class III devices typically require Premarket Approval prior to being marketed.

e.g., Total Artificial disc replacements
Stair climbing wheel chairs
Implanted Neuro stimulators

These Class III devices are allowed to proceed to market via the 510(k) process until such time as either a call for PMAs or a reclassification is finalized.

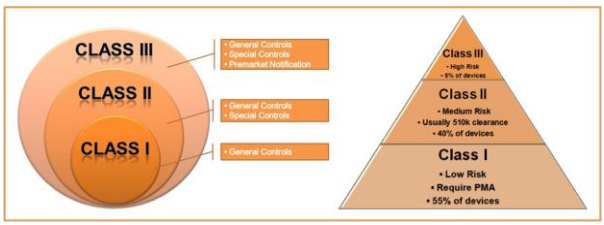

Fig. 1. Classification of Medical Devices based on the risk

510(k) Clearances.

Section 510(k) of the Food, Drug and Cosmetic Act requires device manufacturers who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification - also called PMN or 510(k). This allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories. Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use (3).

510(k) Submission Methods

An applicant may choose from three types of Premarket Notification 510(k) submissions for marketing clearance: Traditional, Special, and Abbreviated.

a) Traditional 510(k)

The Traditional 510(k) may be used for any original 510(k) or for a modification to a previously cleared device under 510(k). The traditional method is the original complete submission as provided in 21 CFR 807. The Traditional 510(k) method may be used under any circumstances.

b) Special 510(k)

The Special 510(k) is used for device modifications and utilizes the design controls aspect of the Quality System (QS) regulation (21 CFR 820.30). Special 510(k)s may be submitted for a modification to a device that has been cleared under the 510(k) process. If a new 510(k) is needed for the modification and if the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device, then summary information that results from the design control process can serve as the basis for clearing the application. Under the Quality System regulation, all Class II and III devices and certain Class I devices are required to be designed in conformance to section 820.30- Design Controls. The Special 510(k) allows the manufacturer to declare conformance to design controls without providing the data. Manufacturers of Class I devices requiring510(k) may elect to comply with the design control provision of the QS regulation and submit a Special 510(k).

Under the Special 510(k) option, 510(k) holders who intend to modify their own legally marketed device will conduct the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements. Once the 510(k) holders have ensured the satisfactory completion of this process, a "Special 510(k): Device Modification" may be submitted. While the basic content requirements of the 510(k) (21 CFR 807.87) will remain the same, this type of submission should also reference the cleared 510(k) number and contain a "Declaration of Conformity" with design control requirements.

c) Abbreviated 510(k)

There are three types of Premarket Notification 510(k)s that may be submitted to FDA: Traditional, Special, and Abbreviated. The Special and Abbreviated 510(k) methods were developed under the "New 510(k) Paradigm" to help streamline the 510(k)-review process.

The Abbreviated 510(k) relies on the use of guidance documents, special controls, and recognized standards. An Abbreviated 510(k) submissions must include the required elements identified in 21 CFR 807.87 (Information required in a premarket notification submission). Under certain conditions, you may not need to submit test data in an abbreviated 510(k).

Device manufacturers may choose to submit an Abbreviated 510(k) when:

- a guidance documents exists,
- a special control has been established, or
- FDA has recognized a relevant consensus standard (4)

Premarket Approval (PMA)

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special

controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. Some Class III pre-amendment devices may require a Class III 510(k).PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by other another.FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

GMP Exemptions

FDA has determined that certain types of medical devices are exempt from GMP requirements. These devices are exempted by FDA classification regulations published in the Federal Register and codified in 21 CFR 862 to 892. Exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (21 CFR 820.198) or from general requirements concerning records (21 CFR 820.180).

Medical devices manufactured under an investigational device exemption (IDE) are not exempt from design control requirements under 21 CFR 820.30 of the QS regulation.

Inspection:

The term **"inspection"** generally refers to the activity of checking products or applies to analyzing manufacturing processes and organizations. The quality inspector usually follows a pre-established checklist that is based on the product specifications. Inspected products can be the components used for production, semi-finished goods, or (most often) finished goods before shipment to a customer (5).

