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Client Alert

DECEMBER 19, 2022

FDA Warns Drug & Device Firms Against Delaying & Limiting Facility Inspections in New Draft Guidance

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On December 16, 2022, the U.S. Food & Drug Administration ("FDA" or "Agency") published an important and noteworthy draft guidance document entitled "Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection."[1] The draft guidance reflects the Agency's latest thinking on the "types of behaviors (actions, inactions, and circumstances) that FDA considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection" of drug and medical device facilities—a topic that the Agency has contemplated for quite some time.[2] Because the guidance is still in draft form, a 2014 final guidance document addressing the same topic remains in effect.[3] FDA is seeking public comments on the draft guidance through February 14, 2023.[4]

LET FDA IN: HOW THE REGULATORS CAME KNOCKING

In issuing this draft guidance, FDA relies on its authority to conduct inspections, as Agency employees are empowered to enter, at reasonable times, and inspect, at reasonable times and within reasonable limits and in a reasonable manner, facilities subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FD&C Act").[5] This authority is granted in section 704(a) of the FD&C Act and was enhanced in 2012 in section 706 of the Food and Drug Administration Safety and Innovation Act ("FDASIA").[6] That law amended section 704 of the FD&C Act to permit FDA to request, inspect, and/or copy certain specified records of drug and device facilities.[7]

Section 707 of FDASIA amended the FD&C Act by adding section 501(j), under which a drug may be deemed adulterated if it "has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or

refuses to permit entry or inspection."[8] In 2017, the FDA Reauthorization Act ("FDARA") amended section 501(j) of the FD&C Act so that it also applies to devices.[9] In October 2014, FDA first expounded on what qualifies as delaying, denying, limiting, or refusing entry or inspection in a guidance entitled "Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection."[10] The primary purpose of the new draft guidance is to expand the scope of the 2014 final guidance to include medical devices, as it largely adopts the language of the 2014 final guidance and will replace it once finalized.[11]

For several years, FDA has bared its teeth in response to drug and medical device facilities' unwillingness to share requested documents. The Agency has done so by citing the delays in Form FDA-483 observations and in Warning Letter citations. We expect a similar response to drug and medical device facilities' attempts to thwart FDA inspections of facilities and records, as detailed in the draft guidance. That said, FDA signals a tempered approach in the draft guidance, as it states that it "will consider reasonable explanations for behavior that may otherwise be considered to be delaying, denying, limiting, or refusing an inspection."[12]

REASONABLE AND UNREASONABLE DELAYS, DENIALS, AND LIMITS

The draft guidance provides a bevy of examples related to what FDA may (and may not) consider an unreasonable delay, denial, or limitation of inspection that would cause a drug or device to be adulterated.

Delay

In the draft guidance, FDA reiterates that while the FD&C Act does not require the Agency to pre-announce inspections of drug facilities, the Agency generally chooses to do so for certain types (pre-approval, pre-license, inspections of non-U.S. facilities), and such pre-announcements may be made by phone or email.[13] Unlike drug facilities, device facilities may rely on section 704(h) of the FD&C Act to ensure that they are notified of an inspection in advance in most circumstances, though this provision does not apply to for-cause inspections, or compliance follow-up inspections.[14] With regard to pre-announced inspections, the Agency provides examples of actions that may constitute an unreasonable delay (which would result in manufactured product being deemed adulterated), including the facility requesting a later start date after scheduling an inspection without giving a reasonable explanation, or failing to respond to FDA's attempts to contact the facility's designated contact.[15] In contrast, the Agency may find that a delay is *not* unreasonable when it occurs because "[m]anufacturing at a drug facility is not on-going, for example running only one manufacturing campaign per month, and the facility requests a different date than that proposed by or agreed to by FDA so that manufacturing will occur during the FDA inspection of the facility."[16]

When addressing delays during an inspection, the draft guidance notes that "[m]inor delays that result from good faith efforts by the facility to comply with FDA requests generally would not be considered unreasonable."[17] Additionally, it would be a reasonable delay for the facility to "not provide the FDA investigator access to aseptic processing areas until the investigator accommodates the facility's documented gowning procedures."[18] A facility runs the risk of imposing an unreasonable delay, however, if, for example, it "agrees to the pre-announced inspection date, but when the investigator enters the facility, the necessary facility personnel are not available, or the firm's management informs the investigator that operations are shutdown, without providing a reasonable explanation."[19] In addition, the Agency may determine an unreasonable delay may occur if a "facility does not allow the FDA investigator access to an area of the facility until a specific future date or time even though the area is operational and is an area of the inspection site that FDA has authority to inspect, without providing a reasonable explanation."[20]

FDA appears to be relatively forgiving in the context of producing records, particularly when the requested records are at a different site, require translation, or are necessarily being used for an in-progress manufacturing operation.[21] The Agency will *not* allow firms to fail to produce the records within a reasonable timeframe unless there is a reasonable explanation for the delay.[22] When the facility provides a reasonable explanation for a delay, the Agency is keen to advise

that the resulting delay itself must also be of reasonable duration and must be agreed upon by the facility and the Agency.[23]

Denial

In the draft guidance, FDA interprets "deny" as "any behavior by the owner, operator, or agent of a drug or device facility to prevent an authorized representative of FDA from conducting an inspection or to prevent FDA from completing an inspection."[24] Denial also "includes statements or physical actions intended to avoid inspection or to mislead, deceive, or impede the investigator."[25] Some examples include the facility not allowing FDA to conduct the inspection because certain staff members are absent, without reasonable explanation, or the facility sending staff home for the day and telling FDA that the facility is not making any product.[26] It might be unobjectionable, however, to decline the performance of an inspection if the investigator arrives unannounced to a facility that is closed for scheduled maintenance.[27]

