CBER Response to OMB on Cooperative Manufacturing Guidance – September 2008

- *Does FDA agree with commenters that the "short supply" requirements are duplicative and burdensome without value-added?*

  No, FDA does not agree that the short supply provision is "outdated, confusing and, at best duplicative of current contract manufacturing arrangements" as stated by the commenters' letters. The short supply provisions offer regulatory flexibility to manufacturers of licensed products, so that these initial and partially manufactured biological products may move in interstate commerce without an approved biologics license application (BLA). The shipments are from persons other than the licensed manufacturer to the licensed manufacturer's location. This provision is especially important for the blood industry, where certain unlicensed blood components (e.g., recovered plasma) are needed for the further manufacture of licensed plasma derivatives which are chronically in short supply.

  In addition, the regulation providing for short supply is not duplicative in that without it, the aforementioned partially manufactured materials could not be legally shipped interstate without an approved BLA. Also, it is not burdensome in that the information contained in such agreements has always been required to be submitted to ensure that the finished (or "final") biological product is safe, pure and potent (see below).

- *If so, please describe any changes made to the guidance as a result, or explain why changes were not made.*

  Please see above.

- *If the information collection requirements in this collection are not new (per discussion in item 12 of the supporting statement that the burden is captured in other FDA collections) then why would FDA be receiving these comments?*

  The information requirements are not new. The information is required to ensure that manufacturers of biological products employing Short Supply Agreements manufacture products that are safe, pure and potent in that the manufacturing process must be fully described in the application (21 CFR 601.2). Without this significant information, FDA is not authorized to approve the BLA. This information has been formally requested since 1970 (see the attached memorandum from 1970) and the practice of obtaining this information dates back to 1948.

  
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  However, there are three points that probably need clarification.

  - It is not entirely clear why industry is raising concern regarding submitting such information, when they have routinely submitted it for decades. Perhaps the confusion is that industry thinks the actual Short Supply Agreement needs to be submitted. We view the actual corporate business Agreement to be outside the scope of an application and we do not expect it to be submitted in the application. To clarify, the "required information" to be supplied to the BLA refers to the "full

description of manufacturing methods" under 21 CFR 601.2 and not the Agreement itself. As such, the manufacturing information covered by the Short Supply Agreement must be listed in the application. We will modify the language in the Short Supply Arrangements section of the guidance (section III, page 4) to clarify that the manufacturing information only is required (and not the actual Agreement): "...file the required *manufacturing process* information and assurances...." (See attached redline revision).

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- The collections of information in 21 CFR 601.2 have been approved under OMB control number 0910-0338.
- It appears that the commenters may be requesting a regulation change. There are established procedures available for this purpose.

- *Please briefly describe the criteria or definition FDA uses to determine whether a product is in "short supply."*

  The concept of "short supply"' was introduced around 1948 when it was recognized that there were only a limited number of persons who could serve as donors of antibodies for the preparation of special blood typing serums and immune globulins containing certain antibodies in high concentration. In order to have access to these donors throughout the country, licensed manufacturers were permitted to use other persons or firms, not a part of their own establishment, to perform the initial and partial manufacturing steps of these products by collecting blood or plasma for shipment to the licensed manufacturer.

  A product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the source required for manufacturing purposes.

- *Would like additional clarification on the distinction between shared and contract manufacturing described on pages 5 and 6 of the guidance document.*

  - Shared manufacturing is a situation where both participants hold biologics licenses, but for different portions of a final product. For example, Chiron holds a license for hepatitis C raw materials and Ortho holds a license to manufacture a test kit, employing that raw material.
  - Contract manufacturing is a situation where a biologics license holder establishes a contract with an unlicensed entity to perform some or all of the manufacture of the product as a service to the license holder.
  - So the main distinction is that in shared manufacturing, there are two license holders; in contract manufacturing a licensed holder contracts with an unlicensed entity to perform all or some of the manufacture of the licensed product.

- *In the "general" discussion, FDA provides a list of example of significant manufacturing steps that FDA would consider adequate for separate licensure and a list of steps that ordinarily wouldn't be considered adequate by FDA. Is it the case, then that a company performing only one or more of those steps would be doing so as a "contract" manufacturer?*

For the less significant steps, yes, the manufacturing situation would most likely be viewed as a "contract" manufacturing situation. However, there may be many different acceptable approaches and FDA generally may consider such manufacturing situations on a case-by-case basis.

- *On page 6 of the guidance, FDA states that, "Each BLA must meet the requirements of 21 CFR 601.2 and fully describe..." A bulleted list of items follows that statement. For any of the items on that list, is the requirement to "fully describe" new? If so, FDA should account in this collection for the burden to manufacturers of providing to FDA. If not, please let me know under which existing collection these are covered.*

  Fully describing the manufacturing methods in a BLA is not new. 21 CFR 601.2 states that an application must contain "A full description of the manufacturing methods..."

- *OMB notes that if/when this collection is approved, FDA must add the OMB number and PRA burden statement prior to use.*

  If/when OMB approves this collection; FDA will add the OMB number and PRA burden statement to the guidance.