IJPSR (2012), Vol. 3, Issue 12 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 August, 2012; received in revised form 28 September, 2012; accepted 20 November, 2012

FDA WARNING LETTER ANALYSIS: A TOOL FOR GMP COMPLIANCE

Darshit S. Patel

Astron Research Limited, Ahmedabad, Gujarat, India

Keywords:
cGMP, GMP, GMP Compliance, GMP Non-compliance, USFDA Warning Letter, USFDA Audit

Correspondence to Author:

Dr. Darshit S. Patel

Team Leader-Regulatory Affairs, Astron Research Limited, Premier House, Opp. Gurudwara, S.G Highway, Bodakdev, Ahmedabad - 380054, Gujarat, India

E-mail: darshit1979@rediffmail.com

QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Website: www.ijpsr.com

ABSTRACT

In the past few years, the US Food and Drug Administration has issued more warning letters, import alert & seizure to manufacturers of finished product for violation of the current good manufacturing practice regulation. Indian and US Pharmaceutical Manufacturer's Warning letter from the FDA's Electronic Reading Room were selected as case study and was analyzed for non-compliance of GMP with 21 CFR 211 and inspection systems. A detailed review of selected Indian and US Pharmaceutical Manufacturer warning letters provides a numbers of useful insights into where the FDA is presently focusing, where Indian Pharmaceutical Manufacturer having lack of compliance and at where Indian Pharmaceutical Manufacturer having stringent compliance. Reviewed and analyzed letters shows that the FDA is taking a more systemic based approach to assessing GMP compliance and paying close attention to such area as the Quality System. Based on review and analysis of selected Warning letter's deficiencies, I believe that pharmaceutical companies, by carefully assessing FDA GMP warning letters from the past year & base on this assessment companies should develop compliance check list/data/trends and incorporate this in internal inspection/compliance program for the clues about how they can enhance their GMP compliance and more effectively manage future FDA establishment inspection and avoiding the non-compliance of GMP or FDA-483 from FDA inspection.

INTRODUCTION: A good manufacturing practice (GMP) is a production and testing practice that helps to ensure a quality product. Many countries have legislated that pharmaceutical companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation.

Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicine.

The cGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.

The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "c" in cGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations [1].

cGMPs are enforced in the United States by the Food and Drug Administration (FDA or USFDA), under Section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act (FD&C Act) [21 USCS § 351], drug may be deemed adulterated if it is found to be manufactured in a condition which violates current good manufacturing regulation [2]. Therefore, complying with GMP is a mandatory aspect in pharmaceutical manufacturing. Ensuring that GMP regulations are followed is referred to as GMP compliance.

Regulatory agencies (including the FDA in the U.S.) are authorized to conduct unannounced inspections, though some are scheduled. FDA routine US domestic inspections are usually unannounced, but must be conducted according to 704(A) of the FD&C Act (21 USCS § 374), which requires that they are performed at a "reasonable time" [3]. USFDA inspects pharmaceutical manufacturing facilities worldwide using scientifically and cGMP- trained inspectors for the evaluation of GMP compliance.

Us Code Of Federal Regulations (CFR) [4]: Drug manufacturers required to comply with following cGMP code of federal regulations;

- 21 Code of Federal Regulations Part 210 (21 CFR 210): Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- 21 Code of Federal Regulations Part 211 (21 CFR 211): Current Good Manufacturing Practice for Finished Pharmaceuticals.

Types of USFDA cGMP Audit/Inspection: According to USFDA's Compliance Programs, the USFDA conducts following inspections for the evaluation of GMP compliance of drug manufacturer:

1. Pre-Approval Inspections
2. Post Approval Audit Inspections
3. Drug Manufacturing Inspections [Routine cGMP (Surveillance) Inspection]

1. **Pre-Approval Inspections:** The Federal Food, Drug, and Cosmetic Act provides that FDA may approve a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), and a Biologic Licensing Application (BLA) if, among other requirements, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate, and ensure and preserve its identity, strength, quality, and purity. A pre-approval inspection (PAI) is performed to contribute to USFDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete [5].

2. **Post Approval Audit Inspections:** Post Approval Audit Inspections program is designed to audit for changes in the production and control practices that occur after approval and to confirm that the approved applications have been appropriately supplemented to reflect those changes. Post Approval Audit Inspections confirms that commitments made by a firm at the time the application was approved have been completed or are underway in accordance with those commitments [6].

3. **Drug Manufacturing Inspections [Routine cGMP (Surveillance) Inspection]**: The goal of this inspection's activities is to determine whether inspected firms are operating in compliance with applicable cGMP requirements and to provide cGMP assessment which may be used in efficient determination of acceptability of the firm in the pre-approval review of a facility for drug applications. Biennial inspections (every two years); sites selected by Center for Drug Evaluation and Research (CDER) & District Office under this inspection program [7].

Six-System Inspection Model [7, 8]: The FDA's Drug Manufacturing Inspection Compliance Program, which contains instructions to FDA personnel for conducting inspections, is a systems-based approach to inspection. The figure below shows the relationship among the six systems: the quality system and the five manufacturing systems. The quality system provides the foundation for the manufacturing systems that are linked and function within it.

