LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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FDA issues final guidance on requirements for postmarketing AE reporting during pandemics

In recognition that widespread illness during pandemics will impact typical industry functions such as adverse events (AE) reporting, the FDA published guidance directing manufacturers to develop continuity of operations plans and outlining its intent not to object if firms do not submit certain required AE reports. As pandemics are resolved, the FDA expects companies to resume meeting all reporting requirements.

The FDA published final guidance addressing postmarketing AE requirements for drugs, biologics, medical devices, combination products and dietary supplements during pandemics such as the current COVID-19 outbreak. The guidance acknowledges that industry and FDA workforces may be limited during pandemics while AE reporting expands due to the widespread use of medical products indicated for treating or preventing the pathogen causing the outbreak. As such, the FDA directs industry to focus limited resources on reports pertaining to medical products indicated for the treatment or prevention of the virus causing the pandemic and those related to products presenting special concerns, as identified by the FDA.

Per the FDA, all firms should plan for pandemics to maintain the highest feasible level of AE monitoring and reporting. As such, the guidance is meant to help firms "strategize use of their resources." Firms that are able to continue reporting operations are directed to continue doing so. The guidance directs firms that are unable to meet normal AE reporting requirements to maintain documentation on the declaration of the pandemic and high absenteeism or other factors preventing normal AE reporting functions.

In order to promote pandemic preparedness, the guidance recommends industry develop continuity of operations plans (COOPs) for when human outbreaks occur, whether overseas or in the U.S., taking into account AE reporting functions for U.S. and

international locations. The FDA directs industry to maintain normal AE reporting processes to the maximum extent possible during a pandemic. Per the guidance, AE data should be handled using the usual standard operating procedures, and regulatory and statutory requirements should be met to the greatest degree feasible. The FDA recommends that when developing a COOP, firms consider factors such as which activities are directly relevant to developing and submitting mandatory AE reports, how domestic and international sites will be differentially impacted by a pandemic and the relative amount of resources committed to mandatory AE reporting at each site.

Per the guidance, the FDA does not intend to object if a firm maintains newly received information about an underlying AE and does not submit reports in required time frames. However, the guidance cautions that delayed reports must be submitted after AE processes have been restored to pre-pandemic states. The guidance instructs firms to maintain records to identify what has been stored and when the processes were restored. The guidance recommends firms submit as many required reports as possible in order to reduce reporting burdens when AE processes are fully restored. The FDA expects firms to submit stored reports within six months of restoration of AE reporting processes to pre-pandemic states. The guidance directs firms to prioritize the order of submission based on regulatory time frames for reporting.

FDA guidance outlines CDRH appeals process for 'significant decisions'

The guidance discusses the Center for Devices and Radiological Health's (CDRH) interpretation of statutory provisions related to requests for appeals of "significant decisions." It outlines the process for requesting a substantive summary of the rationale for certain decisions in the premarket review of device submissions.

The FDA published a Q&A guidance document outlining its interpretation of provisions under Section 517A of the Federal Food, Drug, and Cosmetic Act (FDCA), as well as implementing regulations in 21 CFR 800.75. Section 517A establishes requirements for the documentation and review of certain decisions in the premarket review of device submissions. Under Section 517A, the FDA is required to provide a "substantive summary of the scientific and regulatory rationale for any significant decisions" of the CDRH related to the submission or review of a report under Section 510(k) (premarket notification), Section 515 (premarket approval [PMA]/humanitarian device exemption [HDE]), Section 515B (breakthrough devices) or Section 520(g) (investigational device exemption [IDE]) of the FDCA.

The FDA refers to a "significant decision" made by CDRH within the scope of Section 517A as a "517A decision." Per the guidance, 517A decisions include decisions on substantial equivalence for 510(k)s, approval or denial decisions on PMAs or HDEs, granting or denial of breakthrough designation or de novo classification requests, approval or disapproval of IDEs, clinical holds under Section 520(g)(8) of the FDCA, and failures to reach agreement on a protocol under Section 520(g)(7) of the FDCA. Regulatory actions that do not constitute 517A decisions include requests for additional information; major deficiency letters for PMAs; refuse-to-accept or refuse-to-file letters for 510(k)s, PMAs and HDEs; postmarket surveillance orders; clinical laboratory improvement amendments waiver decisions; and warning letters.

Per the guidance, "substantive summary" includes documentation of how the least burdensome requirements were considered and applied, as well as documentation of significant controversies or differences of opinion and how they were resolved. The substantive summary may be the final version of the review memorandum by the lead reviewer or another summary document that includes:

- A rationale for the decision
- An explanation about the application of least burdensome requirements
- A description of significant controversies, meaning those with a direct bearing on the regulatory decisions
- References to published literature and consensus standards on which the decision-maker relied

The guidance directs sponsors to request substantive summary via the processes established for premarket submissions to CDRH's Document Control Center. The sponsor should clearly indicate that the request is for substantive summary under Section 517A and identify the associated identifying number for the relevant premarket submission.