FDA conducts inspections of establishments that manufacture, process, pack, or hold FDA-regulated products, before approving products and/or after products are on the market, to determine the establishment's compliance with laws administered by FDA. Upon completing the inspection, if objectionable conditions are observed, FDA provides the owner of the establishment with a document, called an FDA Form 483, which includes the name of the firm and the date(s) of inspection, and lists the observations made by the investigator during the inspection. FDA provides initial classification of the inspection based on the observations noted during the inspection, the investigator's report, and FDA District Office supervisory personnel review. Except for instances where procedures indicate that the relevant product center has the right of final classification, the final classification of the inspection is made by the FDA District Office. An inspection classification reflects the compliance status of the establishment at the time of the inspection, based on the observations documented. The conclusions of the inspection are reported as Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI).

An **OAI** inspection classification occurs when significant objectionable conditions or practices were found and regulatory action is warranted to address the establishment's lack of compliance with statute(s) or regulation(s).

A **VAI** inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance. Inspections classified with VAI violations are typically more technical violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

An **NAI** inspection classification occurs when no objectionable conditions or practices were found during the inspection or the significance of the documented objectionable conditions found does not justify further actions. If no enforcement action is contemplated, or after enforcement action is concluded, FDA provides inspected establishments with a final inspection report, called an Establishment Inspection Report (EIR), which includes.

- Brief history of prior inspectional findings, including any action taken by FDA or corrective action taken by the firm in response to a previous inspection
- The investigator's narrative report
- Any refusals, voluntary corrections, or promises made by the firm's management
- Copies of forms the FDA issued to the firm during the inspection, including the FDA Form 483
- A list of observations made during the inspection that is communicated after 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

Inspection conclusion after Form 483 is issued:

- Take time with the inspector after 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 regulation.
- 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.

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 (6).

A Warning Letter

- Includes evidence collected to support observations and provides further explanation
- 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 (7).

When it is consistent with the public protection responsibilities of the agency and depending on the nature of the violation, it is the Food and Drug Administration's (FDA's) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law.

The agency position is that Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the agency's principle means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act).

The Warning Letter was developed to correct violations of the statutes or regulations. Also available to the agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution to achieve correction. Despite the significance of the violations, there are some circumstances that may preclude the agency from taking any further enforcement action following the issuance of aWarning Letter. For example, the violation may be serious enough to warrant a Warning Letter and subsequent seizure; however, if the sizeable quantity fails to meet the agency's threshold value for seizures, the agency may choose not to pursue a seizure. In this instance, the Warning Letter would document prior warning if adequate corrections are not made and enforcement action is warranted at a later time.

Responsible officials in positions of authority in regulated firms have a legal duty to implement whatever measures are necessary to ensure that their products, practices, processes, or other activities comply with the law. Under the law such individuals are presumed to be fully aware of their responsibilities. Consequently, responsible individuals should not assume that they would receive a Warning Letter, or other prior notice, before FDA initiates enforcement action.

The following are the summaries of the important findings and the trends

The number of Warning Letters issued in each year for Medical Devices Collectively:

1. Warning Letter data

Table 1 gives the data regarding the Warning Letters issued for medical devices from 2011 to 2016 which has shown the gradual decrease in the number from the previous years. In FY 2016 the number has almost reduced to half of the previous years.

Table 1. Warning Letters issued for Medical Devices from 2011 to 2016.

S.No	Year of issue	No. of Warning Letters issued
1	2011	122
2	2012	171
3	2013	156
4	2014	141
5	2015	106
6	2016	43

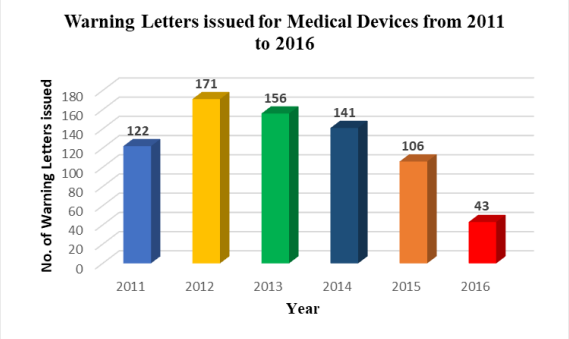

Fig 2. Warning Letters issued for medical devices from 2011 to 2016.

After reviewing the inspection observations, the CDRH warning letters from the same time period and glance at individual deficiencies that were cited in the Warning Letters in different categories like adulterated, misbranded, deficiencies in cGMP.

