COVID-19 Impacts on Manufacturing Operations: A Regulatory Perspective

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CDER - Office of Compliance

MISSION

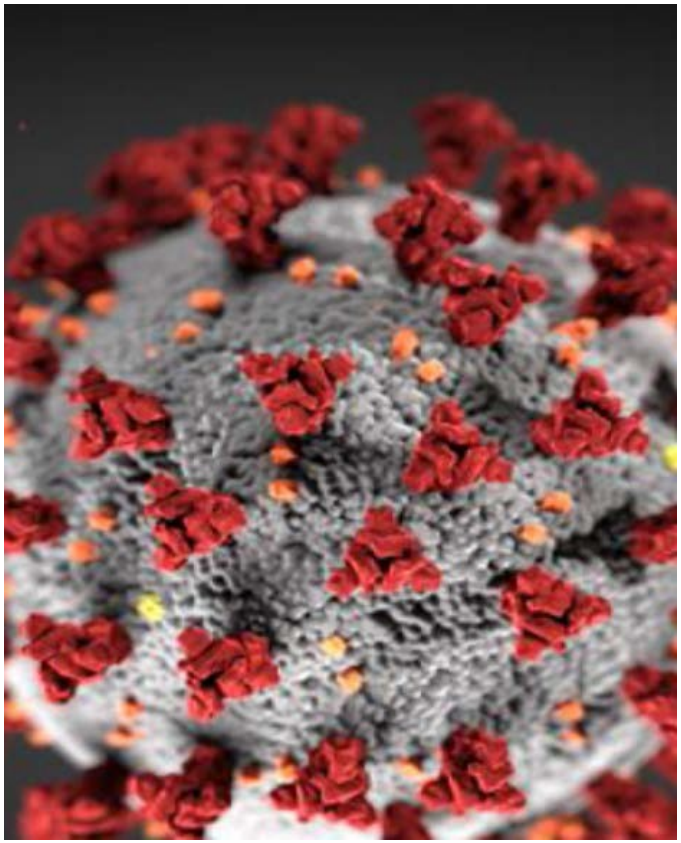
To shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement action

What OMQ* Does

- We evaluate compliance with **C**urrent **G**ood **M**anufacturing **P**ractice (**CGMP**) for drugs based on inspection reports and evidence gathered by FDA investigators.
- We develop and implement compliance policy and take regulatory actions to protect the public from ***adulterated*** drugs in the U.S. market.