FDA publishes final guidance spelling out process for device makers to request nonbinding feedback following inspections

The guidance details how device makers may submit a request for nonbinding feedback to the FDA regarding corrective actions proposed in response to inspectional observations cited on a Form FDA 483. The guidance reflects the FDA's mandate under Section 704 of the FDA Reauthorization Act (FDARA) of 2017.

The FDA issued final guidance outlining how an owner, operator or agency responsible for a device establishment may submit a request for nonbinding feedback to the FDA regarding corrective actions proposed in response to observations cited by the FDA during an inspection. The guidance establishes a standardized process for communicating and submitting requests for nonbinding feedback and discusses how the FDA will assess and respond to such requests. It reflects the directive under FDARA that the FDA provide timely feedback, meaning within 45 days in certain instances, in order to help device makers ascertain whether proposed actions to address inspectional observations are sufficient, potentially avoiding unnecessary investment in solutions that may not be sufficient.

Per the guidance, the request for feedback should be made by the "owner, operator, or agent in charge" of the device establishment, meaning the person to whom the Form FDA 483 was issued or another person who can otherwise demonstrate to the FDA that he or she is in charge. Requests should be made in a timely manner, meaning no later than 15 business days after the Form FDA 483 is issued. The requests should be made to the same FDA contact who is identified to receive the submission of a response to the Form FDA 483 and should include a subject line or cover letter that "clearly and conspicuously states 'Request for Nonbinding FDA Feedback After a Device Inspection,'" along with the contact information of the submitter. The request should also include the name, address and FDA Establishment Identification number of the establishment inspected; the date of the inspection; and a justification as to how the request meets one of the following eligibility criteria:

- Involves a public health priority – The FDA-documented observation requires resolution because such conditions have resulted in or, if left unaddressed, are likely to result in a violative product entering the market that may cause death or serious injury.
- Implicates systematic or major actions – The observation suggests that systematic or major deficiencies with the quality system or subsystems have resulted in or are likely to result in the release of nonconforming, violative or defective devices that may pose a serious risk to public health.
- Relates to emerging safety issues – The observation is related to an emerging safety issue that may result in the release of devices that are likely to cause death or serious injury.

Per the guidance, the justification may relate to a single inspectional observation, more than one observation or all the observations. The requestors should clearly indicate the inspectional observations for which feedback is being sought and describe how they meet one or more of the eligibility criteria. They should also describe the proposed actions to be taken in response to those observations.

The FDA will verify that the request has been made by the owner, operator or agency in charge of the establishment, or a designated representative, and then determine whether one of the eligibility criteria has been met. The FDA will then, within 45 days, either provide feedback to eligible requests or tell the requestor the request is ineligible for feedback. The nonbinding feedback should identify whether the proposed actions appear adequate, partially adequate or inadequate. If the proposed actions

do not appear adequate, the FDA will provide an explanation as to why, along with a recommendation as to what may be needed in order for the agency to consider the proposed actions adequate.

FDA, FTC take joint enforcement efforts to crack down on unapproved new products promoted as treatments for COVID-19

The FDA and Federal Trade Commission (FTC) have joined forces to crack down on companies promoting fraudulent products as cures, preventives or treatments for COVID-19, including makers of essential oils, homeopathic and herbal products, cannabidiol products, and colloidal silver.

The FDA and FTC have been issuing joint warning letters to call out companies selling fraudulent COVID-19 products that are considered unapproved drugs that pose significant risks to patient health and violate federal law. The FTC and FDA are actively monitoring social media, including hashtags, and scrutinizing product descriptions on online marketplaces such as Amazon. They are also closely monitoring incoming complaints to ensure companies do not continue to sell fraudulent products under a different company name or on another website.

Both agencies are closely monitoring false claims related to COVID-19 and have issued several joint warning letters since the outbreak of the pandemic. The regulatory agencies are working to identify potentially misleading marketing claims not supported by competent and reliable scientific evidence. As of April 28, the FDA had issued 38 warning letters to companies promoting unapproved COVID-19 products, including 28 jointly issued with the FTC.

The warning letters direct the companies to take immediate action to correct the violations and caution that failure to do so may result in legal action such as seizure and injunction.

The FDA also created a cross-agency task force to monitor for fraudulent products related to COVID-19 and is working with major retailers and online marketplaces to remove listings of fraudulent COVID-19 products. The agency has also warned commercial manufacturers and laboratory developers against claiming their serological tests for COVID-19 are approved or authorized.

State attorneys general have also taken enforcement actions against companies marketing fraudulent COVID-19 products. For instance, New York's attorney general issued cease and desist letters to a company and a naturopathic doctor promoting a colloidal silver product as a treatment for COVID-19—including claims made on television on The Jim Bakker Show—suggesting it "beats coronavirus" and that there is "clinical documentation" to support that claim. The attorney general in Missouri filed a lawsuit against The Jim Bakker Show and Morningside Church Productions over misrepresentations about the effectiveness of the colloidal silver product.

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