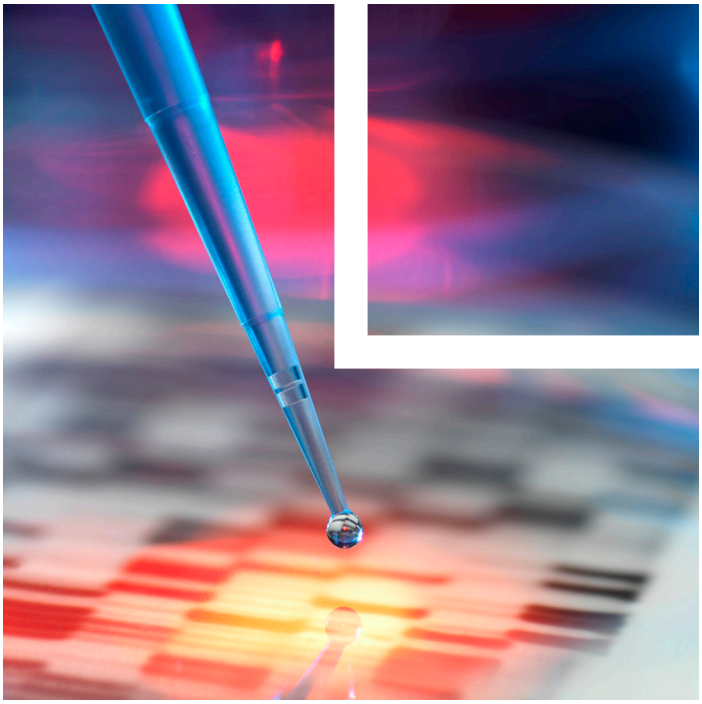
FDA Regulatory & Compliance Monthly Recap
September 2020



FDA issues temporary guidance outlining return-to-normal practices for drug, biologic manufacturers

The FDA issued a temporary guidance providing recommendations to drug and biologic manufacturers for returning to normal production during the COVID-19 pandemic. The guidance outlines a number of recommendations to help firms prioritize products as normal operations resume and as they remediate current good manufacturing practices (CGMP) that were reduced, delayed or altered during the continuing health emergency.

In regard to CGMP, the guidance states that remediation may be necessary for activities that were delayed, interrupted or reduced in frequency due to the COVID-19 public health emergency. Remediation could include modification of a particular activity, creation of a new activity or even a more comprehensive program alteration to mitigate the risk of an issue with drug quality due to deviations from normal operations. In instances where vital CGMP activities were impacted, the agency recommends that the batch of the product should be quarantined and the decision to approve the batch should be delayed until remediation activities to ensure drug quality—such as attribute testing, critical deviation investigations and evaluation of unapproved changes to critical operations—are completed. The guidance also provides considerations for manufacturers to help them determine the need for and the type of remediation for their particular operations:

- In the event investigations into noncritical product or process discrepancies and deviations occurring prior to and during the health emergency, manufacturers should determine whether the scope of those investigations should be expanded to supplement information lost due to staff not being present to observe or gather information about the incident. Whether there was an increased risk to product quality due to short-term changes in normal operations should also be considered.
- When decisions to delay or reduce testing that is indirectly measuring a batch operation, manufacturers should consider the impact of such delays or reductions on drug quality. Firms should also consider whether additional testing should be performed

to ensure their facility is adequate to manufacture quality drugs.
- Manufacturers should also proactively obtain information from suppliers regarding the impact of the public health emergency on their operations. They should be aware of any changes to operations or materials that could affect the quality of the finished product, as well as whether the higher demand for certain materials could lead to doubt regarding the quality or authenticity of those materials.
- Firms should also consider whether a disruption or change in utilities (water, gas, electricity, etc.) could pose a challenge to their operational capabilities. Additionally, manufacturers should consider whether the use of some equipment was altered and not qualified prior to use.

In addition to these considerations, the guidance suggests that once manufacturers have identified the appropriate remediations, if any, they should incorporate these activities into their resumption plan. The FDA recommends that such a plan states that the risk management approach prioritizes the manufacture of drugs at risk of shortage and activities related to resuming batch production. Furthermore, the plan should include a timeline for implementing priorities and should specify all changes to be reviewed and approved by the quality unit. Finally, the plan should state whether a manufacturer decides that a recall is needed, and if so, it should notify the agency as recommended in the Product Recall, Including Removals and Corrections (March 2020) guidance.

