USFDA Warning Letters & 483 Citations Summary

FY 2019

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Introduction

- This summary report is an analysis of 483 citations and warning letters, issued by USFDA in FY 2019, to Indian pharma companies during site inspections.
- FDA maintains a 483 citations database on its website. 483 citation is given by FDA inspectors as a non-compliance observation with the Predictate rule as per FDA code of federal regulations. A **Predicate Rule** is any FDA regulation that requires companies to maintain certain records and submit information to the agency as part of compliance.
- FDA database includes the 483 citations only for finished products manufacturing sites.
- FDA-regulated products originated from approximately 150 countries, estimated to be comprising more than 0.2 million foreign facilities. (Ref. New England PDA ppt)
- As of August 2019, only 28 percent of facilities manufacturing APIs and only 47 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the United States. (Ref. Oversight foreign inspection Article by FDA)
- As of March 2019, India and China had the most manufacturing establishments shipping drugs to the United States, with about 40 percent of all foreign establishments in these two countries. (Ref. GAO-20-262T Report)

FY 2019:- Oct -18 to Sept-19

Introduction

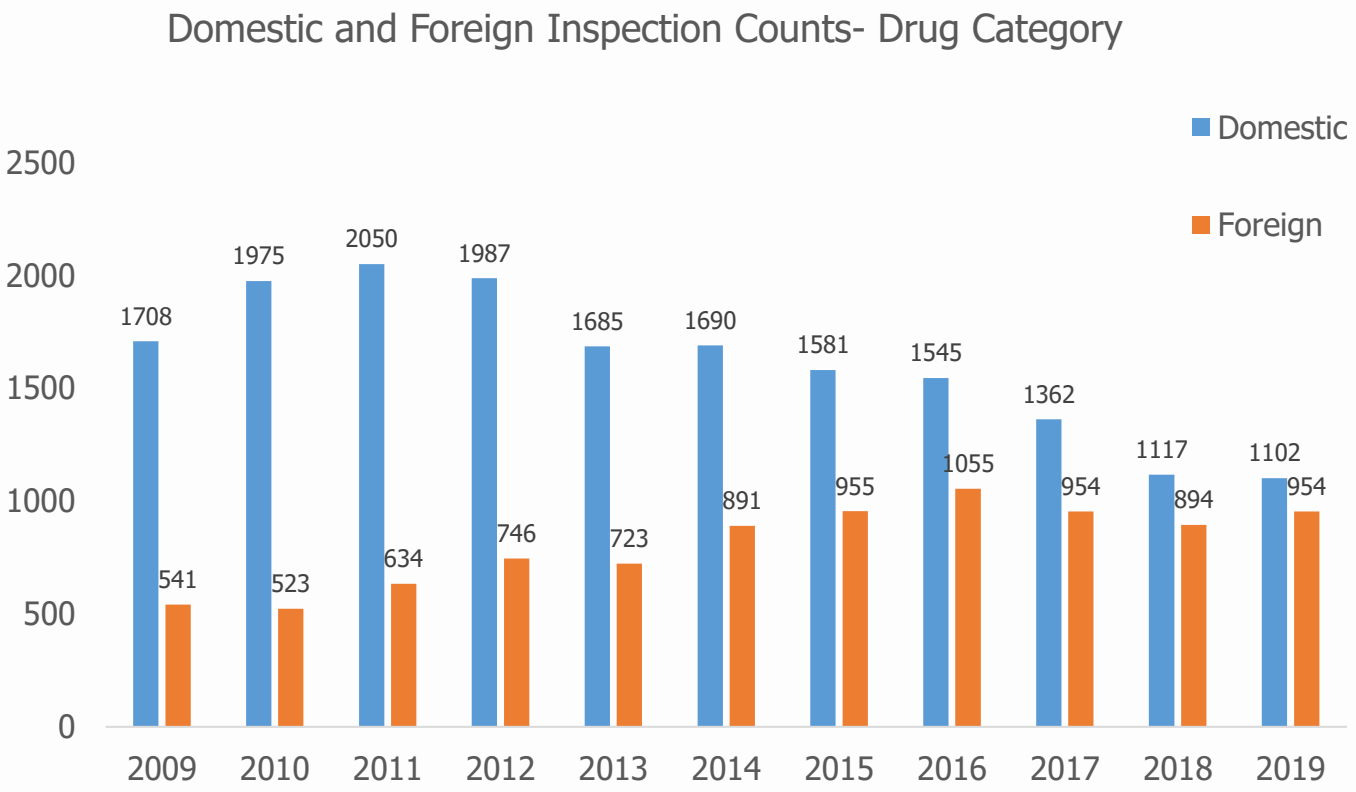
- Due to increase in large number of foreign filings of ANDAs and DMFs, during '90s and thereafter, FDA felt it necessary to improve its resources for faster approval of applications and better oversight of manufacturing sites.
- Food and Drug Administration Safety and Innovation Act (FDASIA) was approved in 2012 facilitating Generic Drug User Fee Amendments (GDUFA)
- Coupled with better resources, following are the key drivers for increased inspections of foreign sites (mainly India and China)
  - To meet the commitment under GDUFA for faster ANDA approval and clearance of huge backlog
  - Better and increased oversight of foreign facilities
  - Increased and repetitive trend of non compliances
  - Meeting the goal of at least biennial inspection