2. Adulterated Medical Devices

According to USFDA, A device is held to be adulterated if it includes any filthy, putrid, or decomposed substance, or if it is prepared, packed, or held under unsanitary conditions. The FD&C Act further states that a device is held to be adulterated if:

- Its container is composed, in whole or part, of any poisonous or deleterious substance
- It contains, for the purposes of coloring only, an unsafe color additive; and
- Its strength differs from, or its purity or quality falls below, that which it claims to represent.
- It is subject to a performance standard and does not comply with all the requirements of the standard

• It is a Class III device and fails to conform to the requirements for an approved premarket approval application or a notice of completion of a product development protocol
• It is a banned device
• It is in violation of good manufacturing practice requirements or
• It fails to comply with an Investigational Device Exemption (IDE).

Table 2: Warning Letters issued for adulterated Medical Devices

S.No	Category	Year	Number of Warning Letters issued
1	Adulterated	2011	82
2		2012	122
3		2013	102
4		2014	105
5		2015	74
6		2016	36

According to the Analysed data , more number of Warning Letters were issued in the year 2012 and there is a drastic fall in the year 2016.

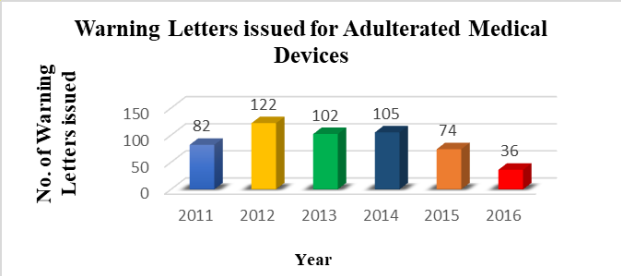

Fig 3. Warning Letters issued for Adulterated Medical devices.

According to the Analysed data, more number of Warning Letters were issued in the year 2013 and there is a drastic fall in the year 2016.

3) cGMP

Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA) provide for systems that assure proper design,monitoring and control of Manufacturing processes and facilities.Adherence to cGMP regulations assures the identity,strength,quality and purity of drug products and medical devices by requiring that manufacturers of Medical devices and drugs adequately control Manufacturing operations .

It is important to note that cGMPs are minimum requirements.Many pharmaceutical manufacturers are already implementing comprehensive,modern quality systems and risk management approaches that exceed these minimum standards.

However, there are still some firms which are not looking upon these requiremnts and hence the warning letters are been issued for these deficiences.

Table 3. Warning Letters issued for Deficiencies in cGMP requirements for Medical devices.

S.No	Category	Year	Number of Warning Letters issued
1	Deficiencies in cGMP Requirements	2011	82
2		2012	122
3		2013	102
4		2014	105
5		2015	74
6		2016	36

According to the analyzed statistics, maximum number of warning letters have been issued in the year 2012 and the number has gradually reduced by 2016 which is reflecting that many firms are maintaining proper cGMPs.

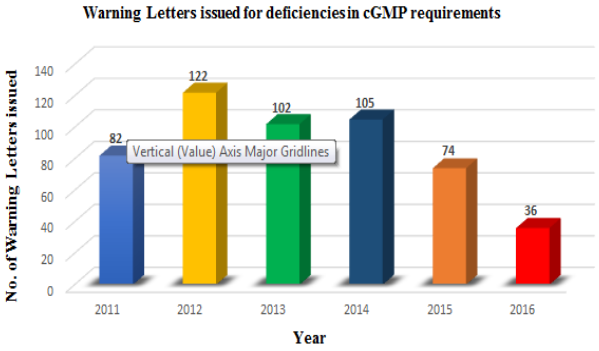

Fig 4. Warning Letters issued for deficiencies in cGMP requirements.

4) Quality System Regulations

Manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products are (food, drugs and devices) are known as cGMPs. Manufacturers should use good judgement when developing their quality systems. Because the QS regulation covers a broad spectrum of devices, production processes, etc., it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices.The QS regulation applies to finished device manufacturers who intend to commercially distribute medical devices (9).

According to the analyzed data the warning letters issued for the medical devices were maximum in the year 2012 and there has been a significant decrease in the year 2016 which shows that the firms are adopting quality system regulations properly.

Table 4. Warning Letters issued for Deficiencies in Quality System Regulations for Medical devices.