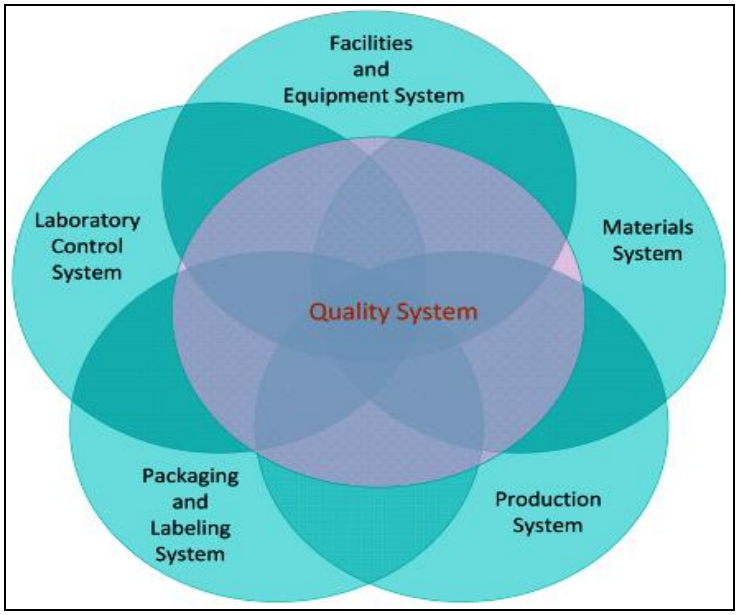

FIGURE 1: SIX-SYSTEM INSPECTION MODEL

1. **Quality System**: This system assures overall compliance with cGMPs and internal procedures and specifications. The system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged drug products.

   See the cGMP regulation, 21 CFR 211 Subparts B, E, F, G, I, J, and K.

2. **Facilities and Equipment System**: This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs or drug products. It includes: a) Buildings and facilities along with maintenance; b) Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate. Process performance qualification will be evaluated as part of the inspection of the overall process validation which is done within the system where the process is employed; and, c) Utilities that are not intended to be incorporated into the product such as HVAC, compressed gases, steam and water systems.

   See the cGMP regulation, 21 CFR 211 Subparts B, C, D, and J.

3. **Materials System**: This system includes measures and activities to control finished products, components, including water or gases, that are incorporated into the product, containers and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records.

   See the cGMP regulation, 21 CFR 211 Subparts B, E, H, and J.

4. **Production System**: This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures.

   See the cGMP regulation, 21 CFR 211 Subparts B, F, and J.

5. **Packaging and Labeling System:** This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations.

   See the cGMP regulation, 21 CFR 211 Subparts B, G, and J.

6. **Laboratory Control System:** This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program.

   See the cGMP regulation, 21 CFR 211 Subparts B, I, J, and K.

USFDA's Inspection Classification [9, 10]: Following inspection classification is related in the USFDA inspection data based;

FIGURE 2: EXAMPLE OF USFDA INSPECTIONS DATABASE

District	Firm Name	City/State	Country/Area	Inspection End Date	Center	Project Area	Classification
ORA	Choksi Laboratory	Panchkula/ Haryana	IN	04/24/10	CDER	Drug Quality Assurance	OAI
ORA	Micro Labs Limited	Salcettte/Goa	IN	04/17/09	CDER	Drug Quality Assurance	VAI
ORA	Strides Arcolab Ltd.	Bangalore/ Karnataka	IN	03/17/09	CDER	Drug Quality Assurance	NAI
CIN	Pharmacia Hepar Inc	Franklin/OH	US	01/14/11	CDER	Drug Quality Assurance	NAI
CIN	GEO Analytical Inc	Twinsburg/OH	US	04/12/10	CDER	Drug Quality Assurance	VAI
DAL	Hospira, Inc	Austin/ TX	US	04/27/11	CDER	Drug Quality Assurance	OAI

Source: USFDA's Inspection Classification Database Search

No Action Indicated (NAI) – No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further action).

Voluntary Action Indicated (VAI) – Objectionable conditions were found and documented but the District and/or Center is not prepared to take or recommend any of the regulatory (advisory, administrative, or judicial) actions, since the objectionable conditions do not meet the threshold for regulatory action. A VAI classification should be made only if a FDA-483 has been issued.

Official Action Indicated (OAI) – Objectionable conditions were found and one of the regulatory actions should be recommended. Typically, an OAI classification should be made only if a FDA-483 has been issued and the documented evidence supports the action recommended.

Impact of cGMP Non Compliance [10]: After FDA site inspection, companies may receive FDA-483 for objectionable cGMP condition with US regulation. If apparent noncompliance with US regulations, the FDA can move ahead with the following regulatory (advisory, administrative, or judicial) actions but often most damaging is the loss of consumer confidence in the product.

- Warning Letter
- Application Action: e.g. [Recommendation for Denial of Pending Application (NDA, ANDA) Recommendation for Revocation of Approved Application (NDA, ANDA)]
- Recall
- Import Alert/Banning
- Implementation of the Application Integrity Policy
- Seizure/Detention
- Injunction
- Civil Penalty
- Prosecution under the FD&C Act

Form FDA 483 [FDA 483 or 483] [11]: This form with the eponymous number 483 is used by the investigator conducting the investigation (FDA investigator) in order to document his findings (Inspectional Observations. It is delivered directly at the end of the inspection and should be answered officially. The answer is expected within 15 working days after issuing Form 483. Good response can usually help a company avoid receiving a Warning Letter from the FDA, withholding of product approval, or regulatory action. However not in every inspection a Form 483 is issued. The 483 will not normally include actual regulatory/regulation references.

