FDA Regulatory and Compliance Monthly Recap

JULY 2017

KEY FINDINGS

CBER annual statistics demonstrate slight increase in biological product deviations in FY2016

The CBER's annual summary signals a moderate increase in deviation reports, with blood and source plasma establishments accounting for the majority. Post-donation information was commonly cited in blood and source plasma reports, whereas product specifications were a frequent issue in non-blood product reports.

The Center for Biologics Evaluation and Research (CBER) published its annual summary for FY2016 of deviation reports by manufacturers of biologics; blood and blood components; and human cells, tissues, and cellular and tissue-based products (HCT/Ps). The Office of Compliance and Biologics Quality's Division of Inspections and Surveillance received a total of 51,229 deviation reports in FY2016, representing a 10% increase over FY2015, though the number doesn't account for reports that didn't meet reporting thresholds. There was a slight increase in the number of reporting establishments, from 1,907 in FY2015 to 1,950 in FY2016..

Blood and source plasma establishments accounted for a large portion of the increase (4,546 more reports compared to FY2015) and 98% of the total reports in FY2016. Source plasma establishments were primarily responsible for the increase, accounting for 3,930 more reports and representing 52% of the blood and source plasma reports. The most frequently reported event among blood and source plasma manufacturers was post-donation information (PDI), which accounted for 71% of the deviation reports. Among licensed blood establishments, 69.5% of reports involved PDI, and just 6.5% involved quality control and distribution deviations or unexpected events. In contrast, quality control and distribution deviations and unexpected events accounted for 56.1% of reports by unlicensed registered blood establishments, labeling accounted for 22.6% and PDI accounted for just 9.1%.

There was only a slight uptick (93) in the number of reports by manufacturers of licensed biological products other than blood and blood components, with 651 total reports. In all, product specifications accounted for slightly more than half (50.7%) of the reports, while quality control and distribution accounted for 14.4%, process control accounted for 9.8% and labeling accounted for 8.8%.

- Vaccine manufacturers accounted for 42 of the 93 additional reports and 265 of the total reports. Of these, 103 reports involved product specifications and 46 involved quality control and distribution, including 35 reports of broken or cracked vials.
- Licensed in vitro diagnostic manufacturers were responsible for 33 more reports in FY2016, for a total of 144. A large portion of these reports (97) related to product specifications, including 61 reports of unexpected reactions in testing and 15 reports of leaking vials or other containers.
- A total of 351 licensed HCT/P manufacturers submitted the same number of reports as in FY2015 (19 total). There was an increase in the number of reports related to labeling controls among licensed HCT/P manufacturers, from eight in FY2015 to 14 in FY2016, primarily involving products labeled with the wrong recipient identification.

Manufacturers of 361 HCT/Ps submitted three more reports in FY2016 than in FY2015, for a total of 259, including 135 by cellular HCT/P manufacturers and 125 by tissue HCT/P manufacturers. The most commonly reported issues related to processing and processing controls (34%); receipt, pre-distribution, shipment and distribution (22.8%); and donor eligibility (20.5%). The number of reports involving contamination or potential contamination during processing in FY2016 was similar to the number in FY2015, whereas the number of reports related to distribution of contaminated products declined in FY2016.

House passes user fee reauthorization bill calling for sequential increases in fees, new fee structure for pharmaceuticals

The House's reauthorization legislation calls for nearly $400 million in new fees in FY2018, with progressive increases through 2022. The bill restructures fees for pharmaceuticals, introduces an independent fee structure for biosimilars and includes several provisions for medical devices. The Senate has yet to schedule a vote on its version of the legislation.

The House of Representatives advanced legislation to reauthorize user fee programs for prescription drugs, generics, medical devices and biosimilars through 2022, and published a report breaking down each section of the bill. The FDA Reauthorization Act of 2017 calls for sequential increases in the amount of user fees through 2022, adding nearly $400 million in new fees in FY2018.

The bill sets the annual base revenue for pharmaceuticals at $878 million, an increase over FY2017's $718.7 million. It calls for fees for pharmaceuticals to generate an additional $20.1 million in FY2018, $21.3 million in FY2019, $16.9 million in FY2020, $5.4 million in FY2021 and $2.7 million in FY2022. Of the total revenue, 20% is to be derived from application fees and 80% from prescription drug program fees. The legislation reauthorizes the orphan drug and pediatric drug programs. It also calls on HHS to commit to working with the House and Senate to address drug costs and the need to balance innovation and affordability. The bill also increases the penalty for knowingly making or distributing counterfeit drugs.

