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Drug, Biologic and Medical Device Development, Quality Assurance and Regulatory Affairs Consulting
Specializing in Combination Products

SUMMARY OF KEY POINTS FROM JANUARY 27, 2014 FDA WARNING LETTER FOR JUNE 14-17 INSPECTION OF AMGEN, THOUSAND OAKS, MAUFACTURE PROLIA PREFILLED SYRINGE AND MANUAL NEEDLE GUARD, ENBREL LYOPHILIZED VIAL AND DILUENT WITH VIAL ADAPTER AND ENBREL PREFILLED SYRINGE WITH "SURECLICK 1.5" AUTO INJECTOR.

These products are combination products under section 503(g) of the FD&CA and 21CFR 3. They include device constituent parts, which are "devices" under the FD&CA. The device constituent parts of the combination products are adulterated, in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation do not conform to current good manufacturing practice requirements of the Quality System regulation, 21CFR 820.

Design Controls

1. Failure to conduct, prior to commercialization, design validation studies of the device constituent part of Prolia (denosumab),
   - Failure to follow, implement and maintain established design validation procedures to ensure that devices conform to user needs and intended uses, including testing of production units under actual or simulated use conditions.
   - June 28, 2013 483 response is inadequate because actions to be taken to ensure that, in the future, established procedures will be followed, were not specified.
   - Consider conducting design validation studies, under actual use conditions, to verify that that currently marketed combination products conform to user needs and intended use.

Change Control

2. Failure to establish, maintain and follow procedures for the identification, documentation, validation, verification, review, and approval of design changes before implementation.
   - Failure to validate the design, prior to implementing design change for Enbrel with vial adapter. The design of the Enbrel combination product was changed resulting in a significant increase in product complaints.
   - June 28, 2013 483 response, indicating that the multiple-use vial kit was redesigned and the new vial adapter replaced, is inadequate, because actions to be taken to ensure

that established procedures will be followed in the future were not specified and evidence was not provided that the revised vial adapter is no longer in use.

- Consider conducting an evaluation of the design changes made to the device constituent parts of currently marketed combination products to ensure that prior to the implementation of design changes complied with requirements of 21CFR 820.30(i)

Purchasing Controls

3. Failure to establish, maintain and document requirements to be met by suppliers, contractors, and consultants, on the basis of their ability to meet specified requirements, including quality requirements, as required by 21 CFR 820.50(a).
   - Failure to implement and demonstrate that established procedures for purchasing controls, requiring contractors to be evaluated, monitored, and approved were followed.
   - June 28, 2013 483 response, committing to ensure that service providers conducting preventive maintenance, is inadequate, because it did not describe how employees will be trained on new procedures and because it did not indicate if records will be reviewed to ensure that suppliers, contractors, and consultants have been appropriately evaluated.

Analysis

This Warning Letter provides the first tangible insight, since the final rule was codified, about how FDA is conducting inspections of combination product development and manufacture and its enforcement of the regulation. In particular, it provides an important insight about FDA's expectations about how legacy products were developed. There is discussion and concern within the medical products industry about the possibility that FDA could require the retrospective application of device QSR requirements to legacy combination products, in particular with respect to the Device History File (DHF), which serves to document that design development was conducted in accordance with a prospectively established design plan. The Warning Letter is evidence that FDA is not only expecting manufacturers to retrospectively comply with QSR Design Control requirements, for legacy products, but also that Purchasing Controls should also be retrospectively applied. It is clear, therefore, that FDA expects manufacturers to be able to demonstrate that the development a marketed combination product took place in accordance with QSR requirements, regardless of whether it was approved before or after the end of the enforcement discretion/transition window for the combination product GMP rule, which was July 22, 2013, 180 days following its publication in the Federal Register.