FDA Warning Letter [11]: A Warning Letter is issued especially in the case of serious findings or if the response to Form 483 is classified as inadequate. After the review by the competent centre, the District Offices issue the warning letters and not the

investigator himself. The company is obliged to comment in due time and explain in detail how the failure will be corrected and its recurrence prevented. Warning letters are generally published on the FDA Web Portal. Unlike the Form FDA 483, the Warning Letter will cite regulatory/regulation references for each violation.

Analysis of FDA Warning Letter: Following Indian and US Pharmaceutical Firm's (Indian and US Pharma or Indian and US Pharmaceutical Manufacturers) Warning letter (WL) from the FDA's Electronic Reading Room [9, 12] were selected as case study and non-compliance were analyzed with 21 CFR 211 and inspection systems.

TABLE 1: WARNING LETTER OF INDIAN FIRMS

District	Firm Name	City, State	Country	Inspection End Date	FEI	Waning Letter Number
ORA	Lupin Limited	Mandideep, Madhya Pradesh	IN	11/12/08	3002807511	WL: 320-09-05
ORA	Stericon Pharma Pvt. Ltd.	Bangalore, Karnataka	IN	03/17/10	3004983128	WL: 320-10-008
ORA	Choksi Laboratory	Panchkula, Haryana	IN	04/24/10	3008299032	WL: 320-10-10
ORA	Claris Lifesciences Limited	Ahmedabad	IN	06/16/10	3004610460	WL: 320-11-003
ORA	Aurobindo Pharma Limited (Unit III)	Hyderabad, Andhra Pradesh	IN	09/24/10	3004021229	WL: 320-11-013
ORA	Aurobindo Pharma Limited (Unit IV)	Hyderabad, Andhra Pradesh	IN	12/22/10	3004021263	WL: 320-11-013
ORA	Cadila Healthcare Limited	Ahmedabad City	IN	02/03/11	3002984011	WL: 320-11-015

Note: Selected base on inspections ending October 1, 2008 through June 30, 2011.

TABLE 2: WARNING LETTER OF US FIRMS

District	Firm Name	City, State	Country	Inspection End Date	FEI	Waning Letter Number
LOS	Apotheca Inc	Phoenix, AZ	US	01/29/09	2016096	W/L 22-09
LOS	Teva Parenteral Medicines Inc	Irvine, CA	US	07/24/09	2027158	W/L 05-10
ATL	Hospira, Inc	Clayton, NC	US	02/23/10	1021343	10-ATL-12
SJN	Bristol-Myers Squibb Holdings Pharma LLC	Manati, PR	US	03/31/10	2650089	10-SJN-WL-06
CIN	Advanced Testing Laboratory Inc	Cincinnati, OH	US	04/09/10	Not Available	CIN-11-108087-01
DEN	Nexgen Pharma, Inc	Colorado Springs, CO	US	05/25/10	2011194	W/L 45-10
SJN	Mylan LLC	Caguas, PR	US	02/24/11	2650176	12-SJN-WL-01

Note: Randomly selected base on inspections ending October 1, 2008 through June 30, 2011.

cGMP deficiencies of each warning letter analyzed with relevant 21 CFR 211 subparts, sections & subsections rules and FDA's cGMP inspection system-based approach. The difficulty is avoided by structuring the short description of deficiency differently, so that one deficiency belongs to one single category.

All cGMP deficiencies/violations of each warning letter are classified as 21 CFR 211 subparts, sections & subsections and cGMP inspection system with short description of deficiency. As per following format in Microsoft excel sheet (**Figure 3**) for analysis & investigation of most frequent GMP deficiencies in Indian and US Pharma firms reported by FDA inspectors.

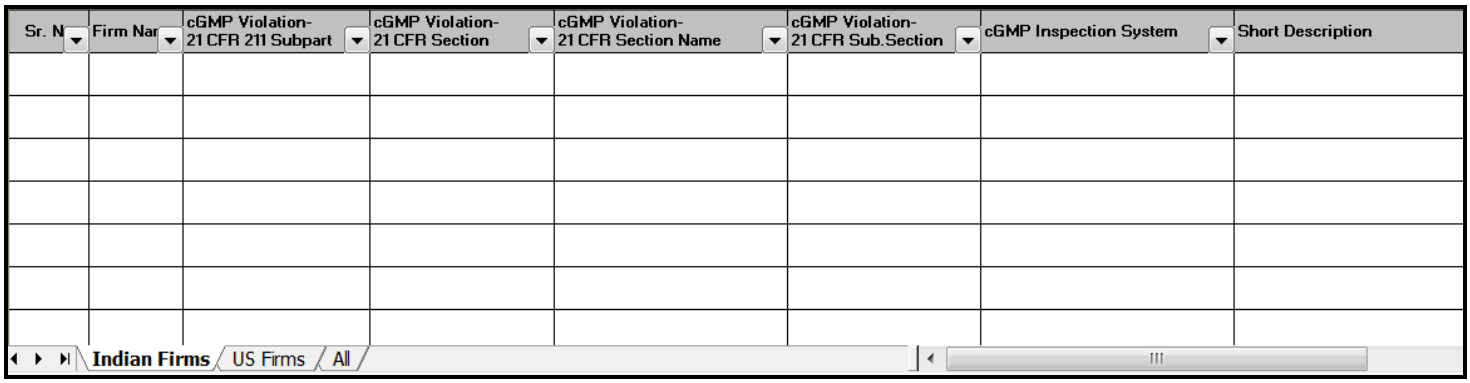

FIGURE 3: CGMP DEFICIENCIES/VIOLATIONS CLASSIFICATION FOR ANALYSIS

RESULTS AND DISCUSSION: The analysis of the selected warning letters of the FDA sent to Indian & US pharmaceutical manufacturers and referring to the 21 CFR 210-211 and FDA's System-based Approach to Inspections. Following are the investigated and discussed in this section of compilation.