Inspection Geographies; from 2009 to 2019

Domestic :- US Sites

Foreign :- Sites other than US

Foreign inspections are showing increasing trend as compared to domestic inspections from last five years.



Source: FDA access database

Dashboard: Warning letters (WL) by USFDA *(2009 – 2019)*

1,01,631
Total WL issued by FDA*

1378
WLs issued to worldwide drug industry

927
US has highest number of Warning Letters

133
WLs issued to India in all categories*

109
WL issued to India in drug category

17
WL issued to India Pharma (1.10.2018 to 30.09.2019)

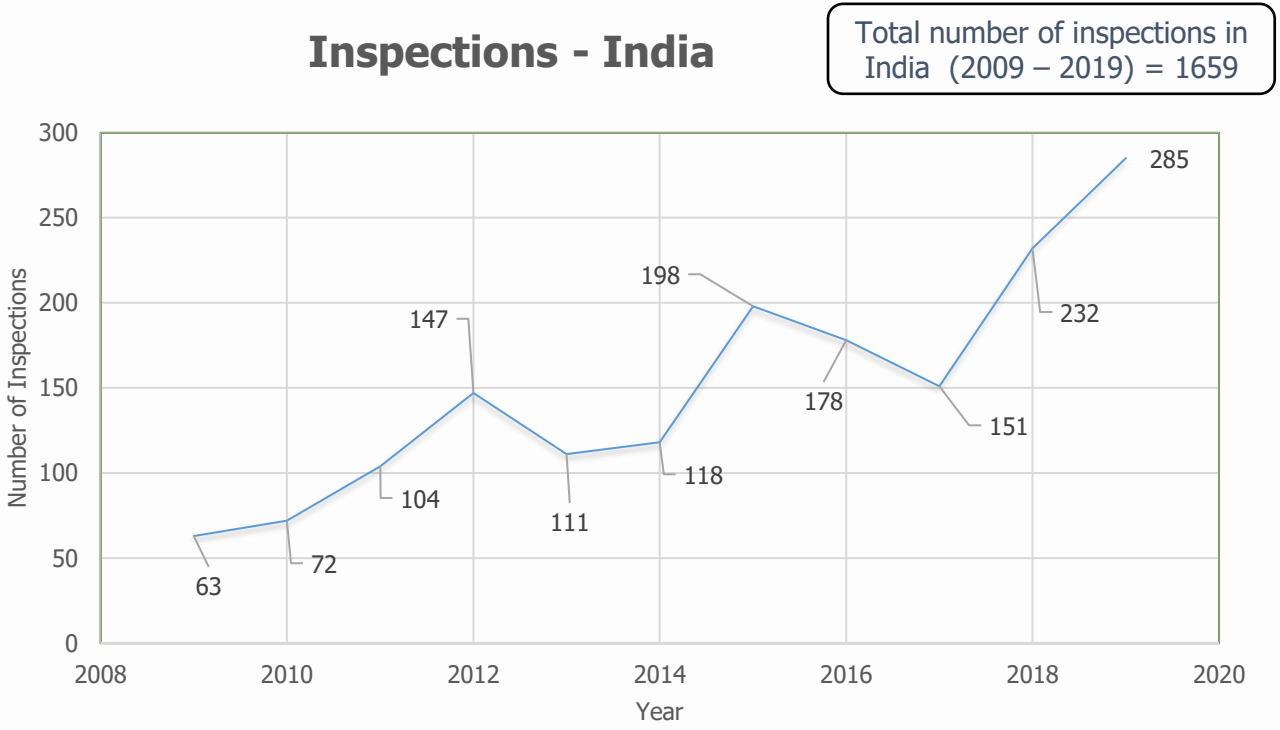
Out of total warning letters issued by USFDA in 2019, 65% issued to US Domestic Sites. 12.6% issued to India and 11.1% issued to China.

