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CLIENT ALERT

New FDA Guidance Issued to Help Drug and Biologics Manufacturers Resume Normal Manufacturing Operations

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The Food and Drug Administration (FDA) recently issued guidance to help drug and biological product manufacturers in assessing the current state of their good manufacturing practice (CGMP) activities in light of the COVID-19 public health emergency and prioritize remedial steps necessary to resume normal manufacturing operations. Unless otherwise stated, the policies in the guidance are intended to remain in effect only for the duration of the COVID-19 public health emergency, as declared by the Secretary of Health and Human Services.

FDA acknowledges that during the public health emergency, drug and biologics manufacturers have faced persistent and unusual challenges, including employee illness and absenteeism, travel restrictions, site closures, and other potential supply chain disruptions. Likewise, measures to prevent COVID-19 transmission (*e.g.*, quarantines and social distancing) have been implemented across companies and have further impacted normal manufacturing operations and CGMP activities. In order to maintain production of the drug supply, drug and biological product manufacturers necessarily delayed, reduced, or modified CGMP activities due to pandemic-related exigent circumstances. This guidance provides detailed considerations for resuming normal operations where such CGMP activities have been impacted by the public health emergency. In the guidance, FDA also pays particular attention to advise on steps that manufacturers should undertake to mitigate the risk that pandemic-related disruptions in manufacturing and quality-assurance activities could lead to shortages of critical products.

While CGMP requirements remain in effect during the COVID-19 public health emergency, and this guidance is not intended to signal specific FDA enforcement priorities, drug and biologics manufacturers whose operations have been disrupted are encouraged to follow an established plan, part of which should address a transition back to normal CGMP operations that will be maintained for an extended period of time.

Addressing Unplanned Deviations From Established CGMP Activities

First, drug and biologics manufacturers should assess the impact of the public health emergency on their CGMP activities and identify necessary remediation to ensure drug quality as they work to return to normal manufacturing operations.[1] Remediation could include a modification to an activity, a new activity, or a more-comprehensive program change that mitigates the risk of a product-quality issue due to the deviation from normal operation. Specifically, where critical CGMP activities were delayed, interrupted, or reduced in frequency, the product batch should be quarantined and the decision to approve the batch delayed until remediation activities ensuring product

quality are completed. Such activities include: critical quality-attribute testing, investigations of critical deviations, and evaluation of unapproved changes to critical operations or materials. Moreover, manufacturers should proactively seek out and obtain information about changes that occurred outside of their control.

FDA has identified examples of areas where remediation may be needed and set forth specific examples of the need and type of remediation in response.

1. If investigations into non-critical product or process discrepancies and deviations that occurred before or during the COVID-19 public health emergency remain unsolved, manufacturers should consider:
    a. Whether the scope of the investigation should be expanded to supplement information lost because staff were not present to fully observe or gather information about the incident or were otherwise delayed in response.
    b. Whether short-term changes to normal operations were implemented and whether these changes may have increased the risk to product quality.
    c. What procedures govern investigations at present and whether these procedures cover discrepancies, deviations, and non-conformances suitable during the public health emergency.
2. Any decision to delay or reduce testing less directly associated with a batch, or not associated with a batch, should have been made based on a risk assessment that included evaluation of available data, the significance of the test to the quality of the product, and whether the product is in shortage. If such testing was incomplete or set forth under conditions that may have compromised the accuracy of the results, manufacturers should:
    a. Assess the impact on product quality for delayed or reduced testing that indirectly measures a batch operation.
    b. Determine whether additional testing should be performed where testing was delayed or reduced but is not associated with a batch.
    c. Determine whether operations or materials used in the production of drugs and biologics changed in any way that could impact the quality or availability of the finished product.
3. Drug and biologics manufacturers should proactively obtain information from suppliers about the impact of the COVID-19 public health emergency on their operations, logistics, and transportation systems. Manufacturers should ask questions regarding such changes, different demands for certain materials, and observable differences in any shipment.
4. If facilities and equipment have been changed, have not been maintained on schedule, or have otherwise been interrupted, manufacturers should determine what conditions, if any, put their operations at risk and:
    a. Consider retrospective evaluation of equipment performance where the use of equipment changed and was not qualified prior to use.
    b. Consider disruptions to water, gas, electricity, or sewage removal utilities.
    c. Consider changes in the frequency of cleaning/disinfection, or to the type of cleaning agent or disinfectant and whether such changes warrant a reassessment of cleaning procedures.
    d. Consider instances where specialized personnel were unavailable for on-site servicing and equipment inspection and whether there are alternative means to ensure the equipment is suitable for use.
    e. Consider whether a delay in preventative maintenance or calibration activities for facilities or equipment impacted their function.

Risk Management and Other Important Elements of a Plan to Resume Normal Drug Manufacturing

FDA encourages drug and biologics manufacturers to develop a resumption plan specific to their operations and organizational needs, and an emergency plan addressing the possibility of additional waves of COVID-19. Appropriate remediation should be incorporated into a manufacturer's resumption plan, and the plan should state that the risk-management approach prioritized the manufacture of products at risk of shortage and activities related to restarting batch production. FDA has set forth the following elements as considerations for developing a plan to resume normal drug manufacturing:

1. Identify, evaluate, and mitigate factors that may impact product quality. These factors include activities performed, not performed, delayed, interrupted, or performed remotely; changes to procedures, processes, or programs; and associated outcomes.
2. Role of management leadership in the successful execution of the resumption plan.
3. Timeline for implementing priorities.
4. A plan should specify all changes be reviewed and approved by the manufacturer's quality unit, all CGMP activities should be documented, and any deviations explained.
5. The plan should specify that manufacturers submit the required Field Alert Reports (FARs), Biological Product Deviation Reports (BPDRs), and animal drug product/manufacturing defect and adverse drug experience reports, as appropriate.
6. The plan should include a plan for recall, including FDA notification.
7. The plan should specify that applicants and manufacturers notify FDA of a permanent discontinuance in the manufacture of certain products or an interruption in the manufacture that may lead to disruption in the supply.

Prioritizing Activities to Resume Normal Drug Manufacturing

Finally, drug and biologics manufacturers should use the findings and conclusions set forth in their risk-management approach to plan and prioritize resumption activities. High priority should be given to products that are in shortage or at risk of shortage. Likewise, activities that must be conducted prior to restarting a production line should be prioritized ahead of normal batch production. Also, recognizing the fluidity of resumption operations, change in priorities and new information impacting priorities should trigger an update to the plan and manufacturers should reprioritize activities as appropriate.

FDA's guidance documents do not establish legally enforceable responsibilities; instead, the guidance describes the Agency's current thinking on a topic.

We note that government orders on the local, state, and federal level are changing every day, and the information contained herein is accurate only as of the date set forth above.

All entities should consult legal counsel for compliance issues and questions related to rapidly evolving COVID-19 legislation and policy.

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For further information or questions on FDA's guidance and plans for the resumption of normal manufacturing operations, please contact Amandeep S. Sidhu, T. Reed Stephens, Christopher Parker, or your Winston relationship attorney.

[1] However, FDA notes that in certain circumstances, remediation activities may not be completed until the conclusion of the public health emergency, and in such cases, the manufacturer should continue to follow the recommendations in this guidance with respect to such activities after the termination of the emergency.

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