1. Warning Letter Analysis Report with 21 CFR 211 Subparts and Sections
2. Warning Letter Analysis Report with System Based Approach

1. **Warning Letter Analysis Report with 21 CFR 211 Subparts and Sections:** Data from selected warning letter analysis, comprising 7 Indian pharmaceutical firms and 7 US pharmaceutical firms warning letter has been analyzed. A total of 63 deficiencies, comprising 25 of Indian Pharma and 38 of US Pharma were observed & recorded during these analyses. A summary of these deficiencies in each 21 CFR subpart category and section is recorded in **Table 3 & 4** respectively.

TABLE 3: ANALYSIS DATA OF DEFICIENCIES FOR 21 CFR 211 SUBPART CATEGORIES

WL Details	Percentage of Deficiencies						
	21 CFR 211 Subpart B	21 CFR 211 Subpart C	21 CFR 211 Subpart D	21 CFR 211 Subpart E	21 CFR 211 Subpart F	21 CFR 211 Subpart I	21 CFR 211 Subpart J
Indian Pharma	8%	12%	12%	4%	20%	4%	40%
US Pharma	10.53%	7.89%	10.53%	5.26%	13.16%	31.58%	21.05%

The following illustration shows the 21 CFR 211 subpart deviations cited in selected warning letters addressed to Indian & US based pharmaceutical manufacturers;

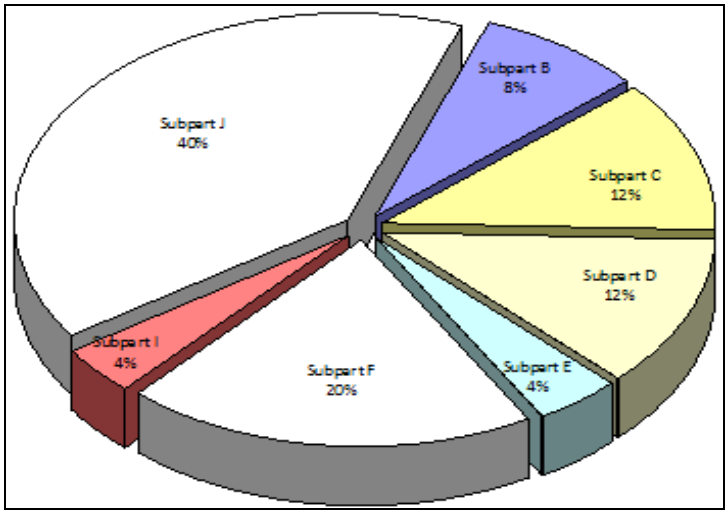

FIGURE 4: 21 CFR 211 SUBPART DEVIATIONS FOR INDIAN PHARMACEUTICAL MANUFACTURERS

From evaluated deficiencies of WL of Indian pharmaceutical manufacturers, a total of 25 deficiencies were recorded during these analyses and that comprising 40% deficiencies of Subpart J Records and Reports, 20% deficiencies of Subpart F Production and Process Controls, 12% deficiencies of Subpart C Buildings and Facilities, 12% deficiencies of Subpart D Equipment, 8% deficiencies of Subpart B Organization and Personnel, 4% deficiencies of Subpart I Laboratory Controls and 4% deficiencies of Subpart E Control of Components and Drug Product Containers and Closures.

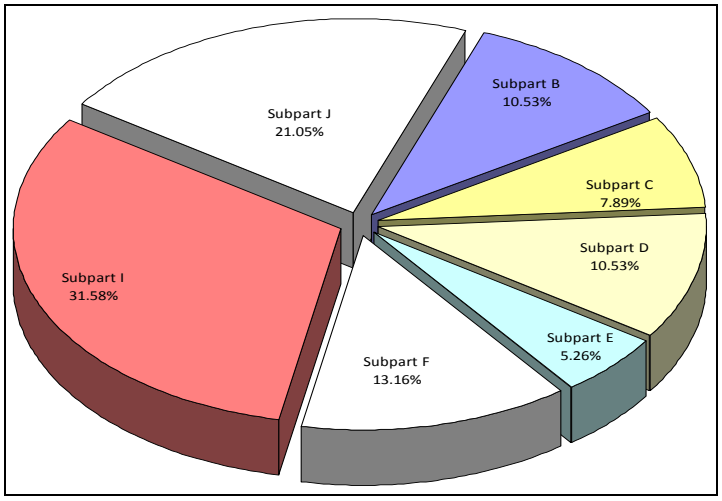

FIGURE 5: 21 CFR 211 SUBPART DEVIATIONS FOR US PHARMACEUTICAL MANUFACTURERS

WL analysis data of US Pharma Company, shows total 38 deficiencies during these analyses and that include 31.58% deficiencies of Subpart I Laboratory Controls, 21.05% deficiencies of Subpart J-Records and Reports, 13.16% deficiencies of Subpart F Production and Process Controls, 10.53% deficiencies of Subpart B Organization and Personnel, 10.53% deficiencies of Subpart D Equipment, 7.89% deficiencies of Subpart C Buildings and Facilities and 5.26% deficiencies of Subpart E Control of Components and Drug Product Containers and Closures.

