REGULATORY FOCUS

Current status and future FDA enforcement of dietary supplements

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FDA observations for adulterated dietary supplements have remained consistent since 2010, even during 2020, when inspections were down 47% and accommodations for compliance were made because of the COVID-19 pandemic. These include requirements to establishment specifications, testing to determine if specifications are met, use of master manufacturing records, preparation of batch production records, and ensuring quality responsibilities are defined. The pandemic has also resulted in an increase in the number of misbranded dietary supplements. Because of these developments, the US Food and Drug Administration (FDA) is using updated, alternative, and remote enforcement tools to ensure compliance.

Introduction

In 2020, the dietary supplement industry has learned that it must be willing to adapt to change and to do so with creative tenacity to remain viable in this competitive, essential business environment, without sacrificing quality or compliance to FDA regulatory requirements. During that same time, throughout the pandemic, the FDA has severely limited its inspectional work of dietary supplement facilities to assess compliance to current good manufacturing

practice (cGMP) regulatory requirements for dietary supplements.[1] It has instead focused enforcement activities on evaluations of company websites and social media platforms for compliance to labeling[2] and misbranded dietary supplements. This is demonstrated by the 47% decrease in 21 CFR 111 cGMP FDA observations issued to the dietary supplement industry in 2020 to 868, compared with the annual average number of observations of 1,639 issued from 2011 through 2019. A total of 159 FDA warning letters were issued in 2020, and 35 more so far in 2021, for products containing dietary ingredients that have disease claims specific to COVID-19, which renders them as misbranded dietary supplements. Typically, only about 25 warning letters are issued for misbranded dietary supplements annually.

Current cGMP enforcement

Top FDA observations

Even with a significant decrease in cGMP FDA observations issued to the dietary supplement industry in 2020, the top five observations have remained unchanged since 2010, when 21 CFR 111 applied to all size companies (**Table 1**). The top observations have been:

- Establishing specifications and testing to determine if those specifications have been met as required in Subpart E[3] (establishing a production and process control system);
- Preparing a master manufacturing record (MMR) for each dietary supplement product at each batch size and using the MMR for the production of each lot manufactured (Subpart H[4]) and packaged as documented in a batch production record (Subpart I[5]); and
- The numerous responsibilities of the quality unit as defined in Subpart F.[6]

This applies to all dietary supplement manufacturers, but the FDA has also been paying particular attention to the small brand owner, referred to as the own label distributor (OLD), in recent years. OLDs often expect that their contract manufacturers are solely responsible for regulatory compliance, but the FDA has made it abundantly clear that adherence to the regulation is ultimately the responsibility of the OLD for all aspects of manufacture, including that of their contractors. FDA warning letters issued to OLDs routinely state:[7-13]

Table 1. Dietary supplement FDA observations from 2010 through 2020

Item	Description	Observations Cited												
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2010-2020	% All
1	Specifications	32	104	176	234	204	154	214	247	226	236	150	**1977**	**12%**
2	Testing	54	111	226	287	188	144	195	213	171	157	95	**1841**	**11%**
3	MMRs	28	53	94	117	82	67	87	94	81	72	91	**866**	**5%**
4	BPRs	18	52	74	93	71	71	72	84	84	69	115	**803**	**5%**
5	QU Operations	18	43	47	66	47	45	55	73	59	74	125	**652**	**4%**
	Total Observations	631	1328	1964	2211	1549	1294	1625	1795	1553	1433	868	**16251**	**38%**

> To the extent that you contract with other firms to manufacture your product that your firm releases for distribution under your firm's name, your firm has an obligation to know what and how manufacturing activities are performed so that you can make decisions related to whether your dietary supplement products conform to established specifications and whether to approve and release the products for distribution [72 Fed. Reg. 34752, 34790 (Jun. 25, 2007)].

and,

> Although a firm may contract out certain dietary supplement manufacturing operations, it cannot contract out its ultimate responsibility to ensure that the dietary supplement it places into commerce (or causes to be placed into commerce) is not adulterated for failure to comply with dietary supplement cGMP requirements. In particular, the Act prohibits a person from introducing or delivering for introduction, or causing the delivery or introduction, into interstate commerce a dietary supplement that is adulterated under section 402(g) for failure to comply with dietary supplement cGMP requirements (see 21 U.S.C. 342(g) and 331(a)).

