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**POLICY AND PROCEDURES**

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**OFFICE OF PHARMACEUTICAL QUALITY**

**Drug Product Distribution After a  
Complete Response Action to a Changes Being Effectuated Supplement**

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**PURPOSE**

This MAPP describes the policies and procedures for the Food and Drug Administration (FDA) to follow when assessing an applicant’s distribution of a drug product manufactured using a change that the applicant had described in a Changes Being Effectuated (CBE) supplement to which FDA issued a complete response (CR) letter. This MAPP applies to CBE supplements that are submitted to a new drug application, an abbreviated new drug application, or a biologics license application managed by the Office of Pharmaceutical Quality (OPQ), the Office of New Drugs (OND), or the Office of Generic Drugs (OGD).

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**BACKGROUND**

Under 21 CFR 314.70(c), an applicant is required to submit a supplement:

for any change in a drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.<sup>1</sup>

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<sup>1</sup> See also 21 CFR 601.12(c).

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Section 314.70(c) provides for two types of supplements for such changes — that is, a Changes Being Effected in 30 Days (CBE-30) supplement and a Changes Being Effected (CBE-0) supplement.

Under §§ 314.70(c)(5) and 601.12(c)(4), an applicant must not distribute a previously approved drug product that is being manufactured using a change proposed in a CBE-30 supplement if, within 30 days following FDA's receipt of that supplement, FDA informs the applicant either that (1) a prior approval supplement is required or (2) any of the information required under § 314.70(c)(4) or § 601.12(c)(3) is missing from the supplement. In the second situation, the applicant must not distribute the drug product manufactured using the change until the CBE-30 supplement has been amended to provide the missing information.

Under §§ 314.70(c)(6) and 601.12(c)(5), an applicant may commence distribution of a drug product manufactured using a change proposed in a CBE-0 supplement after FDA receives that supplement.

FDA may issue a CR letter to the CBE-0 or CBE-30 supplement (21 CFR 314.110(a) and 21 CFR 601.3(a)). On or after the issuance of a CR letter, FDA may issue an order to the applicant to cease distribution of the drug product made using the manufacturing change until the CBE supplement is approved.<sup>2</sup>

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## POLICY

- An applicant may continue marketing a drug product manufactured using the change described in a CBE supplement unless and until FDA sends the applicant an order to cease distribution.
- FDA may determine, after a drug product manufactured using a change described in a CBE supplement has been distributed, that the information submitted in the supplement fails to adequately demonstrate the continued safety and effectiveness of the drug product.<sup>3</sup> If FDA determines either that (1) there may be a danger to public health if the drug product continues to be marketed or (2) the drug product's safety and effectiveness issues may not be resolved, FDA may order that the applicant cease distribution of the drug product manufactured using the change.<sup>4</sup>
- A recommendation to issue a cease distribution order can originate from FDA's assessment of the CBE supplement and may be in conjunction with FDA's

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<sup>2</sup> Sections 314.70(c)(7) and 601.12(c)(6).

<sup>3</sup> See 21 CFR parts 314 and 601.

<sup>4</sup> Ibid.

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assessment of the outcome of a facility inspection or records received in lieu of a facility inspection.

- Before FDA issues a cease distribution order, the OPQ quality team members,<sup>5</sup> the supervisors of these team members, the Office of Program and Regulatory Operations (OPRO)<sup>6</sup> Regulatory Business Project Manager (RBPM), and other FDA partners<sup>7</sup> relevant to that particular supplement and situation will meet internally to discuss whether to recommend that an order be issued to the applicant to cease distribution of the drug product.
- To document the recommendation to issue a cease distribution order, either OPQ staff will create a quality assessment or general assessment memorandum that documents the reasons why the quality team recommends that the applicant cease distribution of the drug product or, in the case of a facility issue, the OPRO RBPM and the Office of Pharmaceutical Manufacturing Assessment (OPMA) team member responsible for the facility assessment will capture the supporting information for the OPMA cease distribution recommendation and the agreements reached in meeting minutes. These meeting minutes will (1) serve as the official record for the OPMA recommendation to cease distribution and (2) be prepared by the OPRO RBPM with assistance from the OPQ quality team members, as needed.
- The quality assessment and recommendation should be signed by the appropriate signatory authorities following the accepted practices of the suboffice of the OPQ quality team member.
- If issuance of a cease distribution order has the potential to create a drug shortage, OPQ will follow MAPP 4190.1 *Drug Shortage Management*.<sup>8</sup>
- If FDA issues a cease distribution order for a CBE supplement, FDA will include the following statement in the order: “Pursuant to 21 CFR 314.70(c)(7) (for drugs) or 21 CFR 601.12(c)(6) (for biologics), products manufactured with the

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<sup>5</sup> For this MAPP, the OPQ quality team includes a product quality, drug substance, drug product, process, microbiology, facility, and biopharmaceutical assessor.

<sup>6</sup> OPRO is a suboffice of OPQ.