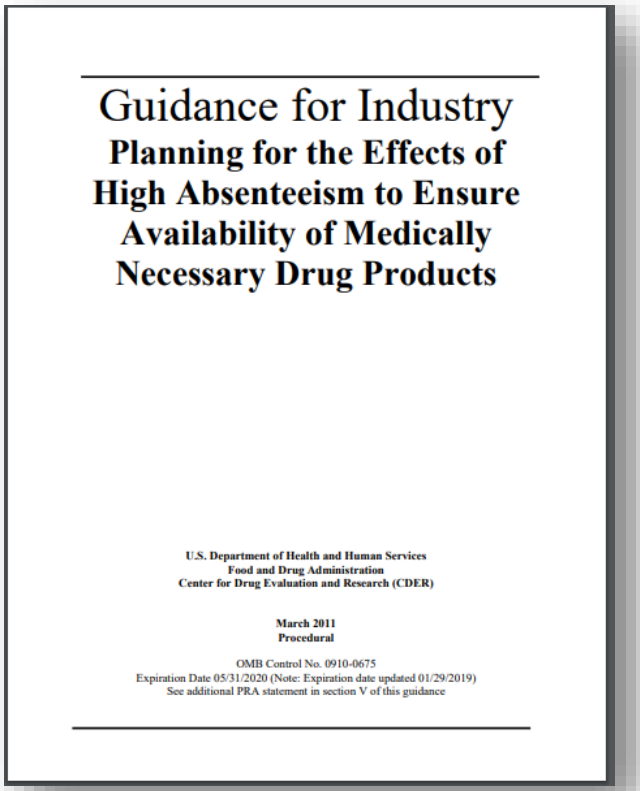
Source: FDA

* CDER/Office of Compliance/Office of Manufacturing Quality



Covid Related Manufacturing Guidances

Manufacturing During the Pandemic



Guidance for Industry

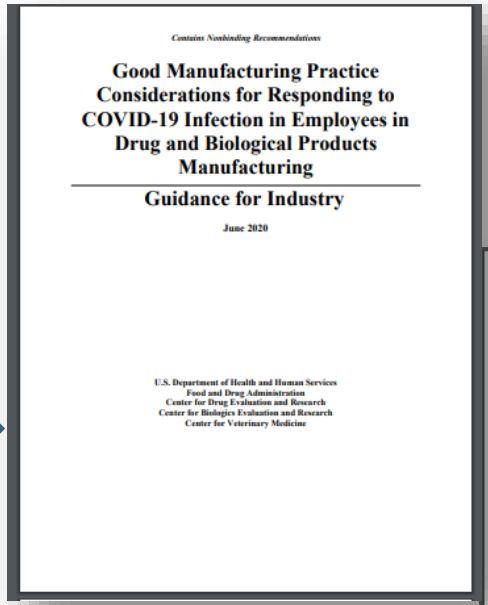
Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2011
Procedural

OMB Control No. 0910-0675
Expiration Date 05/31/2020 (Note: Expiration date updated 01/29/2019)
See additional PRA statement in section V of this guidance

2011



Contains Nonbinding Recommendations

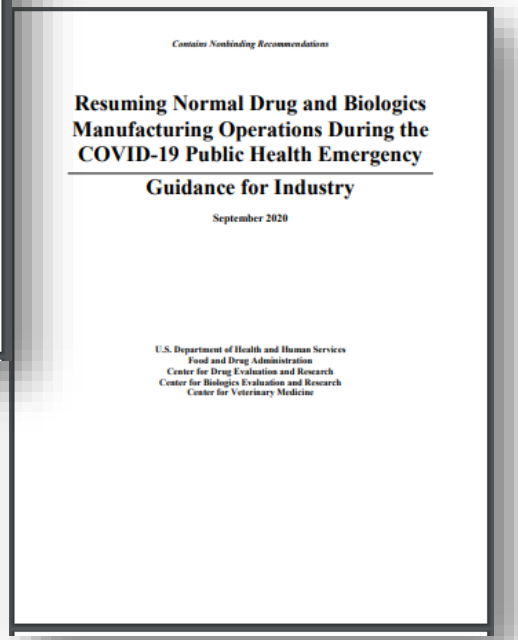
Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

Guidance for Industry

June 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

2020



Contains Nonbinding Recommendations

Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency

Guidance for Industry

September 2020

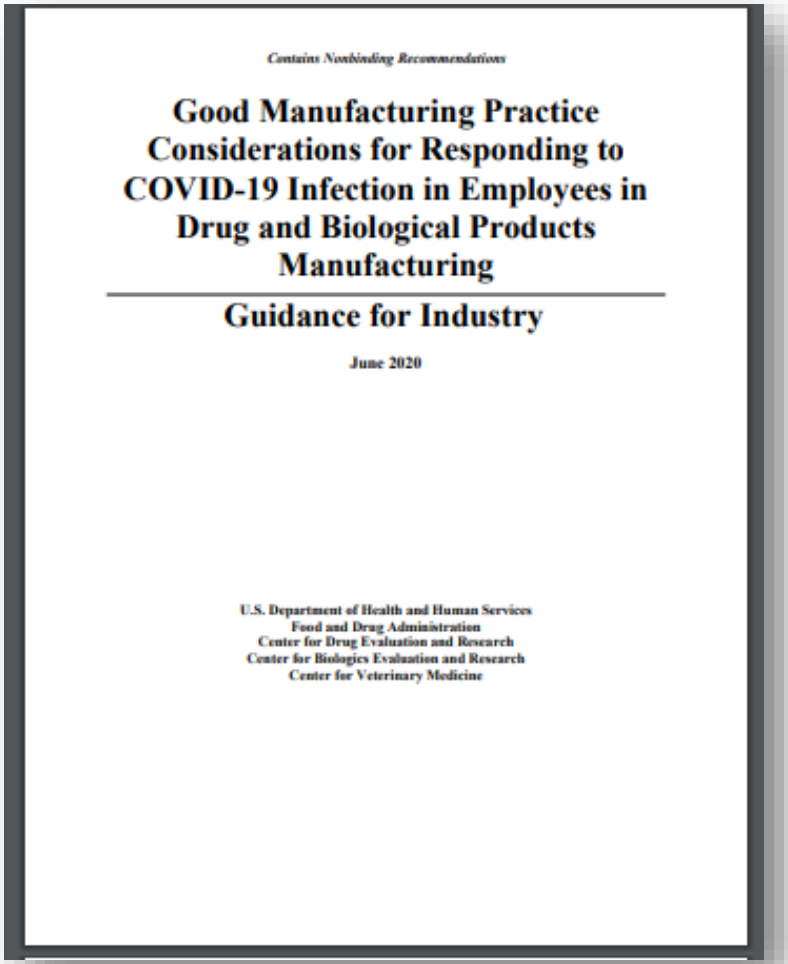
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