Observations regarding holding and distributing operations that require adherence to written procedures as required in Subpart M[14] have also been frequently issued by the FDA. In addition, ensuring that all product complaints are appropriately evaluated and investigated as necessary per Subpart O,[15] and in the event of a serious adverse event (SAE) reported to the FDA within 15 business days to comply with the requirements of the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006[16] are often observations issued to both manufactures and OLDs of dietary supplements. This is an essential for a postmarketing surveillance program because it pertains to dietary supplements. Another essential part of the dietary supplement postmarketing surveillance program is the requirement that all product returns are subject to a material review and disposition decision by the quality unit in accordance with Subpart N.[17]

A closer examination of the 2019 FDA data and the most recent 2020 data show the significance of these additional observations (**Figure 1** and **Figure 2** on p. 4).

Specifications and testing

The continued difficulties of the dietary supplement industry to comply with the cGMP requirements to establish specifications and then test in accordance with those specifications to determine if the specifications have been met are reflective and commensurate with the complexity of this process. Raw material (dietary ingredient and component), in-process material, and finished product specifications must address the identity, purity, strength, composition, and limits of potential contaminants per 21 CFR 111.70(b), (c), and (e), and multiple and sophisticated analytical laboratory techniques and instrumentation are usually necessary, given the chemical nature of the raw materials used for dietary supplement product formulations, especially botanical dietary ingredients. Further, these test methodologies must be experimentally demonstrated and documented to be scientifically valid per 21 CFR 111.75(h)(1) and 111.320(b), which is described in the Preamble to the Final Rule[18] as

specific, accurate, precise, and consistently doing what it is intended to do (also referred to as rugged). All of this requires scientific expertise, a thorough knowledge of the material(s) and product formulation, and an understanding of the manufacturing process. Personnel attributes that are not often available internally at many dietary supplement companies. This is seldom the case when dietary supplements are marketed by OLDs using contracting relationships with manufacturers and laboratories.

Figure 1. Top 2019 dietary supplement FDA observations

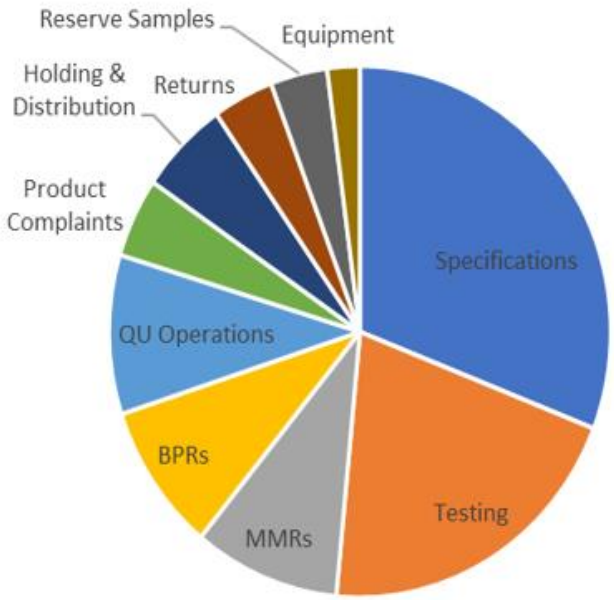
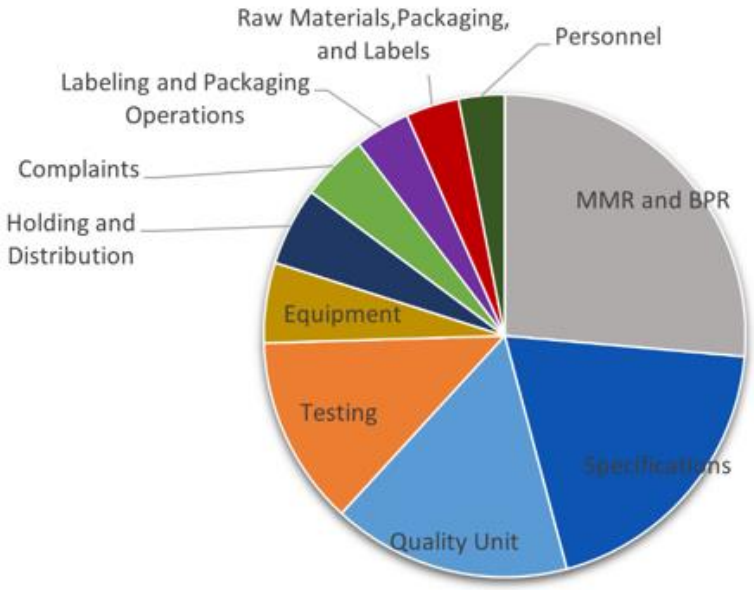