FDA issues final guidance for voluntary consensus standards

The FDA issued final guidance regarding the procedures used by the Center for Devices and Radiological Health (CDRH) when reviewing requests for recognition of voluntary consensus standards for medical products. The document also outlines action potentially taken by the FDA during its review and evaluation of standards recognition requests or withdrawal of recognition requests. The guidance also provides clarification regarding the regulatory framework, policies, and practices of the agency's standards as they pertain to recognition and withdrawal of recognition of voluntary consensus standards.

The guidance first stresses the importance of voluntary consensus standards as a way to help facilitate meeting requirements under the FDCA or other regulations. The use of such standards can increase predictability, streamline premarket review, provide clearer regulatory expectations, facilitate market entry for safe and effective medical products, and promote international harmonization. The FDA considers standards that are developed by voluntary consensus standards bodies, which are defined as any organization involved in planning, developing, establishing, or coordinating standards using a voluntary consensus standards development process that includes a number of attributes or elements, including:

- **Openness**: The procedures or processes used are open to interested parties, and such parties are provided opportunities to participate in standards development. Furthermore, the procedures for participating in the development of standards are transparent.
- **Balance:** The standards development process should include meaningful involvement from a variety of parties, with no one interest dominating the decision-making.
- **Due Process:** This includes documented and publicly available policies and procedures, adequate notice of meetings and standards development, sufficient time to review drafts and prepare objections, access to views and objections of other participants, and a fair and impartial resolution process for conflicting views.
- **Appeals Process:** An appeals process should be available for handling appeals in an impartial manner.
- **Consensus:** This is defined as general agreement but not unanimity. During the process of consensus, comments and objections should be considered using a process that is fair, impartial, open and transparent.

The guidance also clarifies that any interested party may request standard recognition, which should, at least, contain information such as the name and address of the requestor, title of the standard, reference numbers and

dates, proposed product listing for which a Declaration of Conformity (DOC) should generally apply, the basis for recognition, and a brief identification of the testing or performance of the product to be addressed by a DOC.

In addition, the guidance explains the FDA may decide to recognize all or part of a standard, which the agency will outline in its extent of recognition (EOR) determination. For a standard to be recognized in its entirety, the EOR will state "Complete Standard" and provide the basis for such a determination. For a standard recognized only in part, the EOR will state "Partial Recognition" and provide a listing of the sections of the standard that are or are not recognized, along with the rationale for the determination. If a standard contains specifications or methods that are not scientifically acceptable, are not technically feasible or conflict with existing FDA-recognized consensus standards, existing published policies, regulations or the statute, the agency will issue a non-recognition EOR. In this instance, the FDA will provide an explanation for the determination.

FDA issues draft guidance on PRO instruments for use in medical device evaluation

The FDA issued a draft guidance regarding the selection of patient-reported outcome (PRO) instruments in the clinical evaluation of medical devices. The document provides manufacturers with general principles on the selection, development and modification of instruments to capture PROs. The guidance also provides recommendations for best practices for developing relevant, reliable and robust PRO instruments in the easiest way possible.

The guidance outlines key principles for manufacturers to consider when incorporating PRO instruments into their medical device evaluation process. These principles include establishing and defining the concept of interest (COI) the PRO is meant to capture, identifying the role of the PRO in the clinical study protocol and statistical analysis plan, providing evidence showing the PRO instrument properly assesses the COI, and effectively communicating the PRO-related results in the product's labeling to better inform the health care provider and patient decision-making process.