S.No	Category	Year	Number of Warning Letters issued
1	Deficiencies in QSR	2011	82
2		2012	121
3		2013	101
4		2014	108
5		2015	73
6		2016	38

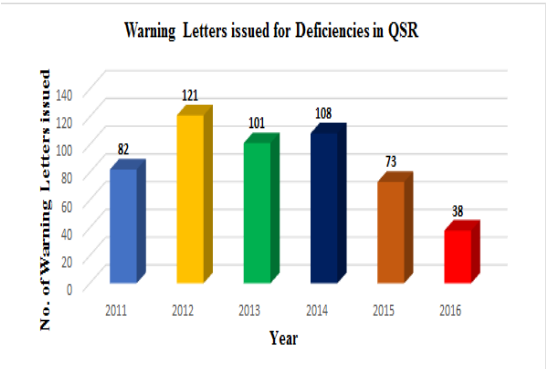

Fig 5. Graphical representation of Warning Letters issued for deficiencies in QSR.

5) Corrective and Preventive Actions (CAPA)

Corrective and preventive action (CAPA) are set of actions which are required to be taken and implemented in an organization at levels of manufacturing, documentation, procedures or systems in order to rectify first and then eliminate the re-occurrence nonperformance identified after systematic evaluation and analysis of root cause of the nonperformance, in manufacturing, documentation or in system, here nonconformance may be a market complaint or customer complaint or a failure of a machinery or a quality management system, or misinterpretation of a written instructions to carry out a work. Corrective Action is the Action to eliminate the cause of a detected nonconformity or other undesirable situation. Preventive Action is to eliminate the cause of a potential nonconformity or other undesirable potential situation. CAPA is an extremely valuable tool for continuous improvement and it Implements risk management and focus on the important issues first(10).

Table 5. Warning Letters issued for not implementing corrective and preventive actions.

S.No	Category	Year	Number of Warning Letters issued
1	Deficiencies in implementing Corrective and Preventive Actions	2011	57
2		2012	76
3		2013	73
4		2014	82
5		2015	56
6		2016	25

According to the analyzed statistics, the warning letters issued for this deficiency had followed the same trend with a slight difference and in 2016 there is a drastic decrease in the warning letters issued.

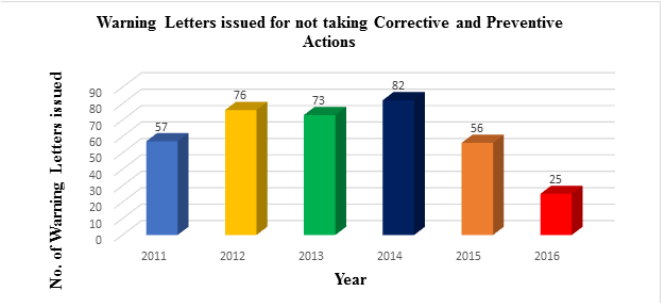

Fig 6. Graphical representation of Warning Letters issued for deficiencies in implementing CAPA.

6) Misbranded Devices

The misbranding provisions of the FD&C Act in Section 502 cover various aspects of drug and device labeling requirements. Many of the provisions apply to drugs and devices both; however, there are also specific misbranding provisions that apply to only drugs or only devices. The misbranding provisions that apply to both drugs and devices are listed in the following:

A drug or device is deemed to be misbranded if:

- Its labeling is false and misleading
- Its packaging does not bear a label containing

a) the name of the place of business of the manufacturer, packer, or distributor, and

b) an accurate statement of the quantity of contents in terms of weight, measure, or numerical count. Reasonable variations and exemptions for small packages may be permitted

- Its label does not bear adequate directions for use.
- It is for use by man and contains any quantity of a narcotic or habit-forming substance, unless its label bears the name and quantity or proportion of the substance or derivative and the statement "Warning - may be habit forming."
- It does not comply with the color additive provisions listed under Section 706 of the FD&C Act etc(11).

Table 6. Warning Letters issued for misbranded medical devices.

S. No	Category	Year	Number of Warning Letters issued
1	Misbranded	2011	57
2		2012	76
3		2013	73
4		2014	82
5		2015	56
6		2016	25

According to the analysis the warning letters issued for misbranded medical devices haven't followed a trend. However, the number have become minimal in the FY2016.