TABLE 4: ANALYSIS DATA OF DEFICIENCIES FOR 21 CFR 211 SECTIONS

21 CFR 211		Percentage of Deficiencies	
Section	**Section Name**	**Indian Pharma**	**US Pharma**
21 CFR 211.22	Responsibilities of Quality Control Unit	4%	10.53%
21 CFR 211.25	Personnel Qualifications	4%	Not Observed
21 CFR 211.42	Design and Construction Features	8%	7.89%
21 CFR 211.56	Sanitation	4%	Not Observed
21 CFR 211.63	Equipment Design, Size, and Location	4%	2.63%
21 CFR 211.67	Equipment Cleaning and Maintenance	4%	7.89%
21 CFR 211.56	Automatic, Mechanical, and Electronic Equipment	4%	Not Observed
21 CFR 211.80	General Requirements (Control of Components and Drug Product Containers and Closures)	4%	Not Observed
21 CFR 211.84	Testing and Approval or Rejection of Components, Drug Product Containers, and Closures	Not Observed	5.26%
21 CFR 211.100	Written Procedures; Deviations	4%	5.26%
21 CFR 211.110	Sampling and Testing of In-Process Materials and Drug Products	Not Observed	2.63%
21 CFR 211.113	Control of Microbiological Contamination	16%	5.26%
21 CFR 211.115	Reprocessing	4%	Not Observed
21 CFR 211.160	General Requirements (Laboratory Control)	Not Observed	13.16%
21 CFR 211.165	Testing and Release for Distribution	Not Observed	15.79%
21 CFR 211.176	Penicillin Contamination	Not Observed	2.63%
21 CFR 211.180	General Requirements (Records and Reports)	4%	Not Observed
21 CFR 211.182	Equipment Cleaning and Use Log	Not Observed	2.63%
21 CFR 211.186	Master Production and Control Records	Not Observed	2.63%
21 CFR 211.188	Batch Production and Control Records	8%	2.63%
21 CFR 211.192	Production Record Review	16%	13.16%
21 CFR 211.194	Laboratory Records	8%	Not Observed
21 CFR 211.198	Complaint Files	4%	Not Observed

The following graphs shows the 21 CFR 211 section deviations cited in selected warning letters addressed to Indian and US pharmaceutical manufacturers;

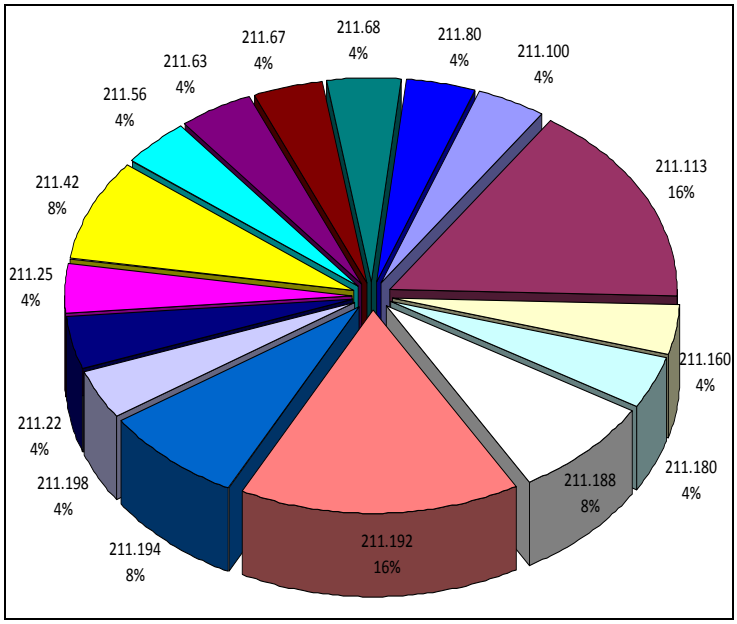

FIGURE 6: 21 CFR 211 SECTION DEVIATIONS FOR INDIAN PHARMACEUTICAL MANUFACTURERS

From evaluated deficiencies of WL of Indian Pharma Company, a total of 25 deficiencies/deviations were recorded during these analyses and that comprising 16% deficiencies of 21 CFR 211.113; Control of microbiological contamination, 16% deficiencies of 21 CFR 211.192; Production Record Review, 8% deficiencies of 21 CFR 211.42; Design and Construction Features, 8% deficiencies of 21 CFR 211.194; Laboratory Records, 8% deficiencies of 21 CFR 211.188; Batch Production and Control Records and 4% of each 21 CFR 211.22; Responsibilities of Quality Control Unit, 211.25; Personnel Qualifications, 211.56; Sanitation, 211.63; Equipment Design, Size, and Location, 211.67; Equipment Cleaning and Maintenance, 211.68; Automatic, Mechanical, and Electronic Equipment, 211.80; General Requirements (Control of Components and Drug Product Containers and Closures, 211.100; Written Procedures; Deviations, 211.115; Reprocessing, 211.180; General Requirements (Records and Reports) & 211.198; Complaint Files. As compared to US Pharma Company, no deficiency is found in area of 21 CRF 211.84, 211.110, 211.160, 211.165, 211.176, 211.182 and 211.186.