Figure 2. Top 2020 dietary supplement FDA observations



Changes in 2020

Facility inspections

On 10 March 2020 then FDA Commissioner, Stephen M. Hahn, MD, issued a statement[19] postponing all foreign facility inspections due to the global outbreak of COVID-19. Only foreign inspections deemed "mission-critical" were considered on a case-by-case basis. The decision was based on a State Department Level 4 travel advisory prohibiting travel of US government employees, Centers for Disease Control and Prevention travel recommendations, access restrictions imposed on foreign visitors by countries, guidance from the Office of Personnel Management, the importance of the health and safety of FDA employees, and FDA confidence in the ability to maintain oversight over international manufacturers and imported products using alternative tools and methods.

This statement was quickly followed by another statement[20] by Dr. Hahn on 18 March 2020 that postponed all domestic routine surveillance facility inspections and directed all eligible FDA employees to begin teleworking. Domestic for-cause inspection assignments were only warranted for "mission-critical" situations such as Class I recalls, a foodborne outbreak, or COVID-19 related issues. It was re-iterated that the decision was based on concerns about the health and well-being of FDA staff and those who conduct inspections for the agency under contract at the State level, as well as industry concerns about visitors. The FDA also stated, "safety and quality need to be owned by the industry and firms have the primary responsibility to reliably produce quality products" and that facilities "must adhere to current good manufacturing practice (cGMP) requirements pertaining to, for example, operating procedures, manufacturing, sanitation, and processing controls, as well as preventive controls to reduce or eliminate food safety hazards."

SAE reporting

Amidst these FDA statements, the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020. The FDA then acknowledged that that both industry and FDA workforces may be reduced because of high employee absenteeism and other limited resources, so on 20 March 2020, the agency issued a revised guidance for industry on reporting postmarketing adverse events for medical products and dietary supplements during a pandemic.[21] That guidance replaced a 2012 guidance, updating and clarifying that the guidance applied to all pandemics. The new guidance dictates that as much compliance and continuity with company complaint processes and SAE reporting requirements as possible should be maintained and that SAEs related to product safety must be of highest priority. However, SAEs can be "stored" internally and reported to the FDA within the 6 months after the pandemic is resolved and a prepandemic, normal state of activities has been obtained. Documentation of the WHO pandemic declaration as well as the particular dietary supplement facility situation of high absenteeism or other factors that is/are preventing normal SAE requirements must both be prepared and available to the FDA upon future inspection. It is expected that firms will resume fulfilling all SAE reporting requirements on time after the pandemic-related situation.

Foreign supplier verification program rule

On 18 March 2020, the FDA also issued a guidance for industry regarding a temporary policy for preventive controls and requirements for Foreign Supplier Verification Program (FSVP) food supplier verification on-site audits during the pandemic emergency,[22] to communicate agency's intention to temporarily not enforce supplier verification on-site audit requirements for receiving facilities and importers under the Food Safety Modernization Act (FSMA)[23] of 2011 during the pandemic, provided other supplier verification methods are used instead. As a classification of foods, dietary supplement companies must also comply with FSMA and its seven major rules:

- Current good manufacturing practice; and hazard analysis, and risk-based preventative controls (HARPCs) for human and animal food;
- Foreign Supplier Verification Program Rule;
- Intentional Adulteration Rule
- Product Safety Rule (fruits and vegetables)
- Sanitary Transportation Rule
- Standard for the growing, harvesting, packing, and holding of produce for human consumption
- Voluntary accredited third-party certification program.

The cGMP and HARPC requirements for foods are dictated in 21 CFR 117.[24] Dietary supplement companies in compliance with 21 CFR 111 are exempt from 21 CFR 117 Subpart C[25] (HARPC) and Subpart G[26] (supply chain program). Both 21 CFR 111 and 21 CFR 117 define the cGMP requirements for sourcing, manufacturing, packaging, holding and distribution of foods so generally compliance with 21 CFR 111 also results in compliance with 21 CFR 117. Moreover, 21 CFR 111 has very rigorous and specific quality specification and testing requirements; detailed requirements for manufacturing, packaging, and labeling operations; and extensive responsibilities that must be conducted by a quality unit. Evidential support of this is clearly provided in the FDA enforcement activities and issuance of observations in these areas from 2010 through 2020. When a dietary supplement product or ingredient is imported from a foreign supplier, the FSMA FSVP rule applies. This is not covered under 21 CFR 111.

