PDA Parenteral Drug Association

Gil Pharma Consulting

FDA FORM 483 INSPECTION OBSERVATION

2021-2022 FDA 483 trends

- *PDA Israel*
- *March 30th 2023*

- *Gil Zomber*
- *Gil Pharma*

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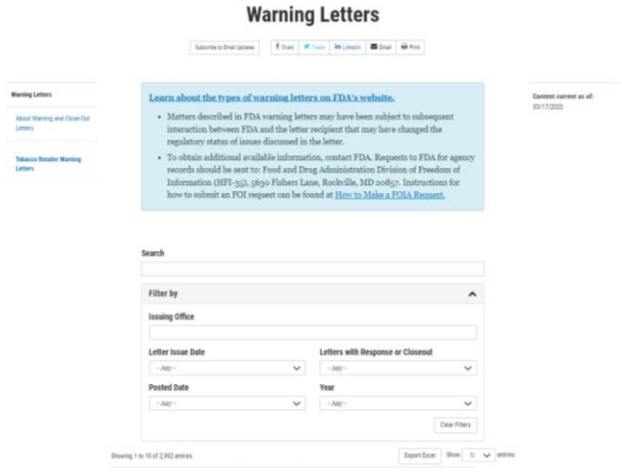
PDA Parenteral Drug Association

FDA - Warning letter web site

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters



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BioForum Applied Knowledge Center

FDA – Dashboards

	A	B	C	D	E	F	G	H	I
115405	Loricon Analytical Test	Keyport	United States		2013 824876	04/12/2013	Voluntary Action Indicated (VAI)	Drug Quality Assurance	
115406	Rushmore Mountain T	Keystone	United States		2010 661995	05/05/2010	No Action Indicated (NAI)	Foodborne Biological Hazards	
115407	Klefeker Swine Finish L	Keystone	United States		2014 868274	02/26/2014	No Action Indicated (NAI)	Monitoring of Marketed Animal Drugs, Feed, an	
115408	Care Rehab And Orthc	Keysville	United States		2009 556305	01/08/2009	No Action Indicated (NAI)	Compliance: Devices	
115409	Care Rehab And Orthc	Keysville	United States		2009 556305	01/08/2009	No Action Indicated (NAI)	Postmarket Assurance: Devices	
115410	S & M Brands, Inc.	Keysville	United States		2018 1047987	03/27/2018	No Action Indicated (NAI)	Tobacco Post-Market Activities	
115411	S & M Brands, Inc.	Keysville	United States		2016 961869	03/09/2016	No Action Indicated (NAI)	Tobacco Post-Market Activities	
115412	S & M Brands, Inc.	Keysville	United States		2014 877273	04/22/2014	No Action Indicated (NAI)	Tobacco Post-Market Activities	
115413	S & M Brands, Inc.	Keysville	United States		2012 787364	05/23/2012	No Action Indicated (NAI)	Tobacco Post-Market Activities	
115414	Frutarom, Ltd	Kfar Baruch	Israel		2019 1107090	09/03/2019	No Action Indicated (NAI)	Foodborne Biological Hazards	
115415	Teva Pharmaceutical Ir	Kfar Saba	Israel		2019 1099394	07/25/2019	Voluntary Action Indicated (VAI)	Drug Quality Assurance	
115416	Teva Pharmaceutical Ir	Kfar Saba	Israel		2015 935223	06/15/2015	Voluntary Action Indicated (VAI)	Drug Quality Assurance	
115417	Teva Pharmaceutical Ir	Kfar Saba	Israel		2013 849301	07/18/2013	No Action Indicated (NAI)	Drug Quality Assurance	
115418	Teva Pharmaceutical Ir	Kfar Saba	Israel		2010 685769	08/26/2010	Voluntary Action Indicated (VAI)	Drug Quality Assurance	
115419	Teva Pharmaceutical Ir	Kfar Saba	Israel		2009 589201	06/11/2009	Voluntary Action Indicated (VAI)	Drug Quality Assurance	
115420	Spatz FGIA, Inc	Kfar Saba	Israel		2019 1107557	09/25/2019	Voluntary Action Indicated (VAI)	Compliance: Devices	
115421	Spatz FGIA, Inc	Kfar Saba	Israel		2019 1107557	09/25/2019	Voluntary Action Indicated (VAI)	Postmarket Assurance: Devices	
115422	Spatz FGIA, Inc	Kfar Saba	Israel		2019 1099803	08/09/2019	Voluntary Action Indicated (VAI)	Bioresearch Monitoring	
115423	Geo-fresh Organic	Khali	India		2015 936448	07/21/2015	No Action Indicated (NAI)	Foodborne Biological Hazards	
115424	Ekta Fresh Foods Pvt. L	Khambhat	India		2014 855177	11/15/2013	No Action Indicated (NAI)	Food Composition, Standards, Labeling and Eco	
115425	Ekta Fresh Foods Pvt. L	Khambhat	India		2014 855177	11/15/2013	Voluntary Action Indicated (VAI)	Foodborne Biological Hazards	