Limiting

Efforts to limit an inspection by ordering the discontinuation of all manufacturing for the duration of the inspection, without a reasonable explanation for doing so, or by unreasonably restricting entry to a particular portion of the facility without a reasonable explanation, would likely lead to a product being deemed adulterated.[28] In contrast, it would be reasonable to limit the inspection if "[t]raining specified by the Occupational Safety and Health Administration is required before an individual may enter a particular area of the facility, and the FDA investigator has not completed such training."[29] FDA's access to records also cannot be unreasonably limited, such as by delivering the requested records only after unreasonably redacting them.[30] Similarly, FDA notes that collecting samples is a "critical part" of its inspectional and regulatory activities and efforts to prevent FDA from exercising this power may be considered limiting the inspection.[31]

SPOTLIGHT ON PHOTOGRAPHY

Facilities' efforts to limit FDA investigators' ability to take photographs during inspections has, for years, been an ongoing point of contention. In the draft guidance, FDA clearly states that photographs are "an integral part of an FDA inspection because they present an objective and contemporaneous representation of facility conditions."[32] For example, FDA may want to take a photograph of faulty construction or evidence of contamination during the inspection, and facilities should generally allow them, as "[i]mpeding or resisting photography by an FDA investigator may be considered a limitation if such photographs are determined by the investigator to be necessary to effectively conduct that particular inspection."[33] A potentially reasonable ground on which to deny photography, however, is when doing so would adversely affect product quality, such as in the case of products with sensitive chemical properties.[34]

BOTH ACTIVE AND PASSIVE REFUSALS TO PERMIT ENTRY ARE PROHIBITED

In the draft guidance, FDA states that a refusal to permit entry or inspection could include not only active but also passive behavior or inaction by the owner, operator, or agent of a facility.[35] Passive actions may include failing to respond to FDA's attempt to contact the facility's designated contact to schedule an inspection or barring the investigator from entering the facility or certain areas of the facility by keeping some areas locked.[36]

KEY TAKEAWAYS

While the interpretations set forth in the draft guidance may be more familiar to drug facilities based on their experiences over many years, the draft guidance puts both drug and device facilities on notice of circumstances that FDA believes would constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection. The draft guidance also highlights the importance of timely communication within an organization. For example, companies should develop and understand formal policies for FDA inspections and ensure that there are adequate lines of communication in place so that all activities that FDA needs to inspect are operating normally (rather than, for example, shutting down for

maintenance or cleaning during the inspection). It is worthwhile to note that even if an event may qualify as an unreasonable example in terms of the draft guidance, FDA has signaled a willingness to cooperate with facilities that have reasonable explanations for inspection-related issues. Importantly, the term "reasonable" has not been defined by FDA in the draft guidance, leaving it to different interpretations by investigators during an ongoing inspection. While all efforts should be made to provide information, facility access, and records to investigators as quickly as possible, it is advisable to establish investigators' expectations concerning what they consider "reasonable."

If you have questions regarding this draft guidance or would like assistance in either developing inspection policies or preparing comments to the open docket, King & Spalding can assist. FDA is accepting comments on the draft guidance through February 14, 2023, at Docket Number FDA-2013-D-0710.[37]

[1] FDA, Draft Guidance for Industry, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection* (Dec. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/circumstances-constitute-delaying-denying-limiting-or-refusing-drug-or-device-inspection-december [hereinafter "*2022 Draft Guidance*"].
[2] *Id.* at 3–4.
[3] *See id.*; *see also* FDA, Guidance for Industry, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* (Oct. 2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/circumstances-constitute-delaying-denying-limiting-or-refusing-drug-inspection [hereinafter "*2014 Guidance*"].
[4] *See* FDA, Notice of Availability, *Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection; Draft Guidance for Industry, Revision 1*, 87 Fed. Reg. 77,125 (Dec. 16, 2022), https://www.federalregister.gov/documents/2022/12/16/2022-27344/circumstances-that-constitute-delaying-denying-limiting-or-refusing-a-drug-or-device-inspection.
[5] *See 2022 Draft Guidance* at 5.
[6] *See id.* at 5–7.
[7] *See id.*
[8] *Id.* at 4 (quoting 21 U.S.C. § 351(j)).
[9] *See id.*
[10] *See id.*; *see also 2014 Guidance*.
[11] *See 2022 Draft Guidance* at 4; *see also 2014 Guidance*.
[12] *2022 Draft Guidance* at 5.
[13] *See id.* at 7.
[14] *See id.*
[15] *See id.* at 8.

[16] *Id.*
[17] *Id.*
[18] *Id.* at 9.
[19] *Id.* at 8.
[20] *Id.*
[21] *See id.* at 9.
[22] *See id.*
[23] *See id.* at 10.
[24] *Id.*
[25] *Id.*
[26] *See id.*
[27] *See id.*
[28] *See id.* at 11.
[29] *Id.*
[30] *See id.* at 12.
[31] *See id.*
[32] *Id.* at 11.
[33] *Id.*
[34] *See id.*
[35] *See id.* at 13.
[36] *See id.*
[37] *See* FDA, Notice of Availability, *Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection; Draft Guidance for Industry, Revision 1*, 87 Fed. Reg. 77,125 (Dec. 16, 2022), https://www.federalregister.gov/documents/2022/12/16/2022-27344/circumstances-that-constitute-delaying-denying-limiting-or-refusing-a-drug-or-device-inspection.