For medical devices, base fee amounts are set at $293,000 for premarket applications and $4,375 for establishment registration in FY2018, with gradual increases to reach $329,000 and $4,978, respectively, by FY2022. Total revenue generated by fees is slated to be $183.3 million in FY2018, $190.7 million in

FY2019, $200.1 million in FY2020, $211.7 million in FY2021 and $213.7 million in FY2022. The bill:

- Adds the term “de novo classification” to allow user fees to be collected for reviews of de novo medical device classification requests;
- Calls for a pilot program to be established by 2020 for the FDA to accredit test labs that assess devices for conformity to FDA-recognized consensus standards;
- Requires that draft guidance be issued outlining how determinations are made on whether a class I or II device is eligible for third-party review;
- Stipulates that the FDA issue a report outlining how it plans to ensure the quality, safety and continued efficacy of devices that have been serviced;
- Outlines a process through which the agency may classify medical device accessories based on their intended use;
- Mandates that the FDA implement a risk-based inspection schedule for medical device establishments and publish draft guidance within 18 months outlining how it will implement the risk-based process; and
- Calls on the FDA to establish one or more pilot projects within a year to generate reliable and timely data on the safety and effectiveness of approved or cleared devices

Fees for biosimilars are slated to generate total revenue of $45 million in FY2018, an increase from $20 million in FY2017. The bill creates an independent fee structure for biosimilars based on an initial development fee, annual development fee and program fee for sponsors of approved biosimilars, in addition to an application fee.

The bill has been criticized by the White House and President Donald Trump, who called for a $1 billion increase in fees. In a statement, the White House warned that the bill would require a “significant investment” by taxpayers rather than ask more of the pharmaceutical industry. The Senate hasn’t scheduled a vote on its version of the legislation.

FDA issues warning letter to Raritan Pharmaceuticals over teething product with belladonna levels exceeding label claims, insufficient quality assurance testing

The letter takes issue with poor quality assurance testing of teething products and levels of belladonna that exceed the levels claimed on labels. In response to the letter, the drugmaker has said it has recalled the products and has since ceased manufacturing them.

The FDA sent Raritan Pharmaceuticals a warning letter after an inspection of its facility in East Brunswick, New Jersey, revealed several significant violations of Current Good Manufacturing Practice (CGMP) regulations and adulteration of the company’s teething product. Inspectors also uncovered misbranded product that contained excessive levels of belladonna, exposing infants using the products to potentially serious harm.

Inspectors observed several deviations from CGMP for finished pharmaceuticals, including Raritan’s failure to test components of its homeopathic teething product for conformity with written specifications for purity, strength and quality. In one instance, Raritan failed to test product received from a supplier for any quality data, including identity, before using it in production. FDA inspectors found some components for which conformity testing wasn’t done were received without a certificate of analysis. A sample of the lot revealed the material exhibited high variability, making it of unacceptable quality for the manufacture of drug product. Inspectors determined that the variability exposed infants given the product to safety hazards from belladonna levels beyond the labeled content.

The drugmaker was chided for failing to establish sufficient procedures for production and process

controls to ensure drug products have the identity, strength, quality or purity they are represented as having. Inspectors found the procedures used when making teething tablets and cold tablets are not supported by sufficient process validation. They noted that an analytical standard used for identity testing is not a properly qualified standard, and process validation studies failed to show the process is able to reliably produce finished drugs that consistently meet label claims. In samples of teething tables, inspectors observed belladonna that exceeded the alleged content levels on the product label. The FDA is asking the drugmaker to implement a scientifically sound program that appropriately identifies and controls sources of variability so that finished product consistently meets quality attributes and label claims.

The warning letter cites Raritan's failure to carefully investigate unexplained discrepancy or failure of a batch or component to meet specifications, regardless of whether it had been distributed. In one case, Raritan's investigation into a complaint about a seizure due to teething tablets included sending samples to QC for analysis, but Raritan didn't document whether additional analysis was conducted. In another instance, expired components were used to make a finished product, but Raritan didn't investigate whether the use of the expired components had any impact on the finished product.

The letter also takes issue with a homeopathic teething product that contained alkaloid content that varied widely from the content stated on the product labeling, making the product misbranded. Inspectors found the quantity of belladonna alkaloids listed on the label failed to accurately reflect the quantity found in the product. The FDA notes that while the product is labeled as a homeopathic drug, it is subject to the same regulatory requirements as other drugs. While Raritan initiated a recall upon the FDA's analysis demonstrating excessive belladonna levels and stopped making the product, the FDA is asking for confirmation that Raritan has permanently stopped production.

FDA holds off on enforcement of product identifier requirements for one year

To address concerns about the industry's readiness to comply with the product identifier requirements under DSCSA, the FDA issued a draft compliance policy indicating that it will hold off on enforcing certain requirements for manufacturers, repackagers, wholesale distributors and dispensers.