NAI – No Action Indicated

VAI – Voluntary Action Indicated

OAI – Official Action Indicated (non-approvable, Application Integrity Policy)

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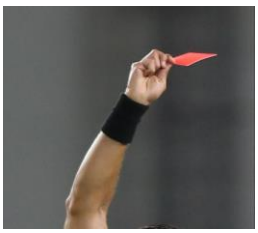
FDA – Inspection Classification

- NAI – No Action Indicated
- VAI – Voluntary Action Indicated
- OAI – Official Action Indicated (non-approvable, Application Integrity Policy)



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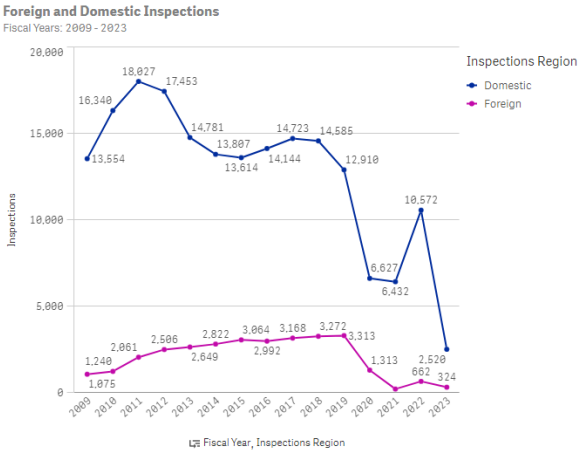
Total Number of inspections Per year



Inspections Classification

NAI – No Action Indicated

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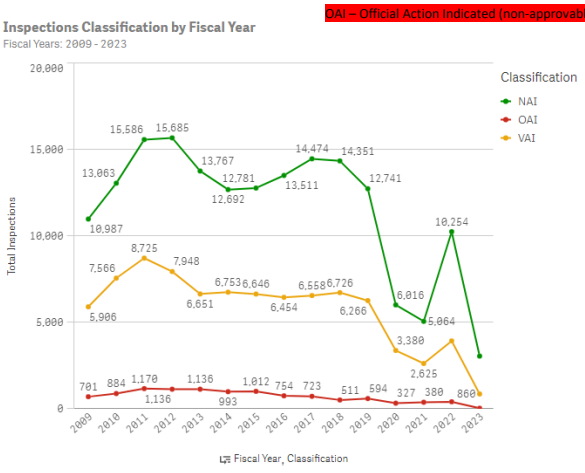

Number of 483 issued 2021 Vs 2022

Number of 483 issued from the System*

Inspections ending between 10/1/2020 and 9/30/2021

Cite Program Area Name	483s Issued
Biologics	17
Bioresearch Monitoring	133
Devices	191
Drugs	215
Foods	1751
Human Tissue for Transplantation	51
Parts 1240 and 1250	3
Radiologic Health	6
Veterinary Medicine	105
Sum Product Area 483s from System*	**2472**
Actual Total in System 483s**	**2430**

2021

Number of 483 issued from the System*

Inspections ending between 10/1/2021 and 9/30/2022

Cite Program Area Name	483s Issued
Biologics	61
Bioresearch Monitoring	126
Devices	538
Drugs	466
Foods	2399
Human Tissue for Transplantation	81
Parts 1240 and 1250	23
Radiologic Health	9
Veterinary Medicine	184
Sum Product Area 483s from System*	**3887**
Actual Total in System 483s**	**3838**