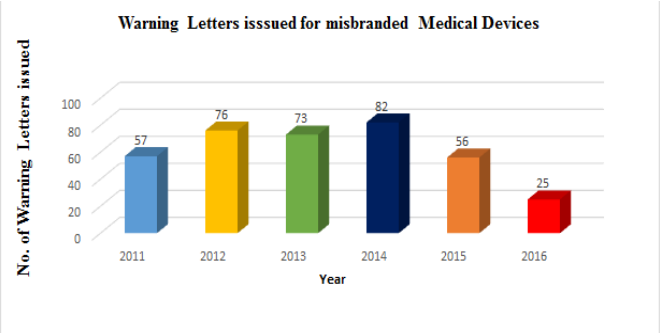

Fig 7. Warning Letters issued for Misbranded Medical Devices – Values in table and graph not matching.

7) Pre-Market Approval:

Section 510(k) of the FD&C Act requires a manufacturer who intends to market a medical device to submit a premarket notification [510(k)] to the Agency at least 90 days before introducing the device onto the market. Premarket approval status is automatic for all devices found to be not substantially equivalent to pre-amendment devices. Based on the information provided in the notification, the Agency must determine whether the new device is substantially equivalent to a device already marketed or if it is not an equivalent device. A nonequivalent device must have an approved premarket approval (PMA) application or be reclassified into Class I or Class II before being marketed. The final determination of whether a device is substantially equivalent or nonequivalent resides with the FDA (12).

Table 7. Warning Letters issued for deficiencies in PMA.

S. No	Category	Year	Number of Warning Letters issued
1	Deficiencies in PMA	2011	19
2		2012	10
3		2013	19
4		2014	9
5		2015	25
6		2016	3

The number of warning letters issued for the deficiencies in PMA showed that in least number of warning letters have been issued in the year 2016 comparatively more in the year 2011 and 2013.

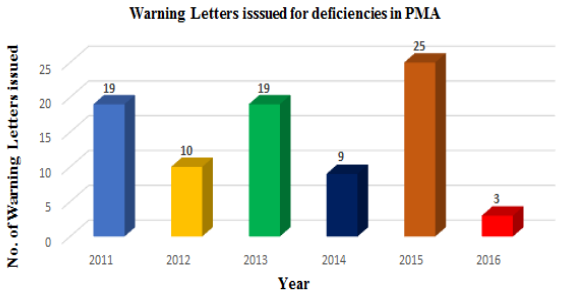

Fig 8. Graphical representation of Warning Letters issued for deficiencies in PMA.

8) DHR/MDR:

The FDA's Quality System Regulation (21 CFR Part 820) requires medical device manufacturers to establish and maintain device history records for each batch, lot, and unit they produce. The electronic Drug Master Files(eDHR) software is a compilation of all records pertaining to the production of a finished medical device. It entails extensive documentation that includes dates of manufacture, quantity manufactured and when they were released, acceptance records to show that the device was produced according to device master records (DMR), identification labeling, and device identification and lot numbers.

Medical Device Reporting (MDR) is one of the post market surveillance tools the FDA uses to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. Mandatory reporters (i.e., manufacturers, device user facilities, and importers) are required to submit certain types of reports for adverse events and product problems to the FDA about medical devices.

The Medical Device Reporting (MDR) regulation (21 CFR 803) contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems to the FDA.

Table 8. Warning Letters issued for not maintaining DHR/MDR.

S. No	Category	Year	Number of Warning Letters issued
1	Deficiencies in maintaining DHR/MDR	2011	42
2		2012	69
3		2013	70
4		2014	63
5		2015	46
6		2016	20

The above derived data shows that there has been a continual decline in the warning letters issued for this category.

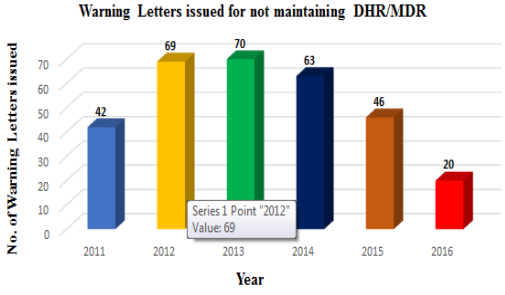

Fig 9. Warning Letters issued for deficiencies in maintaining DHR/MDR.