2020

COVID-19 Guidance: Responding to Infection in Employees (June 2020)

- Prevent or mitigate potential adverse effects on the safety and quality of drugs from an infected or potentially infected employee engaged in drug manufacturing

- Lots or batches adversely affected in terms of safety or quality must not be distributed



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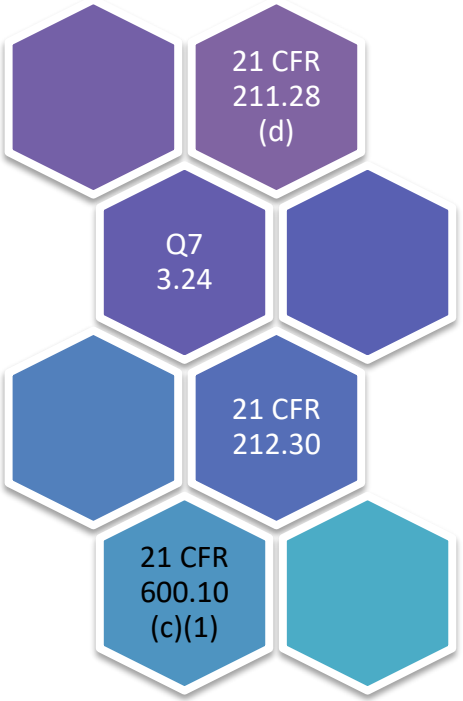
https://www.fda.gov/media/139299/download

COVID-19 Guidance: Responding to Infection in Employees (June 2020)

- Employees must be excluded from drug manufacturing areas in accordance with the applicable CGMP requirements who
  - (1) test positive for COVID-19 (regardless of whether they have symptoms) or
  - (2) have symptoms of COVID-19



Sec. 211.28 Personnel responsibilities.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

COVID-19 Guidance: Responding to Infection in Employees (June 2020)

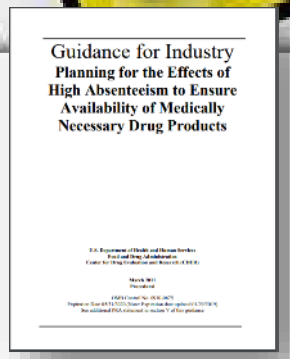
"In accordance with quality risk management principles, drug manufacturers are expected to take the following steps to *prevent or mitigate potential adverse effects on the safety and quality of drugs* from an infected or potentially infected employee engaged in drug manufacturing:"

"To ensure compliance with CGMP requirements, drug product manufacturers must ensure that *all evaluations (including risk assessments) to determine if drug safety or quality were adversely affected*, as well as any follow-up and changes, are approved by the manufacturer's quality unit and documented within the manufacturer's quality management system…"

Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products (Mar 2011)

- Originally developed after H1N1 – not COVID-19 specific

- Encourages manufacturers of ***medically necessary drug products*** (and related components) to develop emergency plans



https://www.fda.gov/media/120092/download

Planning for the Effects of High Absenteeism: *Plan Ahead*

- Written emergency plan to maintain an adequate supply of MNPs
  - Criteria for plan activation – reallocation of resources to MNPs, outsourcing
  - Identify decision makers (activation, deactivation, and manufacturing decisions)
  - Prospective Quality Risk Assessments on prioritization of MNPs and CGMP activities