2022

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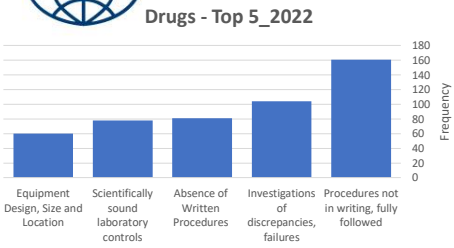
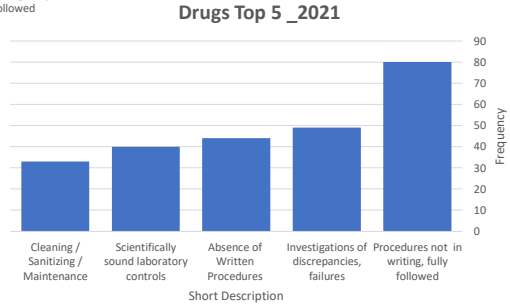
Top 5 observations - Drugs





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Top 5 observations - Drugs

Reference Number	Short Description	Long Description
21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***
21 CFR 211.192	Investigations of discrepancies, failures	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. Specifically, ***
21 CFR 211.100(a)	Absence of Written Procedures	Your firm failed to establish [adequate] written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess. Specifically, ***
21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***
21 CFR 211.63	Equipment Design, Size and Location	Equipment used in the manufacture, processing, packing or holding of drug products is not [of appropriate design] [of adequate size] [suitably located] to facilitate operations for its [intended use] [cleaning and maintenance]. Specifically, ***

WARNING LETTER
Sanitor Corporation 21 CFR 211.22

1. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Inadequate investigations/Lack of process control

You contract manufacture over-the-counter drug products including benzalkonium chloride-based hand sanitizer.[1] Multiple batches of hand sanitizer drug product failed microbial total plate count (TPC) testing with results of Too Numerous to Count (TNTC). Your quality unit (QU) failed to adequately investigate and identify the root cause for the microbial contamination in your hand sanitizer drug product. Instead of conducting a thorough investigation and implementing corrective action to prevent contamination, your QU:

- Approved the addition of an antimicrobial preservative to batches that initially failed microbial TPC testing, and were then released for distribution by your customer; and
- Approved the addition of an antimicrobial preservative to batches not yet tested for microbial TPC so that they would yield a passing result, and were released for distribution by your customer.

WARNING LETTER
Sanitor Corporation 21 CFR 211.22
Data Integrity

2/22, 8:57 AM Sanitor Corporation - 616232 - 11/29/2021 | FDA

During the review of a batch record for your **(b)(4)** hydroquinone **(b)(4)** drug product, batch **(b)(4)**, our investigators noted that production activities were not recorded contemporaneously. For example, the batch record documented that one employee performed multiple manufacturing steps, such as measuring containers and bulk reconciliation on two separate dates, and a second employee documented the verification of the activities. However, the second employee (verifier) stated to our investigator that they were not at work when these steps were documented as being performed. Your QU oversight does not provide adequate assurance that manufacturing records are accurate, and that production was performed as documented.

In your response, you acknowledge that good documentation practices were not followed. You also stated that you performed training of all personnel. Your response is inadequate. Your quality system has not adequately

WARNING LETTER
Takeda Pharmaceutical Company Limited 21 CFR 211.22

Your firm failed to establish adequate written responsibilities and procedures applicable to

the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

- Our inspection found that your Quality Unit (QU) did not take appropriate steps prior to resumption of aseptic manufacturing after a shutdown that included multiple significant activities that compromised cleanroom control.
- Your QU allowed manufacturing operations to resume for **(b)(4)** filling operations without performing an aseptic process simulation (i.e., media fill) as indicated by your procedure.
- Your firm manufactured and shipped several batches of **(b)(4)** to the U.S. market after this deviation.

Warning letter
Toyobo Co. Ltd. 21 CFR 211.192

לא תיחקרתם כראוי בעיית חלקיקים משמעותית במוצר סטרילי כולל מיקרים חוזרים ונשנים של בעייה זאת

You did not adequately investigate significant particulate defects in your sterile drug product, including recurring incidents of extrinsic particle contamination.