* Number includes all industries covered by USFDA (Foods, Drugs, Cosmetics, devices, Tobacco)

Source: FDA access database

Number of Inspections conducted in India

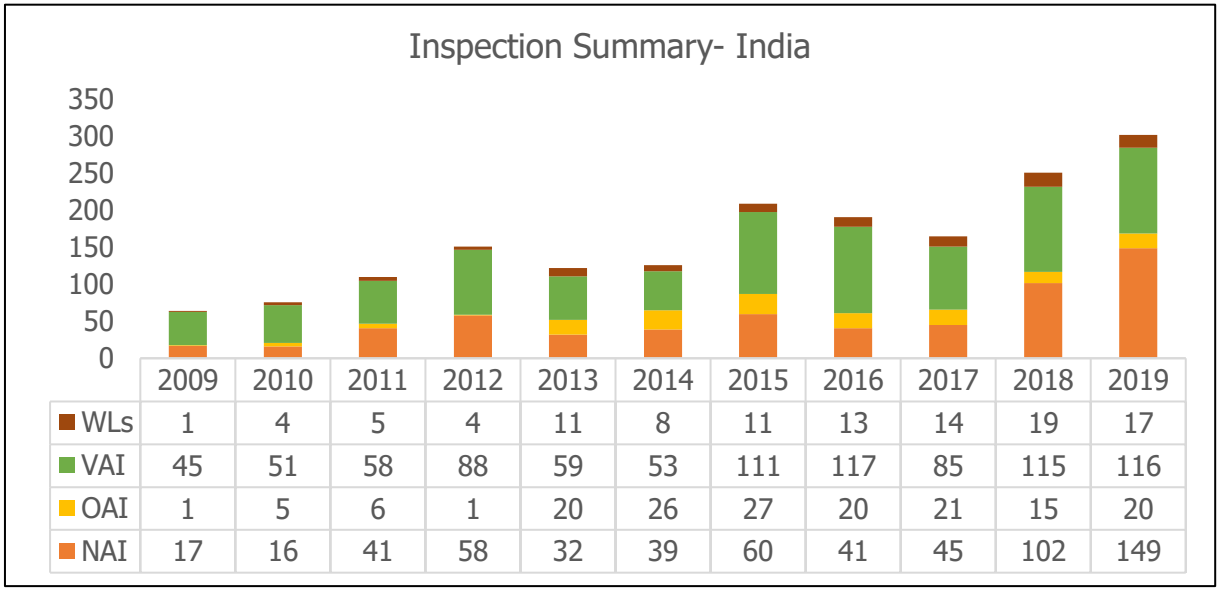
USFDA increasing its inspections of facilities of drug makers in India, the third largest provider of finished dosage products to the US, to ensure compliance with manufacturing norms.



Source: FDA access database

Year wise Inspection Summary- India

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total no.of Inspections (NAI + OAI + VAI)	63	72	105	147	111	118	198	178	151	232	285



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
WLs	1	4	5	4	11	8	11	13	14	19	17
VAI	45	51	58	88	59	53	111	117	85	115	116
OAI	1	5	6	1	20	26	27	20	21	15	20
NAI	17	16	41	58	32	39	60	41	45	102	149

Inspections are classified in three categories- NAI, OAI and VAI.