9) Process and Design Validation:

Process validation is the analysis of the data gathered throughout the design and manufacturing of a product in order to confirm that the process can reliably output products of a determined standard. Effective process validation contributes significantly to assuring drug or device quality.

Process Validation can be achieved in three stages:

Stage. I-Process design

Stage.II-Process Qualification

Stage.III- Continued process verification

Design controls are a component of a comprehensive quality system that covers the life of the device. The assurance process is a total systems approach that extends from the development of device requirements through design, production, distribution, distribution, use, maintenance and eventually obsolescence, Design control begins with development and approval of design inputs, and includes the design of device and the associated manufacturing processes.

Table 9. Warning Letters issued for deficiencies in Process and Design Validation.

S. No	Category	Year	Number of Warning Letters issued
1	Deficiencies in design validation	2011	12
2		2012	27
3		2013	19
4		2014	24
5		2015	16
6		2016	12

The number has gradually reduced by 2016.

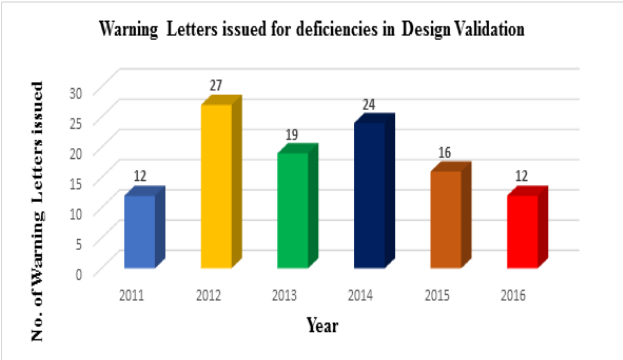

Fig 10. Graphical representation of Warning Letters issued for deficiencies in Process and Design Validation.

10) Clinical Trials:

Clinical Trials for Medical Devices are designed to support a reasonable assurance of safety and effectiveness. Normally, Clinical trials are mandatory for Class II and Class III Medical devices. The trials may be blind, randomized or control. Typically, single pivotal trial follows feasibility stages.

Table 10. Warning Letters issued for deficiencies in performing clinical trials.

S. No	Category	Year	Number of Warning Letters issued
1	Deficiencies in performing clinical trials	2011	1
2		2012	2
3		2013	2
4		2014	1
5		2015	2
6		2016	0

Compared to the other deficiencies least number of warning letters were issued were issued for not conducting

clinical trials. The trend is almost constant and there were no warning letters issued in the year 2016.

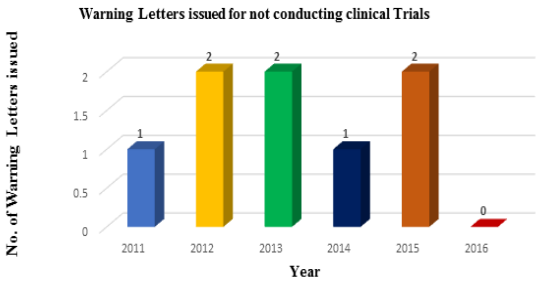

Fig 11. Graphical representation of Warning Letters issued for not containing Clinical Trials.

Summary and Conclusions

Pharmaceutical Market has witnessed a tremendous growth in the present decade. The medical device companies are constantly modifying their market medical devices or innovating to develop the healthcare sector, thus providing better service to the patients and the healthcare system.

A total of 739 Warning Letters were issued for medical devices from the year 2011-2016, out of which the maximum number were issued in the year 2012 and there was a gradual decline in the number of warning letters from 2016.

Among the Warning Letters issued from the past five years, the following were the recurring defects that were encountered in the descending order:

- Adulterated Medical devices
- Quality System Regulations
- Deficiencies in cGMP requirements
- Corrective and Preventive Actions
- Deficiencies in maintaining DHR/MDR

The Medical Device companies must analyze all appropriate data sources for input into the CAPA system, and then perform adequate investigations and root cause analyses to reduce the violations of regulatory significance. This may retard issuance in the intensity and number of warning letters.

The implementation of quality improvement strategies, such as Six sigma, Quality by Design (QbD), Total Quality Management (TQM) can also contribute in minimizing the number of deviations and defects, will ultimately leads to reduction in 483 observations and FDA warning letters.

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