נכשלתם בפתיחת חקירת חריגה בזמן ובהגעה לסיבת השורש

During 2019 and 2020, multiple batches of (b)(4) injection solution were found to have significant particulate contamination defects, many of which are defined in your procedure and response as "foreign" (i.e., extrinsic). When extrinsic particulates were identified within batches, you failed to initiate a timely investigation to determine root causes and assess the drug product impact. Our review revealed that your in-process quality standards, limits, categories, and triggers for investigations do not sufficiently differentiate intrinsic from extrinsic particulate contamination.

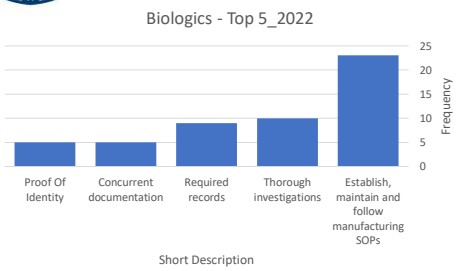
החקירה שלכם הגיעה למסקנה שהבעייה נובעת
מספק הפקקים שלכם אך יישמתם פעולות מתקנות ומונעות סבירות

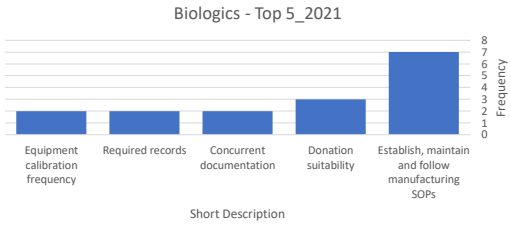
A recent investigation update, submitted to FDA on June 18, 2021 (four months after FDA's inspection), indicates that you have improved your procedures and are performing supplier audits. While your investigation concluded that it is "highly possible" that your washing and sterilization processes could not remove certain particles adhered to the (b)(4) stoppers or vials, you failed to adequately address the upstream root causes of the contamination and implement timely corrective action and preventive actions (CAPA).

ספק פקקי הגומי שלכם ציין שבעיית החלקיקים לא מגיעה מהטיפול שלהם בפקקי הגומי

However, your stopper supplier indicated that their process was not the cause of the problem at the time, and your CAPA was inadequate to resolve the problem.

Top 5 observations - Biologics





Top 5 observations - Biologics

21 CFR 606.100(b)	Establish, maintain and follow manufacturing SOPs	Written standard operating procedures including all steps to be followed in the [collection] [processing] [compatibility testing] [storage] [distribution] of blood and blood components for [allogeneic transfusion] [autologous transfusion] [further manufacturing purposes] were not always [established] [maintained] [followed] [available to personnel in the areas where procedures were performed]. Specifically, ***
21 CFR 606.100(c)	Thorough investigations	Failure to [perform a thorough investigation] [make a record of the conclusions and follow-up] of [an unexplained discrepancy] [a failure of a lot or unit to meet any of its specifications]. Specifically,***
21 CFR 606.160(b)	Required records	Failure to maintain [donor] [processing] [storage and distribution] [compatibility testing] [quality control] [general] records. Specifically, ***
21 CFR 606.160(a)(1)	Concurrent documentation	Records are not concurrently maintained with the performance of each significant step in the [collection] [processing] [compatibility testing] [storage] [distribution] of each unit of blood and blood components so that all steps can be clearly traced. Specifically, ***
21 CFR 630.10(g)(1)	Proof Of Identity	Failure to obtain from the donor on the day of donation [proof of identity] [a postal address where the donor may be contacted for 8 weeks after donation]. Specifically, ***
21 CFR 606.40(a)(1)	Provide space for examination	Failure to provide adequate space for [private] [accurate] examinations of individuals to determine their eligibility as blood donors. Specifically, ***

WARNING LETTER
www.ivermectin4covid.com — unapproved drugs

Certain products offered for sale by www.ivermectin4covid.com are drugs within the meaning of section 201(g) of the FD&C Act [21 U.S.C. § 321(g)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or because they are intended to affect the structure or function of the body. commerce violates sections 301(d) [21 U.S.C. § 331(d)] and 505(a) of the FD&C Act.
For example, www.ivermectin4covid.com offers ivermectin marketed as "Iverheal 12mg" manufactured by Healing Pharma. Your website states, "Ivermectin (Iverheal 12) is an antiparasitic, and also an antiviral drug manufactured by Healing Pharma. It is used to kill the parasites in the body. **It is also useful in Covid 19 care**." While there are FDA-approved versions of ivermectin on the market in the U.S., there are no approved drug applications pursuant to section 505 of the FD&C Act in effect for the "Iverheal 12mg " manufactured by Healing Pharma and offered by www.ivermectin4covid.com. ivermectin has not been approved by FDA for use in the prevention, diagnosis, treatment, mitigation, or cure of COVID-19.