- **WLs**- Inadequate response to OAI or VAI observations is resulting into Warning Letters.
- **VAI**- Voluntary Action Indicated, FDA found objectionable conditions, but they did not warrant regulatory significance
- **OAI**- Official Action Indicated, FDA found significant objectionable conditions or practices and action must be taken to address the issues
- **NAI** - No Action Indicated, Zero 483 observations

Source: FDA access database

Warning Letters number is not included in total inspections.

Inspections Summary for FY2019- India

- Many of the bigger Indian organisations like Cipla, Dr. Reddy's, Lupin, Sun Pharma, Torrent Pharma, Cadila Health Care, Aurobindo, Windlas etc. were issued with 483 observations in FY2019 by USFDA.
- Significant increase (26.6% and 29.9% respectively in 2018 and 2019) in number of inspections of Indian companies in the last two years as compared to the total number of foreign inspections (in 2017, the percentage was 15.6%).
- There is no significant change in number of warning letters issued in 2019 as compared with 2018.
- There is steady increase in NAI inspections (2017-29.8%, 2018- 44.0% and 2019-52.3%) indicative of improvement in approach towards quality systems and employee capabilities.

Highlights of year 2019

- Two big companies, Aurobindo Pharma and Cadila Healthcare, holding 100+ approved ANDAs are under FDA scanner.
- Aurobindo Pharma
  - Unit-4, Sterile Injectable Facility : Fourteen 483 observations, a 37- page 483 letter- one of the major site contributing for US sales. Nearly 40+ ANDAs are in pipeline for approval, filed from this site.
  - Unit-1 and Unit-9: inspections are classified as "OAI"- Official Action Indicated.
  - Unit -11: API facility has been issued warning letter by FDA on 20th June 2019.

  https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aurobindo-pharma-limited-577033-06202019
- Cadila Healthcare
  - Cadila Healthcare, Moraiya facility, Ahmedabad, inspected between 22nd Apr to 3rd May 2019: Fourteen 483 observations, one of the major site supplying both solid oral and injectable products to US, was issued a warning letter on 29th October 2019.

  https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cadila-healthcare-limited-584856-10292019

483 Citation Analysis

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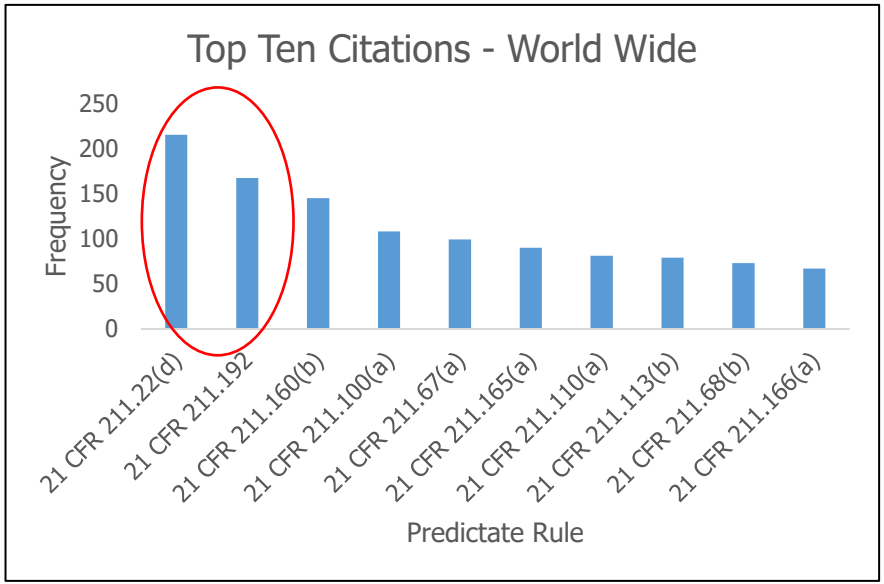
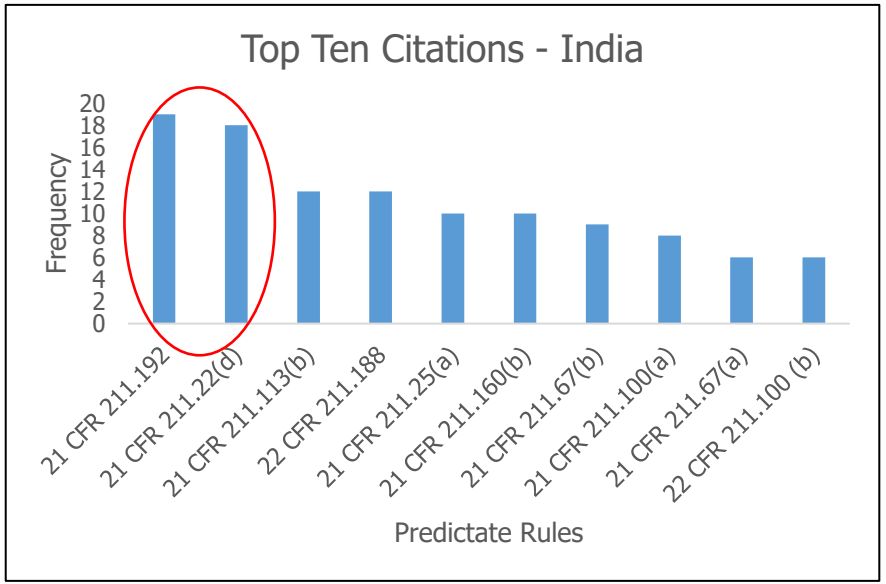
Top Ten 483 Citations