Also included in the guidance are best practices for the least burdensome selection development, modification and adaptation of PRO instruments, including:

- The PRO should measure concepts important to the patients using the device. Incorporating outcomes that reflect patient priorities in the clinical study protocol can help integrate factors included in patients' decision-making processes into the FDA's benefit-risk determination.
- PRO instruments should include instructions, items, recall period and response options, which should all be composed in plain language to ensure patients with varying degrees of literacy can understand and provide informed responses. Proper benchmarks, activities or symptom wording should also be used to allow for more accurate reporting of patient health statuses.
- The COI and the concept of use (COU) should be conveyed clearly in the clinical study protocol and the statistical analysis plan. This should come in the form of the COI being clearly defined by a statement of what is being measured and how, as well as how the results will be communicated in the labeling. Similarly, the COU should describe the PRO instrument's role in the development and evaluation process of the medical device, including a defined endpoint the PRO instrument is being used to capture.
- Sponsors should also elect to choose from existing PRO instruments, rather than developing new ones. Using an existing instrument as is or adapting it to suit a specific need is often less resource-intensive than developing a new instrument. Therefore, the agency recommends referring to peer-reviewed literature to help identify the validity evidence associated with a particular instrument.
- Real-world evidence derived from sources outside the clinical setting can also be used to generate validity evidence for PRO instruments. These can include electronic health records, claims and billing activities, product and disease registries, or health-monitoring devices. The FDA encourages sponsors to consider such alternative approaches to generate validity evidence as they are often less burdensome.
- Whenever possible, the agency encourages sponsors and other stakeholders to work together in the pre-

competitive space to develop, modify or adapt PRO instruments. Sponsors are also encouraged to consider relevant stakeholders for possible collaborations, including patient organizations, health professional organizations and research institutions with expertise in the development of PRO instruments.

FDA issues draft guidance on reducing, preventing nitrosamine contamination in drugs

The FDA issued a draft guidance addressing the detection and prevention of nitrosamine impurities in drugs for manufacturers. Nitrosamines are impurities found commonly in water and food, which have been found to increase cancer risk in certain individuals exposed to them above an acceptable level over an extended period of time. The FDA has been working over the past two years to find and remove drugs containing unacceptable amounts of nitrosamines, as well as to ensure drugs can be free of these impurities in the future.

The guidance outlines potential sources for nitrosamine impurities, the formation of which can be in the presence of secondary, tertiary, or quaternary amines and nitrate salts under acidic conditions. Under such conditions, nitrate salts may form nitric acid, which can react with an amine to form a nitrosamine. The FDA also notes that nitrates used as reagents in one step can carry over into subsequent steps, even if purification processes are conducted, and react with amines to create nitrosamines. Contamination can occur during a drug's manufacturing process, through material used in manufacturing, the chemical structures of some drugs, or the conditions in which the drugs are stored or packaged. Therefore, the agency highlights that manufacturers are responsible for mitigating the conditions leading to nitrosamine contamination and provides recommendations to assist in these efforts.

The guidance provides a list of recommendations for active pharmaceutical ingredient (API) manufacturers. The agency recommends API manufacturers optimize their manufacturing process during route of synthesis (ROS) development to minimize or prevent the formation of nitrosamines, such as:

- Manufacturers should also consider the following during process development, including avoiding reaction conditions that may produce nitrosamines and use caution when the ROS involves the use of amide solvents.
- Consider removing quenching steps from the main reaction mixture to reduce the risk of formation.
- Audit and monitor supply chains for any at-risk raw materials, starting materials and intermediates. API manufacturers should also maintain records including the name of the raw material manufacturer and its supplier.
- Avoid cross-contamination by using recovered materials, such as solvents and reagents, only in the same step or in an earlier step from which it was collected.
- Be aware that potable water used in API manufacture may contain low levels of nitrite and possibly even nitrosamines from environmental contamination. Therefore, manufacturers should use purified water to remove any unacceptable impurities.
- API batches may be reprocessed or reworked to control nitrosamine levels. If such action is taken, it should be done under the supervision of the quality unit.

The guidance also provides recommendations for drug product manufacturers, including conducting risk assessments to determine the potential for nitrosamine impurities in drug products. These assessments should involve collaboration with the API manufacturer to assist in the identification of the API ROS or other process conditions during the API manufacturing process. If a risk of contamination is identified, the drug product manufacturer should conduct confirmatory testing of batches using appropriately validated methods. Manufacturers should also investigate the root cause of any contamination and implement any changes necessary to mitigate or reduce the impurities. Such changes must be reported to the FDA in accordance with existing regulations.

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