מכתבי אזהרה רבים הוצאו לחברות שבאתר
שלהן מצהירות על
מניעה, טיפול וריפוי של קורונה ללא אישור FDA לאינדיקציה

WARNING LETTER
Hand Sanitizer Products

מכתבי אזהרה רבים הוצאו ליצרנים של חומרי חיטוי לידיים

- There has been a recent accumulation of Warning Letters from the U.S. Food and Drug Administration (FDA) to manufactures of hand sanitizer products:
- High impurities content
- Too low Ethanol Content
- High Methanol concentration
- Potentially Carcinogenic Contaminants in Hand Sanitizers
- Poor analytical testing
- No microbial testing on the finished hand sanitizer drug products

Warning letters in numbers

- The COVID-19 pandemic astounded everyone, regulators, and industry alike, with the scope and depth of changes that occurred almost immediately, and this is reflected in the decreased number of warning letters issued in FY2020 and FY2021. FDA has resumed domestic inspections, along with many of those outside the U.S. where travel restrictions permit, and the number of warning letters in FY2022 are beginning to inch up.

	FY'13	FY'14	FY'15	FY'16	FY'17	FY'18	FY'19	FY'20	FY'21	FY'22
Total Warning Letters	41	49	43	102	114	127	130	106	42	54
Compound-ing Pharmacies	3	27	24	56	45	32	19	23	12	7
U.S. - non Compounding	13	4	3	11	20	22	68	40	16	37
OUS	25	18	16	35	49	73	43	43	14	10

TABLE 1 | DRUG GMP WARNING LETTERS, FY2013 THROUGH FY2022

Drug GMP Warning letters

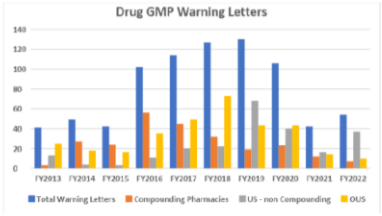


FIGURE 1 | TOTAL DRUG GMP WARNING LETTERS

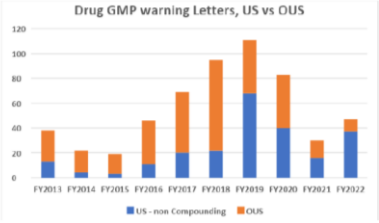


FIGURE 2 | DRUG GMP WARNING LETTERS ISSUED TO SITES IN AND OUTSIDE THE US

PERCENTAGE of US vs OUS Warning Letters

Drug Warning letters –% Data Integrity

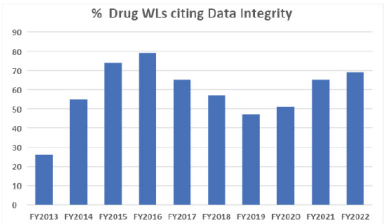


FIGURE 4 | WARNING LETTERS THAT CITE DATA INTEGRITY

	FY2020	FY2021	FY2022
STERILE NON-COMPOUNDED	14	3	10
OTC	1	0	2
HCT/P	8	1	6
COMPOUNDED	23	12	7

TABLE 4 | TYPE OF FIRMS

Forecast for 2023

Fiscal year 2022 saw the beginning of a return to pre-pandemic enforcement that will likely increase in FY2023. FY2022 however, was a year of transition, particularly in the performance of global on-site inspections.

Following are the things I'm watching for in FY2023 (which began October 1, 2022):

Continued focus on OTC manufacturers inside and outside the U.S. because of the number of the public that these product impact, and the failures in fundamental GMP requirements that FDA has identified at these firms over the past few years.

As we return to more on-site inspections, I'd expect an **increase in warning letters to pharmaceutical (not OTC) firms** as corners were likely cut when limited staff were on site and the pressures to produce with limited staff likely became more intense.

Enforcement focus will continue to focus on **extraneous particulates** in sterile parenteral products, **cross-contamination and inadequate or missing risk assessments**.

Thanks, and good luck in your future inspection