Predicate Rule	Top 2 observations commonly seen for entire world wide pharma industry
21 CFR 211.192	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.
21 CFR 211.22(d)	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].

Source:-Citations database-USFDA

483 Citations Summary-2019

- 483 observation is a violation of applicable 21 CFR 211/210 predicate rule.
- Fundamentally, all data integrity deficiencies identified in 483 letters and warning letters are violations to follow cGMPs as required by the predicate rules.
- The number of 483 letters issued to pharma companies world wide during FY2019 - 779.
  - The above number does not represent the complete set of 483 letters as some of the inspection letters were issued manually.
  - The above number was the actual number of the letters issued by the system.

*A **predicate** rule is any **FDA** regulation that requires companies to maintain certain records and submit information to the agency as part of compliance.*

Source: https://www.pharmaceuticalonline.com/doc/fda-fy-drug-inspection-observations

483 Citations Summary-2019 for India

- Number of citations available in the database for Indian drug industry -
  - 254 citations for year 2019
  - 262 citations for year 2018
  - 128 citations for year 2017
- Repeatedly observed 483 citations during inspections in FY 2019 -
  - In the Indian pharma industry, for past 3 years, citation as per 21 CFR 211.192 *(Investigations of failures)* non-compliance is leading the trending table.
  - The citation regarding procedure for sterile drug product and validation of sterile process (21 CFR 211.113b) was noted 12 times during inspections in 2019.
  - Batch manufacturing records (21 CFR 211.188) not prepared for each batch and incomplete with respect to process information, process controls for each batch. This citation was noted 12 times during inspections in 2019.
  - Cleaning of equipment (21 CFR 211.67b) is also a aspect where Indian companies are struggling to comply with written procedures.
- All the citations are interlinked within each other, associated with manufacturing / testing process of each respective drug product.

Comparison of 483 citations between companies world-wide and Indian companies

Predicate Rule No.	Short Description	Frequency Worldwide
21 CFR 211.22(d)	Procedures not in writing, fully followed	215
21 CFR 211.192	Investigations of discrepancies, failures	167
21 CFR 211.160(b)	Scientifically sound laboratory controls	145
21 CFR 211.100(a)	Absence of Written Procedures	108
21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	99
21 CFR 211.165(a)	Testing and release for distribution	90
21 CFR 211.110(a)	Control procedures to monitor and validate performance	81
21 CFR 211.113(b)	Procedures for sterile drug products	79
21 CFR 211.68(b)	Computer control of master formula records	73
21 CFR 211.166(a)	Lack of written stability program	67