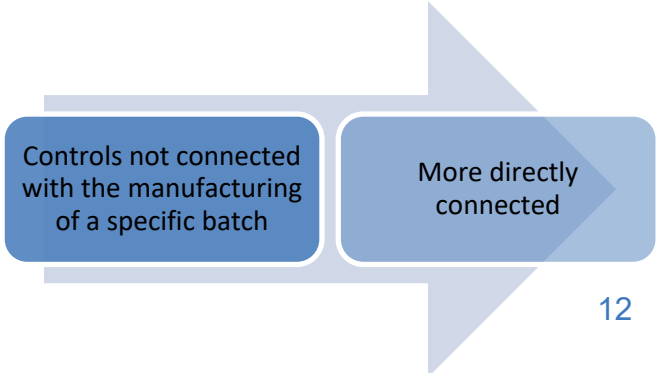
It is especially important for manufacturers of finished drug products to be aware of their suppliers' and contractors' responses to personnel shortages and, when appropriate, work with them to ensure the availability of high quality materials and services that contribute to the manufacture of MNPs.

Planning for the Effects of High Absenteeism

- Additional preparation for emergencies through prevention and risk mitigation
  - Employee education
  - Encouraging immunization
  - Encouraging family emergency preparedness plans
  - Appropriate sanitation practices and restriction of ill or sick employees from production areas

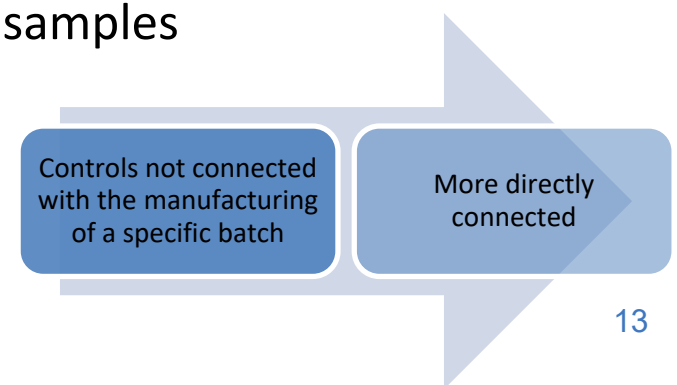
Planning for the Effects of High Absenteeism: Prospective Quality Risk Assessments

- Prospective Quality Risk Assessments
  - First: focus on meeting MNP demand
  - Second:
    - Identify activities that might be reduced in frequency, delayed, or substituted by a suitable alternative **and**
    - Ensure that the anticipated actions…are not expected to unacceptably reduce assurance of product quality
- Cascade approach for CGMP activities which may be reduced in frequency, delayed, or substituted by a suitable alternative to meet MNP demand



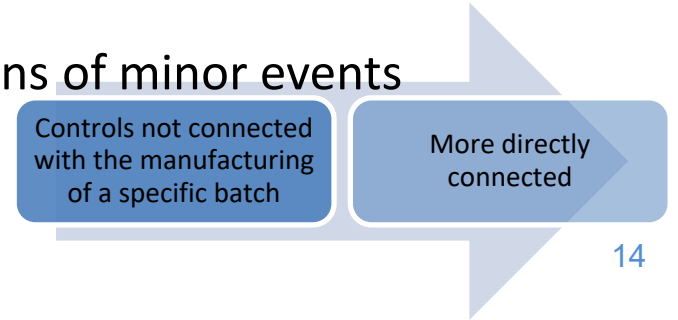
Planning for the Effects of High Absenteeism: Cascade Approach to CGMP Activities

- First, identify and consider activities that are intended by the CGMP regulations to provide controls not connected with the manufacturing of any specific batch
  - Production equipment routine maintenance
  - Utility system performance checks and maintenance
  - Environmental monitoring of facilities during production
  - Stability testing for certain drug products and components
  - Periodic examinations of data and of reserve samples



Planning for the Effects of High Absenteeism: Cascade Approach to CGMP Activities

- If the demand cannot be met by these measures…consider reducing activities that are more directly connected with batch manufacturing or a product accept/reject decision
  - Not requiring a second-person verification of activities for *less critical steps*
  - *Reducing* the number of samples for labor-intensive laboratory testing
  - Forgoing an in-process test to assure adequacy of mix, particularly when making successive batches, where the *risk of safety/efficacy is judged to be low*
  - *Delaying* completion of deviation investigations of minor events



Planning for the Effects of High Absenteeism: Cascade Approach to CGMP Activities

- For all CGMP controls that are delayed, reduced in frequency, or substituted with a suitable alternative:
  - Maintain documented rationale/risk assessment to show that the proposed changes will not unacceptably reduce assurance of product quality
- Carefully monitor indicators of product quality to note any unfavorable trends or shifts as a result of the implementation of the emergency plan
- Retain samples for testing at a later date in cases where testing is reduced or omitted because of lack of resources