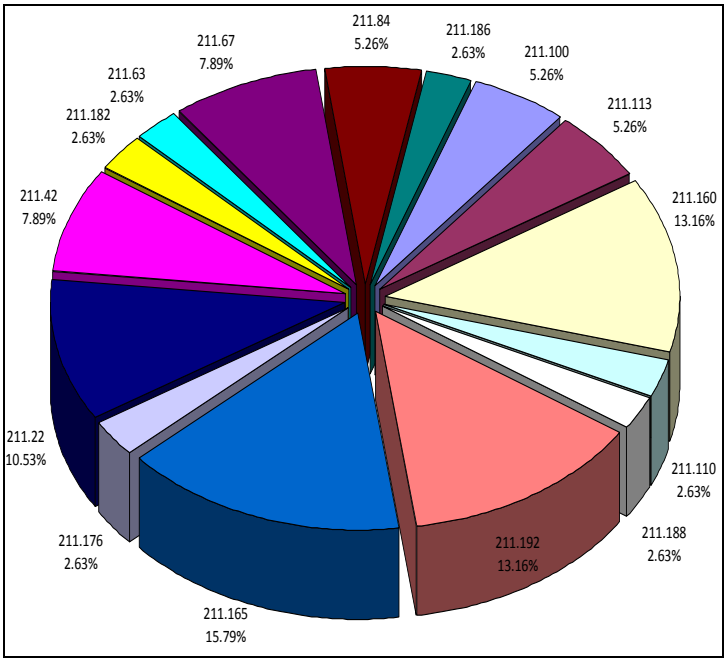

FIGURE 7: 21 CFR 211 SECTION DEVIATIONS FOR US PHARMACEUTICAL MANUFACTURERS

From analysis of WL deficiencies of US Pharma Company, a total of 38 deficiencies/deviations were evaluated during these analyses and that comprising 15.79% deficiencies of 21 CFR 211.165; Testing and Release for Distribution, 13.16% deficiencies of 21 CFR 211.160; General Requirements (Laboratory Control), 13.16% deficiencies of 21 CFR 211.192; Production Record Review, 10.53% deficiencies of 21 CFR 211.22; Responsibilities of Quality Control Unit, 7.89% deficiencies of each 21 CFR 211.42; Design and Construction Features & 21 CFR 211.67; Equipment Cleaning and Maintenance, 5.26% deficiencies of each 21 CFR 211.84; Testing and Approval or Rejection of Components, Drug Product Containers and Closures, 211.100; Written Procedures; Deviations & 211.113; Control of Microbiological Contamination, and 2.63% deficiencies of each 21 CFR 211.63; Equipment Design, Size, and Location, 211.110; Sampling and Testing of In-Process Materials and Drug Products, 211.176; Penicillin Contamination, 211.182; Equipment Cleaning and Use Log,, 211.186; Master Production and Control Records & 211.188; Batch Production and Control Records. As compared to Indian Pharma Company, no deficiency is found in area of 21 CRF 211.25, 211.56, 211.56, 211.80, 211.115, 211.180, 211.194 & 211.198

Most Frequent Deficiencies/Deviations in Indian & US Pharmaceutical Company: With regard to topics and frequency of GMP deficiencies, the following sections in the CFR were violated the most:

Indian Pharma	US Pharma
21 CFR 211.113; Control of Microbiological Contamination	21 CFR 211.165; Testing and Release for Distribution
21 CFR 211.192; Production Record Review	21 CFR 211.192; Production Record Review 21 CFR 211.160; General Requirements (i.e. Laboratory Control)
21 CFR 211.42; Design and Construction Features *21 CFR 211.188; Batch Production and Control Records* *21 CFR 211.194; Laboratory Records*	21 CFR 211.22; Responsibilities of Quality Control Unit

The following short/ representative quotations explain in detail which facts were considered to be non-compliant with current GMP i.e. 21 CFR 210/211.

- 21 CFR 211.113; Control of Microbiological Contamination – Inadequate/Remarkable procedures for sterile drug products.
- 21 CFR 211.192; Production Record Review – Inadequate/Remarkable Investigations of Discrepancies, Failures.
- 21 CFR 211.42; Design and Construction Features – Inadequate/Remarkable environmental monitoring system.
- 21 CFR 211.188; Batch Production and Control Records – inadequate/Remarkable Identification of persons involved each significant step and inaccurate reproduction.
- 21 CFR 211.194; Laboratory Records – Incomplete test data included in records.
- 21 CFR 211.165; Testing and Release for Distribution – Inadequate/Remarkable acceptance criteria for sampling & testing; Inadequate/Remarkable testing and release for distribution.
- 21 CFR 211.160; General Requirements (i.e. Laboratory Control) – Lack of scientifically sound laboratory controls.
- 21 CFR 211.22; Responsibilities of Quality Control Unit – Procedures not in writing, fully followed.

From comparative result, Indian Pharmaceuticals require to strengthening the control procedure for sterile drug product [21 CFR 211.113; Control of Microbiological Contamination], design and construction feature [21 CFR 211.42; Design and Construction Features], batch production and control records [21 CFR 211.188; Batch Production and Control Records] and laboratory record [21 CFR 211.194; Laboratory Records]. Both Indian and US Pharma companies showing comparable deviations in discrepancies/failures investigations thus both the region Pharma companies required to establish adequate/unremarkable control in the area of investigations of discrepancies & failures [21 CFR 211.192; Production Record Review].