Predicate Rule No.	Short Description	Frequency India
21 CFR 211.192	Investigations of discrepancies, failures	19
21 CFR 211.22(d)	Procedures not in writing, fully followed	18
21 CFR 211.113(b)	Procedures for sterile drug products	12
22 CFR 211.188	Prepared for each batch, include complete information	12
21 CFR 211.25(a)	Training--operations, GMPs, written procedures	10
21 CFR 211.160(b)	Scientifically sound laboratory controls	10
21 CFR 211.67(b)	Cleaning / Sanitizing / Maintenance	9
21 CFR 211.100(a)	Absence of Written Procedures	8
21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	6
22 CFR 211.100 (b)	SOPs not followed / documented	6

Frequency:- Number of times the citation was observed during inspections in FY 2019

Sidvim Observations

- Along with Global Pharma Industry, Indian pharma industry is also struggling to comprehensively justify compliance with a common regulation, 21 CFR 211.192 - failure investigations
  - Lack of appropriate OOS/deviations failure investigation procedure/process/technique.
  - OOS investigations are insufficient and do not include scientifically sound conclusions.
  - The impact assessment for failure investigations is inadequate/incomplete.
- Non-compliance with regulations, 211.192 and 211.22(d), raise questions for 211.25(a) which is for Training-operations, GMPs, written procedures.
- In spite of well established and rarely-changed GMP requirements (nearly two decades), inspectors are repeatedly observing violations.
- Non-compliance with failure investigations, testing & release, manufacturing documentation et al indicates cultural and behavioural issues along with deficient Quality management system.
- Non-compliance with 21 CFR 211.22, most commonly noted citation, also indicates that there is a gap in understanding the requirements expected by FDA from Quality Unit and implementing the same effectively throughout the product cycle.

Be proactive : *Remediation is Costly !!!*

- Average remediation period to resolve the warning letter is 18 to 24 months.
- Regulatory authorities like US, EU are increasingly emphasising on areas of frequent deficiencies (of Indian companies) like data integrity, inadequate failure investigations and laboratory controls.
- Management commitment is required to develop and maintain a culture of quality, deployment of resources necessary for continuous employee training and retraining, upgradation of software's/systems and need for quality management from the highest level in the organization.
- Encourage & appreciate employees for openly discussing problems / issues associated with systems.
- Develop processes/procedures which are robust and rugged.
- Identify gaps between process / procedures flow and mitigate them with appropriate risk assessment.
- Ensure that all the data generated is always valid and trustworthy.

