July 30, 2019

From: Pharma & Biopharma Outsourcing Association
10 Alta Vista Dr.
Ringwood, NJ 07456

To: Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-1845 *"Fixed-Quantity Unit-of-Use Blister Packaging for Certain Immediate-Release Opioid Analgesics for Treatment of Acute Pain; Establishment of a Public Docket; Request for Comments"*.

To whom it may concern,

On behalf of the Pharma & Biopharma Outsourcing Association ("PBOA"), a trade association representing Contract Manufacturing Organizations and Contract Development & Manufacturing Organizations ("CDMOs"), I appreciate the opportunity to offer feedback on *"Fixed-Quantity Unit-of-Use Blister Packaging for Certain Immediate-Release Opioid Analgesics for Treatment of Acute Pain; Establishment of a Public Docket; Request for Comments"* (Docket No. FDA-2019-N-1845) as cited in Federal Register Notice (FRN) 2019-11283.

The PBOA represents a sector responsible for manufacturing, packaging and supporting development of more than one-third of all doses distributed to patients in the U.S., on behalf of our customers, the marketing authorization holders of drugs and biologics. Therefore, we comment not as the license-holders of opioid products, but as the companies that provide manufacturing and packaging services for such products.

We applaud FDA's efforts to address the opioid crisis through implementing provisions of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act. However, the FDA should take into consideration the operational logistics and the public health limitations of requiring fixed-quantity unit-dose blister packaging under REMS authorities for certain solid oral dosage forms of immediate release (IR) opioid analgesics.

Regarding the specific topics FDA has requested for comment in the FRN, PBOA will focus on three of the nine topics:

*5. Comment on the potential challenges, including technical and logistical challenges, with the potential blister packaging requirement. What factors could impact application holders' ability to produce blister packaging of the type described in this notice?*

Not all manufacturing/packaging facilities – whether that of a contractor or an in-house operation — are equipped for blister-packaging opioids, regardless of the volume specified by an FDA requirement. A changeover in packaging modes will involve significant length of time to operationalize. Acquisition of new equipment, validation, tooling, and stability studies will be required and could take two years or longer to complete.

If a license-holder elects to use a CDMO for packaging rather than invest in a blister-line for its own facilities, it will take additional time to identify and contract with such a company. If the license-holder currently uses a contract manufacturer and packager of an opioid product that does not have unit-dose blister-packaging equipment, the license-holder may choose to ship the bulk product to a packaging facility for that step. In some cases, the contract packaging facility may need to register with DEA and achieve compliance with that administration's controlled substance regulations before accepting product for blister packaging.

If new packaging equipment must be purchased, this will require extended timelines for installation, qualification and validation. In other cases CDMOs may have the requisite equipment, but it may need to be commissioned for commercial use. Some CDMOs that possess blister-packaging capabilities, for example, currently employ it primarily for physician samples or clinical materials; changing over to commercial production would require adding DSCSA-compliant hardware and software that could also cause delays and add complexity. Such delays can occur with both CMOs and in-house manufacturing/packaging lines.

These steps will add complexity and cost to the supply chain and may result in a temporary mismatch of demand and capacity. A glide path to compliance may be necessary, as addressed below.

*6. How much time would be needed for application holders to submit prior approval supplements for blister packaging that would satisfy the proposed REMS requirements discussed in section II.C? How much time would be needed for an application holder to develop REMS-compliant packaging and manufacture sufficient quantities to perform the stability and other product*

*quality testing necessary to support the approval of a PAS, and how much time would be needed to perform such testing? How much time after approval of a PAS would be needed for an application holder to manufacture and make the product commercially available?*

Based on experience, it may take as long as 3 years for CDMOs and their customers to select, develop and source the packaging system, perform testing for CR requirements, perform stability studies, prepare a prior approval supplement (PAS) and get Agency approval for it. From a CDMO perspective, commercial availability will be more difficult to estimate, as it will be driven by the customer and outside market forces.

*7. Comment on the idea of implementing a blister packaging mandate in a staggered fashion, targeting the products most commonly prescribed to treat acute pain first, as well as the idea of imposing a conditional mandate for discontinued products. Are there other ways the Agency could consider staggering implementation of this requirement to minimize burden on manufacturers and other stakeholders, while maximizing the public health benefit?*

We recommend that if FDA elects to pursue this requirement following a scientific study into its efficacy, it phases in the implementation, whether by choosing a subset of the most-abused opioid products/doses or another set of criteria. Implementation of too broad of a blister-packaging requirement may cause packaging capacity constraints. We cannot stress strongly enough that such a requirement must include enough time not only for license-holders to develop OA REMS, but for the manufacturing and packaging infrastructure to prepare for effective deployment.

In the case of approved but discontinued products, we agree with FDA's suggestion that the agency should require application holders to seek approval for blister-package configurations only if they decide to reintroduce those products to the market.

Our members provide services for both innovator and generic license-holders, and we are concerned that ANDA-holding clients may face increased complexity when faced with the decision to develop their own OA REMS or model theirs after that of the Reference Listed Drug (RLD). As a result, CDMOs may face multiple packaging and labeling setups for identical products, based on the paths chosen by their clients.

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We appreciate the opportunity to work with FDA to help fight opioid abuse in America, and hope we can continue this discussion as the agency develops new policies and recommendations.

Sincerely,

Gil Roth
President
Pharma & Biopharma Outsourcing Association

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