US Pharmaceuticals are showing higher deviations rate than Indian Pharmaceuticals in the area of sampling & testing and testing & release for distribution [21 CFR 211.165; Testing and Release for Distribution], scientifically sound laboratory controls [21 CFR 211.160; General Requirements (i.e. Laboratory Control)] and quality unit procedures [21 CFR 211.22; Responsibilities of Quality Control Unit].

2. **Warning Letter Analysis Report with System Based Approach:** A total of 63 deficiencies, comprising 25 of Indian Pharma and 38 of US Pharma were recorded & evaluated against general scheme of inspection systems. A summary of deficiencies according to system of audit are recorded in **Table 5**.

TABLE 5: ANALYSIS DATA OF DEFICIENCIES FOR SYSTEM

System	Percentage of Deficiencies	
	Indian Pharma	Abroad Pharma
Quality System	40%	38.64%
Facilities and Equipment System	20%	18.18%
Materials System	4%	4.55%
Production System	24%	11.36%
Packaging and Labeling System	Not Observed	Not Observed
Laboratory Control System	12%	27.27%

The following illustration shows the systems-based deviations/deficiencies cited in selected warning letters addressed to Indian and US Pharmaceutical Manufacturers;

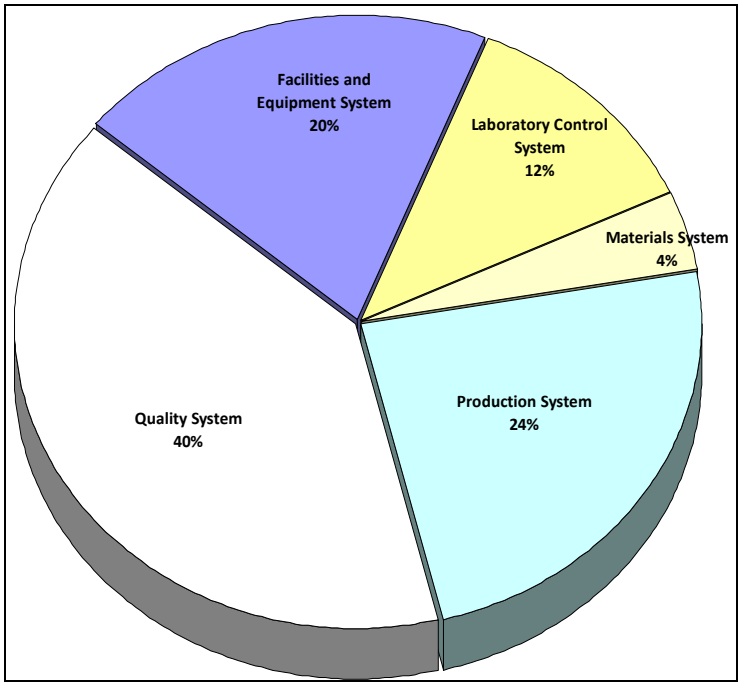

FIGURE 8: SYSTEM BASED DEVIATIONS FOR INDIAN PHARMACEUTICAL MANUFACTURERS

From evaluated deficiencies of WL of Indian Pharma Company, a total of 25 system based deficiencies/deviations were recorded during these analyses and that comprising 40% deficiencies related to Quality System, 24% deficiencies related to Production System, 20 % deficiencies related to Facilities and Equipment System, 12% deficiencies related to Laboratory Control System and 4% deficiencies related to Materials System. No deficiency is found Packaging and Labeling System.

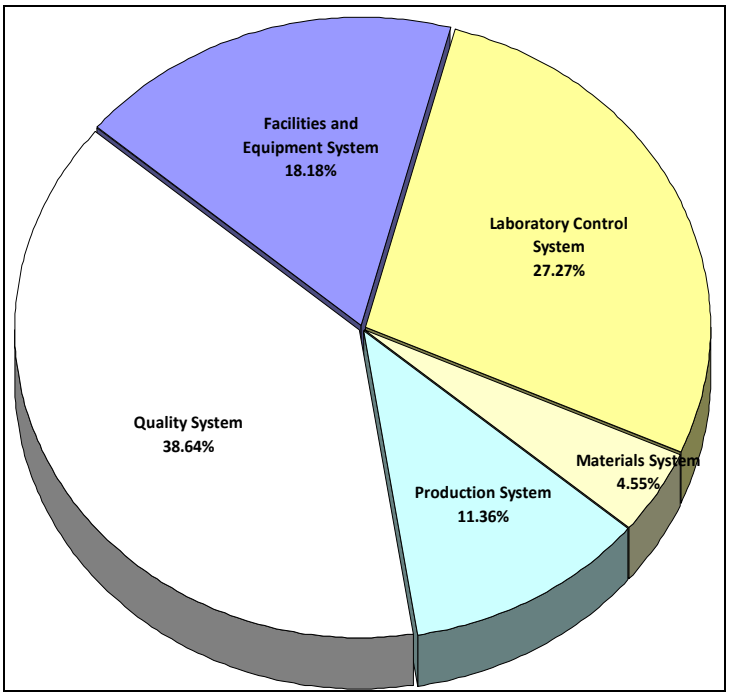

FIGURE 9: SYSTEM BASED DEVIATIONS FOR US PHARMACEUTICAL MANUFACTURERS

From evaluated deficiencies of WL of US Pharma Company, a total of 38 system based deficiencies/deviations were recorded during these analyses and that comprising 38.64% deficiencies related to Quality System, 27.27% deficiencies related to Laboratory Control System, 18.18% deficiencies related to Facilities and Equipment System, 11.36% deficiencies related to Production System and 4.55% deficiencies related to Materials System. No deficiency is found Packaging and Labeling System.