Comparative analysis of warning letters issued to Indian & Chinese Companies

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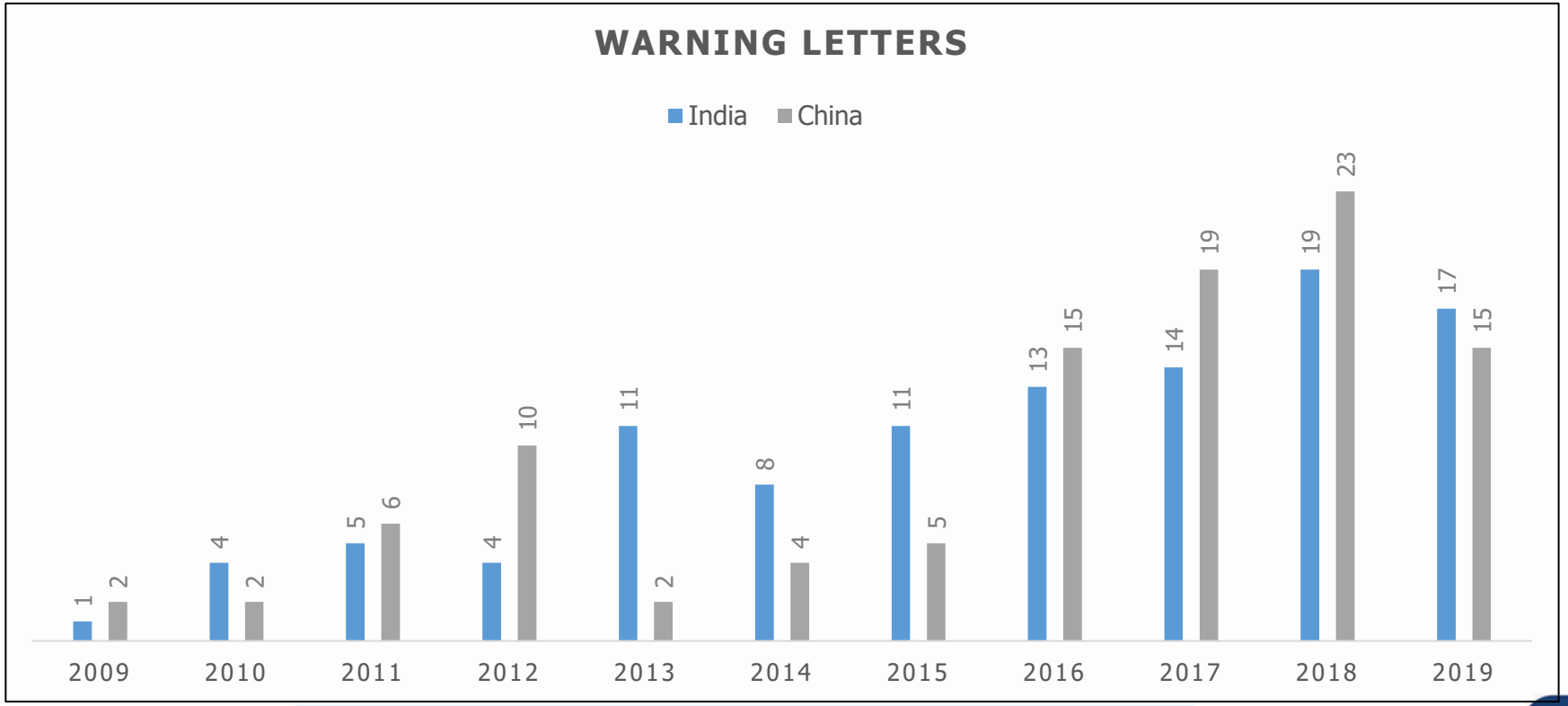
India and China; Increase in Inspections

- India and China are major global contributors of drugs and pharmaceuticals.
- Together, India and China have about 465 USFDA approved manufacturing sites (API and FDF).
- Indian pharma companies received more than 300 approvals in 2017 to launch generic drugs in the US, which is an all-time high. Out of the total ANDA approvals in the year 2016-17, Indian players have the highest share of ~40% *(IQVIA report Feb-2019)*
- Consequently regulators have increased vigilance on the quality of products being produced in these two countries.
- In recent years, many India and China based manufacturers (API and FDF) have been frequently flagged by the USFDA for deficiencies in GMP compliance (483 observations).

Comparison of Warning Letters



2014 onwards noticeable increase in number of Warning letters

Source: FDA access database

Warning Letters, India: Duration - 01.10.2018 to 30.09.2019

Sr.No.	FEI no.	Firm Name	Date of WL Issued
1	3002807511	Lupin Limited	10/9/2019
2	3012390454	Lantech Pharmaceuticals Limited	12/8/2019
3	3005151215	Emcure Pharmaceuticals Limited	2/8/2019
4	3006644152	Indoco Remedies Limited (Plant I)	12/7/2019
5	3006254924	CTX Lifesciences Private Ltd.	12/7/2019
6	3012448465	Strides Pharma Science Limited	1/7/2019
7	3004611182	Aurobindo Pharma Limited (Unit XI)	20/6/2019
8	3005269310	Rxhomeo Private Limited	17/6/2019
9	3009729392	Glint Cosmetics Pvt Ltd	31/5/2019
10	3008342939	Centurion Laboratories Private Limited	4/5/2019
11	3006217304	Contacare Ophthalmic & Diagnostics	23/4/2019
12	3010212308	B. Jain Pharmaceuticals Limited	21/3/2019
13	3006895982	Jubilant Generics Limited	6/3/2019
14	3008386908	Pfizer Healthcare India Private Ltd.	4/3/2019
15	3007450508	Anicare Pharmaceuticals Pvt Ltd.	28/2/2019
16	3003090962	Vipor Chemicals Private Ltd.	1/2/2019
17	3003658163	Skylark CMC Private Limited	3/12/2018

Thank You!

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