<sup>7</sup> These partners include, among others, the OPQ Drug Shortage Coordinator, OND, OGD, the OGD Drug Shortage Coordinator, the CDER Drug Shortage Staff, and the Office of Compliance. In addition, the Office of Manufacturing Quality in the Office of Compliance is a partner for a manufacturing facility that either has a Potential Official Action Indicated or an Official Action Indicated alert associated with it or is related to an ongoing Office of Manufacturing Quality case.

<sup>8</sup> We update MAPPs periodically. To make sure you have the most recent version of a MAPP, check the Manual of Policies & Procedures (CDER) web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp>.

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changes proposed in this supplement can no longer be distributed until this CBE supplement is approved.”

- If FDA receives pertinent information to address a concern about the product potentially posing a danger to public health, FDA may reconsider its cease distribution order, document the decision internally, and communicate accordingly with the applicant.

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## RESPONSIBILITIES

- **The OPQ Quality Team**

When conducting quality assessments of CBE supplements, the OPQ quality team members will follow the accepted practices of their suboffice.

- **The OPRO RBPM Staff**

- If the OPQ quality team has identified a potential danger to public health related to a proposed change described in a CBE supplement, the OPRO RBPM staff will convene a meeting with their supervisors, the OPQ quality team and their supervisors, and other relevant FDA partners<sup>9</sup> to discuss whether to recommend that a cease distribution order be issued for the drug product.
- The OPRO RBPM staff will document the outcome of the internal meeting mentioned above. If OPMA recommends a cease distribution order, the meeting minutes, which will be written by the OPRO RBPM and the OPMA team member responsible for the facility assessment, will serve as the official record for the OPMA facility recommendation.

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## PROCEDURES

1. The OPQ quality team will perform the quality assessment of the CBE supplement according to the accepted practices of the team’s suboffice.
2. If an OPQ quality team member recommends a cease distribution order, he or she will:
  - 2.1. Notify the other members of the quality assessment team and the OPRO RBPM of the recommendation to issue a cease distribution order.

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<sup>9</sup> See footnote 7.

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- 2.2. Discuss — with his or her team members, his or her Division Director, the Secondary Quality Assessor, and the OPQ supervisor, as applicable — any product quality issues that may pose a danger to public health if the proposed change is implemented.
  3. The OPRO RBPM will:
    - 3.1. Notify the OPQ Drug Shortage Coordinator of the recommendation to issue a cease distribution order and initiate a meeting with the quality team members, the supervisors of the quality team members, and the appropriate partners.
    - 3.2. Coordinate with the OPQ Drug Shortage Coordinator, as necessary, to identify the appropriate partners to contact and to schedule the meeting.
    - 3.3. Invite the relevant OPQ assessment divisions and the OPQ Drug Shortage Coordinator as required attendees.
    - 3.4. Alert the identified non-OPQ partners (e.g., the Office of Compliance, relevant OND division(s), OGD, the OGD Drug Shortage Coordinator, and the CDER Drug Shortage Staff (DSS) about this meeting, and each of these offices will determine if any of its representatives should participate in the meeting.
  4. The partners will meet to discuss and decide the course of action for the cease distribution recommendation. The OPRO RBPM — or, in the case of an inspectional issue, the OPRO RBPM and the OPMA team member — will document the meeting minutes.
  5. The quality assessment or quality recommendations (in a general assessment memorandum) will include a justification for the recommendation to issue a cease distribution order and be signed by the appropriate signatory authorities following the accepted practices of the quality team member's suboffice.
  6. If the recommendation to issue a cease distribution order is a result of a facility issue:
    - 6.1. The meeting minutes will serve as the official record for the OPMA facility recommendation and be signed by the OPMA Supervisor or designee.
    - 6.2. The facility assessor will document a brief summary of the OPMA facility recommendation in the comments section of the Overall Manufacturing Inspection Recommendation and will reference the meeting minutes in Panorama.

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7. For all CR letters for product quality supplements, the responsible OND RPM, the OGD RPM, or the OPQ RBPM will draft the CR letter and distribute the draft to the appropriate OPQ assessment staff, the OPQ Drug Shortage Coordinator, and involved DSS members. Subsequently, the designated signatory (the Division Director or designee) will assess, edit (as appropriate), and sign the letter.
  
  8. If a CR letter with an order to cease distribution is issued and an applicant responds to the deficiencies in the CR letter, FDA may find that there is sufficient information to lift the cease distribution order and communicate this decision to the applicant in the subsequent action letter.
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**REFERENCE**

MAPP 4190.1 *Drug Shortage Management*

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**EFFECTIVE DATE**

This MAPP is effective on October 4, 2017.

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**CHANGE CONTROL TABLE**

Effective Date	Revision Number	Revisions
10/4/17	Initial	N/A
11/23/2022	N/A	Recertified. No Changes.
N/A	N/A	12/31/2024 Administrative revisions to align with OPQ reorganization and update website address