The following lists the most frequent systems deviation:

Indian Pharma	US Pharma
Quality System	Quality System
Production System	Laboratory Control System
Facilities and Equipment System	Facilities and Equipment System

From comparative result, Indian pharmaceuticals require to strengthening in Production System and Facilities & Equipment System. From above comparative data, Quality System & Materials System is comparable between the Indian & US pharmaceuticals companies. US Pharmaceuticals are showing higher deviations rate than Indian Pharmaceuticals in the area of Laboratory Control System. Indian Pharmaceuticals and Abroad Pharmaceutical are stronger in Packaging & Labeling System.

CONCLUSION: From the analysis of the selected warning letters of FDA sent to Indian and US pharmaceutical firms/manufacturers, it becomes clear that Indian Pharma having most frequent deficiencies/non-compliance or deviations in the control producer of sterile drug product, design & construction feature of buildings & facilities and batch production and control records as compare to US Pharma. Indian Pharmaceuticals are stronger in the area of drug product testing & release for distribution, laboratory control and quality assurance responsibilities as compare to US Pharma.

According to these analyses, both the region companies are not giving adequate attention to investigation discrepancies/failures/out-of-specification (OOS) results and it's remained the dominant theme in the FDA warning letters.

From this compilation, it becomes clear that deficiencies in the Quality System were the most frequent ones in Indian Pharma and US Pharma, Indian Pharma was higher finding concerning the Production System and Facilities & Equipment System as compared to US Pharmaceuticals. While US Pharma companies shows more deviations in Laboratory Control System as compare to Indian Pharma that shows Indian Pharma are stronger in the area of laboratory system or giving more attention to the laboratory system.

Based on the analysis, also find that the FDA inspections are mainly focusing on the quality system, because quality system provides the foundation for the manufacturing systems that are linked and function within it.

Based on review & analysis of selected posted Warning letter's deficiencies, find that the recently posted FDA warning letter (e.g. Wintac Limited, WL: 320-12-09) showing almost similar trend of deficiencies in GMP compliance and concluded that posted FDA warning letter analysis data/trend or develop compliance GMP checklist based on warning letter analysis can be included in internal audit system and so that the same will providing satisfactory or valuable clues to future FDA establishment cGMP inspection and helps in avoiding the non-compliance of GMP or FDA-483 from FDA inspection.

DISCLAIMER: The author does not claim anything; the purpose of this review article is solely educational. This review article is built from my work and experience. It is not the official position of Astron Research Limited or its subsidiary companies policies and position.

REFERENCES:

1. Facts About Current Good Manufacturing Practices (cGMPs). Available: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing /ucm169105.htm [Accessed on June 18, 2012]
2. Sec. 501, Chapter V: Drugs and Devices, Federal Food, Drug, and Cosmetic Act. Available: http://www.fda.gov/RegulatoryInformation/Legislation/%20FederalFoodDrugandCosmeticActFDCAct/%20FDCActChapterVDrugsandDevices/default.htm [Accessed on June 18, 2012]
3 Sec. 704, Chapter VII: General Authority, Federal Food, Drug, and Cosmetic Act. Available: http://www.fda.gov/RegulatoryInformation/Legislation/%20FederalFoodDrugandCosmeticActFDCAct/%20FDCActChapterVIIGeneralAuthority/default.htm [Accessed on June 29, 2012]
4 Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations. Available: http://www.fda.gov/Drugs /DevelopmentApprovalProcess/Manufacturing /ucm090016.htm [Accessed on June 28, 2012]
5 Pre-Approval Inspections, Program 73456.832, Chapter 46, New Drug Evaluations, FDA Compliance Program Guidance Manual. Available: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf. [Accessed on September 24, 2012]
6 Post Approval Audit Inspections, Program 7346.843, Chapter 46, New Drug Evaluations, FDA Compliance Program Guidance Manual. Available: http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125398.pdf [Accessed on September 24, 2012]
7 Drug Manufacturing Inspections, Program 7356.002, FDA Compliance Program Guidance Manual. Available: http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125404.pdf [Accessed on September 24, 2012]
8 Food and Drug Administration, Guidance for Industry; Quality Systems Approach to Pharmaceutical CGMP Regulations.

Available:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf [Accessed on June 28, 2012]

9 Inspection Classification Database Search. Available: http://www.accessdata.fda.gov/scripts/inspsearch/[Accessed on June 18, 2012]

10 Field Management Directive – Establishment Inspection Report Conclusions and Decisions (FMD# 86), Office of Regulatory Affairs, Food and Drug Administration. Available: http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ ucm056246.htm [Accessed on June 28, 2012]

11 FDA Inspection Reports: What is what? GMP News, 20/10/2010. Available: http://www.gmp-compliance.org/pa4.cgi? src=eca_new_news_print_data.htm&nr=2213 [Accessed on June 28, 2012]

12 Food and Drug Administration, Warning Letters and Notice of Violation Letters to Pharmaceutical Companies. Available: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm [Accessed on June 28, 2012]

How to cite this article:
Patel DS: FDA Warning Letter Analysis: A Tool for GMP Compliance. *Int J Pharm Sci Res*. 3(12); 4592-4603.