The FDA issued draft guidance outlining its compliance policy for product identifier requirements and indicated that it doesn't plan to take action against manufacturers that fail to meet the requirement until November 26, 2018. The agency is delaying by one year the enforcement of the requirement under the Drug Supply Chain Security Act (DSCSA) that manufacturers include a product identifier on product packages meant to be introduced in a transaction into commerce, which was initially slated to go into effect November 27, 2017. The decision follows feedback from manufacturers and their trading partners raising concerns about readiness to meet the requirements due to the limited number of vendors able to provide the IT systems and equipment needed. There were also concerns about contract facilities' readiness to meet the requirements on behalf of manufacturers.

The compliance policy also indicates the FDA will not enforce the requirement that manufacturers use identifiers to verify product at the package level, when investigating suspect product or upon receipt of a verification request by the agency, for product introduced prior to the new enforcement date without a product identifier. Similarly, action won't be taken against manufacturers that don't verify a package or sealed homogeneous case of such product if it is meant for further distribution as a saleable returned product. However, the FDA notes that manufacturers must validate any applicable transaction history and information if it's determined that a product it possesses or controls is suspect or if a verification request is received from the FDA or an authorized trading partner.

In recognition that downstream trading partners may want to acquire product introduced to market between the initial enforcement date and the new enforcement date that don't bear an identifier, the FDA states that it does not intend to take action against repackagers, wholesale distributors or dispensers that:

- Take part in a transaction involving such product, irrespective of when the transaction takes place,
- Do not verify the product identifier for such product, or
- Do not verify the product identifier on each package or sealed homogeneous case of such product meant for distribution as a saleable return.

The FDA cautions, however, that there is an exception in instances in which a repackager's transaction triggers an independent responsibility to include a product identifier. The compliance policy is not applicable to the requirement, slated to take effect November 17, 2018, that repackagers include a product identifier on each package or homogenous case of product meant to be introduced to market. As such, wholesalers or dispensers that acquire products from a repackager after the effective date should make sure they have product identifiers. The FDA encourages trading partners who believe product may be subject to the compliance policy to take steps to verify the product was introduced during the required time frame based on at least one document of the transaction history or other documentary evidence established by a trading partner in the ordinary course of business.

Ohio Board of Pharmacy passes resolution requiring changes to request forms for drug samples and complimentary supplies

The Ohio Board of Pharmacy (BoP) notified manufacturers and distributors July 14, 2017, of a resolution creating a modified process for verifying the Terminal Distributor of Dangerous Drugs (TDDD) License of a recipient of a non-controlled dangerous drug sample or complimentary supply. The BoP Resolution: Non-Controlled Dangerous Drug Licensure Verification Prior to the Sale of Sample Drugs or Complimentary Supplies adopted July 12, 2017, updates and clarifies expectations for license verification under O.R.C. 4729-9-12, including a change that could require industry to create new sample and complimentary supply request forms.

What products are included in the modified process?

The resolution applies only to samples or complimentary supplies of "dangerous drugs" that are not also controlled substances. Under O.R.C. 4729.01, dangerous drugs generally include legend drugs, drugs intended for injection and biologics.

The resolution is forward-looking, using definitions for "sample" and "complimentary supply" that are in the process of being incorporated into O.R.C. 4729-9-13. Here, samples include dangerous drugs marked as samples. Complimentary supplies include dangerous drug starter packs, initial dose packs, replacement product and similar products distributed without charge that are not marked as samples.

What is a TDDD License?

A TDDD is any "person who is engaged in the sale of dangerous drugs at retail, or any person, other than a wholesale distributor or a pharmacist, who has possession, custody, or control of dangerous drugs for any purpose other than for that person's own use and consumption, and includes pharmacies, hospitals, nursing homes, and laboratories and all other persons who procure dangerous drugs for sale or other distribution by or under the supervision of a pharmacist or licensed health professional authorized to prescribe drugs" (O.R.C. 4729.01).

The BoP requires all TDDDs to obtain a license, with limited exceptions described in O.R.C. 4729.541. Manufacturers and distributors are expected to verify

the TDDD license before the distribution of free samples and complimentary supplies.

Will sample and complimentary supply request forms have to change?

Under the modified process, in addition to 1) verifying the requesting prescriber's license to practice as required by the federal Prescription Drug Marketing Act and the BoP and 2) verifying the TDDD license number if provided, the manufacturer or distributor must update the company's sample/complimentary supply request forms to state the TDDD license requirements and obtain an attestation of a prescriber's exemption from TDDD license requirements if claimed.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

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