FSVP rules that apply to dietary supplement companies are modified and vary depending on the materials and products imported, responsible party, designated importer of record, and cGMP regulation in place. This is discussed in the FDA guidance for industry regarding small entity compliance,[27] issued in January 2018 to help firms understand the various requirements. An adaptation of the table in the guidance document is provided in **Table 2** (p. 7). The FSVP requirements that apply should be incorporated into the supplier qualification program that is required in 21 CFR 111.75(a)(2)(ii) that encompasses:

- Supplier documentation audit via a supplier qualification questionnaire;
- Supplier certificate of analysis (CoA) confirmation testing;
- Onsite supplier facility audit; and
- Requalification of supplier periodically.

Table 2. FSVP requirements for importing dietary supplement materials and products

Importer Type – 21 CFR 111 Quality System Adherence			
FSVP Requirements	Self	Customer	Neither
	Identify Importer at Entry (21 CFR 1.509)	Identify Importer at Entry (21 CFR 1.509)	Identify Importer at Entry (21 CFR 1.509)
	Qualified Individual Used (21 CFR 1.503)	Qualified Individual Used (21 CFR 1.503)	Qualified Individual Used (21 CFR 1.503)
		Recordkeeping (21 CFR 1.510)	Recordkeeping (21 CFR 1.510)
		Annual Written Assurance of 21 CFR 111 Compliance	Modified FSVP Program (21 CFR 1.511(c))
			Foreign Supplier Evaluation (21 CFR 1.505)
			Corrective Actions (21 CFR 1.508)

Enforcement of the FSVP rule has significantly increased amid the COVID-19 pandemic. A total of 61 FDA warning letters have been issued to firms failing to comply with the rule, with most not having a program at all. All but nine of those warning letters have been issued since the initial postponement of foreign and domestic inspections.

Future FDA enforcement

Alternative tools and methods

On 20 July 2020, the FDA officially announced the resumption of prioritized field inspections for domestic inspections only.[28] Foreign facility inspections remain on hold. These prioritized inspections are and will be focused on "mission critical" work (relevance to COVID-19 response; public health impact such as food safety or limited availability of a drug; preapproval inspections (PAIs) to bring new drugs to market and/or increase supply availability; product and process complexity as is the case for sterile injectables; and on-going compliance risks of open inspections involving warning letters, consent decrees, recalls, and seizures). However, their conduct depends on the regional conditions on the ground to account for state and local COVID-19 outbreaks and guidelines, as well as the safety of FDA staff. The fluid situation also necessitates that the agency preannounce the inspections and that they are coordinated with the dietary supplement firm. Aside from these inspections, the FDA is using alternative tools and methods to meet its responsibility of protecting the public health by ensuring the safety, efficiency, and security of human and veterinary drugs, biological products, and medical devices, as well as the safety of the US food supply, cosmetics, and products that emit radiation.

For foreign facilities alternative tools and methods may include any or all of the following:

- Denying entry of unsafe products into the US;
- Physical examinations and/or product sampling at US borders;
- Reviewing a firm's previous compliance history;
- Using information sharing from foreign governments as part of mutual recognition and confidentiality agreements and requesting records "in advance of or in lieu of" on-site inspections;
- Working with Customs and Border Protection to target products intended for importation into the US that violate applicable legal requirements;
- Focusing on first-time importers and repeat offenders; and
- Use of PREDICT, a risk-based import screening tool.

Virtual inspections

Virtual inspections, or partial virtual inspections, may also be used in lieu of on-site facility inspections, both foreign and domestic. In April 2021, the FDA issued a guidance for industry, remote interactive evaluations during the pandemic,[29] in which it described various remote interactive tools the agency could use. These remote interactive evaluation (RIEs) are being conducted in place of on-site inspections for PAIs and prelicense inspections; post-approval inspections; surveillance inspections; follow-up and compliance inspections; and bioresearch monitoring inspections. The expectation is that facilities will demonstrate the same level of transparency and forthrightness as with a formal inspection. An RIE does not constitute an inspection. The FDA will use information gathered during the RIE to determine the scope, depth, and timing of a future inspection.

