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October 15, 2020

Dear Ms. Stember,

Thank you for your August 12, 2020 letter to Dr. Jacqueline Corrigan-Curray, Lubna Merchant, and Lonnie Smith. Your inquiry was received and referred to the Center for Drug Evaluation and Research for a response. Your letter expressed concerns about the November 2019 revisions to labeling for insulin pens, stating that they should be dispensed in their original sealed cartons. We appreciate you raising these concerns and giving us this opportunity to provide clarification about this labeling.

Insulin pens are generally marketed in cartons containing 2 to 5 pens,[1] based on the packaging configuration requested by applicants and approved by the U.S. Food and Drug Administration (FDA) in marketing applications.[2] Individual insulin pens in multiple-pen cartons were approved to be dispensed in their original sealed cartons. The pens are not labeled for dispensing as individual units. Because sealed cartons of insulin pens are intended to be dispensed to a single patient, each carton contains a single copy of the drug's prescribing information and Instructions for Use (IFU). Although each carton is sealed to alert healthcare providers and patients when it has been opened, individual insulin pens within the cartons do not have their own sealed packaging. The carton label and sealed packaging are important for both healthcare providers, who prescribe, dispense, and/or administer insulin pens, and patients, who may be prescribed more than one type of insulin pen (e.g., both short- and long-acting insulin), as both healthcare providers and patients may store different types of pens together. Individual insulin pens with different dosages and/or formulations often have similar appearances and can be difficult to distinguish. The cartons help healthcare providers and patients differentiate between the insulin pens through the use of various colors, font size, style, etc., displayed on the cartons.

In 2017, FDA became aware of safety concerns reported after cartons were opened to dispense individual insulin pens. Pens dispensed individually outside of their cartons may have contributed to medication

[1] On June 11, 2020, the first single-pen carton size was approved for an insulin product. See https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210605s000lbl.pdf.

[2] Insulin products historically have been approved in new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Pursuant to the Biologics Price Competition and Innovation Act of 2009, approved NDAs for biological products (such as insulin) recently were deemed to be licenses (i.e., approved biologics license applications) for the biological products under section 351 of the Public Health Service Act. For additional information, see https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act.

errors including wrong-drug and wrong-dose errors resulting in hyper- or hypoglycemia,[3] missed doses,[4] complaints of possible tampering,[5] and dispensing without the IFU. There is an increased risk of a dispensing error and patients using the wrong product if individual insulin pens are stored outside of their carton or placed in an incorrect opened carton. For example, a report submitted to the FDA Adverse Event Reporting System (FAERS) indicated that a patient received an opened carton labeled as insulin lispro mix 75/25, but an insulin lispro pen was also in the carton. The patient did not notice the error until after administration, when he became "profoundly hypoglycemic." He then looked at the label on the individual pen and realized that he had injected insulin lispro instead of insulin lispro mix 75/25.

In response to the above concerns, in 2019, FDA requested that label statements on the cartons of insulin pen products be added to emphasize the agency's recommendation for dispensing insulin pens to a single patient in their original sealed carton. Per FDA's request, insulin manufacturers submitted supplemental new drug applications updating insulin pen carton labels and prescribing information to clarify that insulin pens should be dispensed in their original sealed cartons to a single patient. On November 15, 2019, FDA approved the supplemental new drug applications that revised the prescribing information and carton labels for insulin pens.[6]

FDA understands that there are situations in which healthcare providers may choose to dispense individual pens (outside of the carton), not in accordance with FDA approved labeling, based on their professional judgment. In these situations, healthcare providers should consider the known risks of dispensing individual pens and incorporate additional safety measures (e.g., adding tamper-indicator tape; providing a copy of the IFU to the patient; labeling individual pens for patient use) to mitigate those risks. FDA will continue to monitor the safety risks associated with such dispensing practices and will consider further steps as warranted. FDA has also strongly encouraged the manufacturers of insulin pens to consider developing smaller carton sizes (e.g., 1-2 pens per carton) to better accommodate variable insulin doses and needs. We suggest that organizations facing challenges with large carton sizes (multiple-pen cartons) also contact the manufacturers to express the need for smaller (and single-pen) carton sizes.

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[3] Wrong-dose errors can occur due to the absence of an IFU when a patient uses the insulin pen incorrectly or does not know how often to use the insulin pen. Wrong dose errors can also occur when pharmacy dispenses the wrong strength of the insulin pen (individual pens, particularly those marketed by the same applicant, look alike).

[4] FDA is aware of patients missing doses due to patients not being able to identify if the individual insulin pens were new, unused pens when dispensed outside of the cartons. A contributing factor in this case is that the cartons were opened and patients were concerned that the pens had been used. FDA is also aware of missed doses because patients realized they were dispensed the wrong insulin pens and had to go back to the pharmacy to get the correct pens. A contributing factor in this case is that the cartons were opened and the individual pens were mixed up with different types of insulin pens at the pharmacy.

[5] Patients are at risk of receiving a used or tampered product when an individual pen is dispensed outside of the carton as the individual pens do not have a safety seal to alert the dispenser or user that the pen has been used or was subject to tampering.

[6] These supplemental new drug applications provided for the following updates to the prescribing information and carton label: (1) revised the carton label to state: "Dispense in this sealed carton" on the principal display panel; and (2) added the following statement to Section 16 (How Supplied/Storage and Handling) in the prescribing information: "Dispense in the original sealed carton with the enclosed Instructions for Use".

As reflected in the labeling of approved insulin pens, FDA's recommendation is to dispense the pens in the original sealed carton to a single patient. However, as discussed above, we understand that there may be some situations where healthcare providers may choose to dispense single pens from a multiple-pen carton. For more information, please see https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-health-care-professionals-and-patients-about-insulin-pen-packaging-and-dispensing for a recent statement by the Center for Drug Evaluation and Research regarding our recommendation. If you have any additional questions, please let us know.

Sincerely,

CDER Executive Operations
Office of Executive Programs
Center for Drug Evaluation and Research