Planning for the Effects of High Absenteeism: CDER Notification

- Notification when the Plan is activated and when returning to normal operations
  - To help maintain awareness of any potential shortage situations
  - CDERStaffingNotice@fda.hhs.gov
- If a released product may be defective, contact CDER immediately in adherence to existing reporting requirements

Planning for the Effects of High Absenteeism: Examples

- ✓ Received multiple notices of plan activation
  - Some have activated/deactivated multiple times
- ✓ Notification Example Type 1
  - Included a list of MNP
  - Date of activation
  - Absenteeism threshold for deactivation

Disclaimer: These examples are generalized descriptions and not specific to certain firms

Planning for the Effects of High Absenteeism: Examples

Notification Example Type 2

- Did not include indication of prioritization of MNP
- Included notification that CGMP activities associated with batch release were reduced
  - Release of components/intermediates/recovered solvents without testing
  - Delays in stability testing of validation batches
  - Delays in preparation, review, and approval of certain quality activities, such as investigations into out-of-specification results

Notification Example Type 3

- Received via post-marketing submission requesting certain waivers, such as certain tests and skip lot release testing

Disclaimer: These examples are generalized descriptions and not specific to certain firms

Planning for the Effects of High Absenteeism: Enforcement Discretion

- "CDER is prepared to exercise enforcement discretion in such cases as appropriate to meet the national public health needs so long as the product remains safe and effective"

- Any CGMP deviations beyond the examples of the guidance may require formal FDA regulatory discretion

COVID-19 Guidance: Resuming Normal Operations (September 2020)

- Plan and prioritize products (e.g., medically necessary) and return to normal CGMP operations
  - Consider risk of shortage
  - Develop an established plan

- CGMP requirements remain in effect during the COVID-19 public health emergency and this guidance is not intended to describe FDA's enforcement priorities

https://www.fda.gov/media/142051/download

COVID-19 Guidance: Resuming Normal Operations (September 2020)

- Utilize a risk management approach to prioritize resumption activities

- For those activities which were delayed, reduced, or otherwise modified
  - Identify deviations from CGMP
  - Identify necessary remediations that ensure drug quality

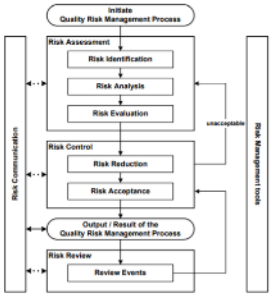
- Where critical CGMP activities were delayed, interrupted, or reduced in frequency
  - Batch should be quarantined
  - Decision to approve the batch delayed until remediation activities are complete
  - Investigations into critical deviations should continue to be a high priority during COVID-19

COVID-19 Guidance: Resuming Normal Operations (September 2020)

- Examples of remediation and questions to consider
  - Investigations into non-critical product or process discrepancies and unresolved deviations
  - Decision to delay or reduce testing less directly (or not) associated with a batch
    - A decision to delay or reduce testing directly connected with batch manufacturing or a product accept or reject decision (e.g., testing associated with a critical quality attribute) should generally be avoided
  - Impact of COVID-19 on suppliers
  - Changes or interruptions to facilities/equipment

COVID-19 Guidance: Resuming Normal Operations (September 2020)

Figure 1: Overview of a typical quality risk management process



- Prioritizing Activities to Resume Normal Manufacturing
  - Use findings and conclusions from risk management approach
  - High priority to products in shortage or at risk of shortage
  - Some activities must be conducted prior to restarting production, some may be accomplished in tandem
  - May be a fluid process

In Summary

- Guidance is available for manufacturing during COVID-19, including responding to infections in employees, handling high absenteeism, and resuming normal operations
  - Appropriate justification and documentation is key
- CDER is prepared to exercise enforcement discretion in such cases as appropriate to meet the national public health needs so long as the product remains safe and effective
  - Any CGMP deviations beyond the examples of the guidance may require formal FDA regulatory discretion
- OMQ works to minimize consumer exposure to unsafe, ineffective, potentially dangerous, or poor quality drugs
  - We take actions against firms with poor CGMP or when other information calls into question the quality of drugs for U.S. patients

Thank you

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