Notification of an intended RIE is performed electronically or by phone, using the facility's registration or application information. Section 305 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act) requires owners, operators, or agents in charge of domestic and foreign facilities that manufacture, process, pack, or hold food for human or animal consumption in the US to register their facilities with FDA and since dietary supplements are classified as a category of foods this registration requirement applies. Correspondence or phone contact will include a request for confirmation of the facility's willingness and ability to participate in the RIE, including the use of teleconference, livestream video, and screen sharing of data and documents. The request will indicate the name and address of the facility to be evaluated, the reason for the use of an RIE, and the names of FDA participants, if known. Once the facility confirms its willingness and ability to participate in an RIE, FDA will schedule a brief virtual meeting to discuss logistics, responsibilities, and expectations. A Form FDA 482, notice of inspection, to announce or open an RIE will not be issued.

The RIE will often include extensive requests for documents, records, and other information, such as electronic systems for review. These can be provided electronically or as scanned and searchable PDF files. Documents, records, and other information requested are expected to be provided within a reasonable timeframe, just as requests for documents or other information made during an on-site inspection. Livestream discussions and "interviews" and/or prerecorded video to examine facilities, operations, and data will also be incorporated into

the RIE. Platforms currently in use by the FDA for RIEs are FDA Microsoft Teams, FDA Zoom for Government, and FDA Adobe Connect. In addition, and as appropriate, verbal updates, evidence, and documentation that corrective and preventative actions dictated as necessary from previous inspections and enforcement activities will be assessed. A closeout meeting will be conducted upon completion of the RIE. A written list of observations, if any, will be provided as part of the meeting and discussions about the observations may also be had. This written list is not a final agency action or decision, nor will a formal Form FDA 483 (inspectional observations), be issued. Despite this, the FDA expects a written response to the observations within 15 US business days. A final RIE report will be issued to the facility when all observations have been appropriately addressed and the FDA deems the RIE closed.

Dietary Supplement Compliance Program Guidance Manual

An updated Dietary Supplement Compliance Program Guide (CPG)[30] was recently issued on 30 September 2020. A CPG contains FDA compliance policy and regulatory action guidance for FDA staff. It is a valuable resource to the industry as it is what the FDA Investigator uses to conduct an inspection and determine needed regulatory enforcement.

It is noted that in the new version, a new Inspectional Type for Distributors or OLDs are designated which is consistent with the increased enforcement activities of OLDs over the past few years. Required elements for OLD inspections include:

- Labeling compliance to 21 CFR 101 and to ensure products are not misbranded dietary supplements;
- The assignment of quality unit responsibilities with the contract manufacturer, preferably as documented in a Quality Agreement;
- Product Review requirements at OLD for product release and the performance of necessary material reviews;
- Complaint handling and SAE reporting, when dictated; and
- Additional coverage for other operations performed at the OLD such as packaging, labeling, and holding; and the requirement to establish specifications and conduct tests and examinations to determine whether those specifications have been met.

Conclusion

The dietary supplement cGMPs dictated in 21 CFR 111,[1] have been in place or more than 13 years, and FDA enforcement of the regulation has been ongoing for all size companies for more than 10 years. Given this elapsed time and input from the agency through enforcement, the entire dietary supplement industry must strive for a more robust understanding and heightened expectations for compliance with the regulation. This can be accomplished by focusing compliance improvement efforts on the essential quality systems that include:

- Establishing specifications and testing to determine if those specification have been met;
- Preparing MMRs for each dietary supplement product at each batch size;

- Use of the MMR for the production of each lot manufactured and packaged as documented in a BPR; and
- Ensuring that the numerous responsibilities of the quality unit are defined in written processes and executed as evidenced in records.

In addition, a strong process for triaging and investigating, as necessary, all product complaints must be developed and implemented. This form of postmarketing surveillance is vital for ensuring dietary supplement products are safe, and, if there are any accusations of SAEs, those complaint investigations are prioritized and reported to the FDA. OLDs must also take note that the need to have all of these same essential quality systems applies to them as they are ultimately responsible for the quality of the dietary supplements that they place, or cause to be placed, into commerce.

When a firm imports raw materials or products, an FSVP, or at least a modified version of an FSVP, must be established and should be incorporated within the supplier qualification program. Increased FDA enforcement of the FSVP Rule means that this has become another higher risk area to the dietary supplement industry.

The FDA has resumed prioritized on-site facility inspections and is armed with alternative tools including the use of RIEs to continue to enforce all of the regulatory requirements that apply to dietary supplements. As such, firms should always be in state of readiness for either. One good way to do this is to become familiar with the various compliance programs that are applicable to the facility, especially the recently updated Dietary Supplement CPG and conduct internal audits to ensure all areas discussed in the CPG are in good order and compliant to the regulation. Following FDA warning letters is also an excellent way in which to observe trends and expectations for compliance of the agency in order to be prepared.

About the author

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