LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA publishes final guidance on postmarket safety reporting requirements for combination products and their constituent parts

The FDA released final guidance detailing postmarket safety reporting (PMSR) requirements for combination products and their constituent parts—medical products that combine devices, drugs and/or biologics—that have received marketing authorization from the agency.

In response to growing interest from manufacturers looking to develop medical products that combine devices, drugs and/or biologics, the FDA released final guidance detailing PMSR requirements for combination products and their constituent parts. The document addresses ways to comply with PMSR requirements issued by the agency in 2016, codified in 21 CFR Part 4, Subpart B.

To ensure consistent and complete reporting while avoiding duplication, Section I of the guidance explains that its aim is to help applicants comply with PMSR requirements for combination products that received FDA marketing authorization, and briefly describes the subsequent sections. Section II of the guidance offers general information on combination products and how the agency regulates them. Section III summarizes the final rule and provides an overview of those entities subject to the rule as well as the safety reporting requirements applicable to them. Section IV further describes specific combination product PMSR report types. Section V offers guidance on how, where and when to submit PMSR reports to the agency. And Section VI gives hypothetical scenarios showing how to comply with certain combination product PMSR requirements.

The guidance also looks at other PMSR requirements applicable to entities not covered by the rule that are involved in the manufacture or marketing of combination products. Such entities include manufacturers, distributors and packers named on the label of over-the-counter combination products not subject to premarket review that include a drug constituent part; nonapplicants listed as a manufacturer, distributor or packer on the label of a combination product that has a drug or biological product component; manufacturers, distributors and packers of unapproved prescription combination products that include a drug constituent part; manufacturers, user facilities and importers for combination products that include a device constituent part; and manufacturers and importers of combination products that include a device constituent part.

The document details how makers of combination products can comply with a final rule issued in 2016 that established safety report submission requirements based on all the constituent parts of the product in addition to application-type reporting. That rule also required makers of constituent parts to share certain postmarket safety information with one another.

The FDA does not plan to enforce 21 CFR 4.102(c) and (d) (constituent part-based PMSR requirements), 4.104(b)(1) and (b)(2) (submission process for constituent part-based Individual Case Safety Reports (ICSRs)), and 4.105(b) (recordkeeping requirements) until:

- July 31, 2020, for combination product applicants using the FDA Adverse Event Reporting System and Electronic Medical Device Reporting System to report ICSRs; and
- Jan. 31, 2021, for combination product applicants using the Vaccine Adverse Event Reporting System to report ICSRs.

OPDP issues untitled letter to CooperSurgical for advertisement for intrauterine contraceptive device flagged under Bad Ad program

The Office of Prescription Drug Promotion (OPDP) issued an untitled letter to CooperSurgical after determining a direct-to-consumer (DTC) advertisement for a contraceptive device made false or misleading representations about the product by failing to disclose important risk information. The letter calls into question the net effect of repetitive claims about the contraceptive being hormone-free and lack of disclosure of material risk information.

The FDA's OPDP issued its fourth enforcement letter of the year to CooperSurgical after it received a complaint about an ad for the intrauterine contraception ParaGard under its Bad Ad program. The FDA reviewed the DTC advertisement, which was submitted under Form FDA 2253, and determined that it made false or misleading representations about the intrauterine device, misbranding it under the Federal Food, Drug, and Cosmetic Act (FDCA) and rendering its distribution violative.

The untitled letter raises concerns about the failure to reveal important risk information for ParaGard. Although the advertisement includes a statement in superimposed text (SUPER) cautioning patients with "certain cancers" not to use the product, the ad does not disclose additional contradictions for the product, such as acute pelvic inflammatory disease (PID). Similarly, while the advertisement includes a statement as an audio voice-over directing patients to call their health care practitioners if they experience pain or pelvic infection, it does not sufficiently disclose the material fact that ParaGard is associated with an increased risk of PID, nor does it communicate the warning for expulsion of the

product. Without such information, the advertisement misleadingly suggests the product is safer than it has been demonstrated to be.

The letter also takes issue with how certain risk information is communicated, noting that the presentation of risk information in the "major statement" of risks through audio and SUPERs is undermined by the corresponding use of fast-paced visuals of choreographed dancing and music. The OPDP determined that the use of "compelling and attention-grabbing visuals," which are unrelated to the risk information in the audio and SUPERs, may make it more difficult for consumers to understand the risk information.

The OPDP also raised concerns with the representation of risk information only in the visual portion of the advertisement, as TV advertisements are supposed to provide information on contraindications and major side effects in the audio portion as well. In addition, displaying the risk information in SUPERs while disclosing unrelated information in the audio portion of the advertisement may minimize the representation of risk information. For instance, the advertisement discloses information about the contradiction for certain cancers in SUPERs while the audio portion directs patients to call a provider if they experience pain, pelvic infection or a missed period.

Taken together, the issues cited about the advertisement undermine the communication of risk information, downplaying the risks associated with the use of the product. Going further, however, the OPDP also criticized the net impression created by ParaGard as a result of the "overwhelming, repetitive nature" of claims that it is hormone-free. Though the statement that ParaGard is hormone-free is true, the OPDP found the overuse of the claim, paired with the misleading impression of risk, created a misleading impression of the safety profile of ParaGard, which is associated with many of the same serious risks as other long-acting reversible contraceptives.

The letter directs CooperSurgical to immediately cease violating the FDCA and to provide a list of all promotional materials that contain similar violations along with a plan for discontinuing use of the violative material.

FDA releases user fees for FY2020, increasing some and decreasing others

The FDA published the user fee amounts it anticipates collecting in FY2020 from drugmakers, generics makers, biosimilar manufacturers, medical device makers and outsourcing facilities that produce compounded drugs.

The FDA published the user fees it expects to collect in FY2020 under the Prescription Drug User Fee Act (PDUFA VI), Generic Drug User Fee Amendments (GDUFA II), Biosimilar User Fee Amendments (BsUFA II), Medical Device User Fee Amendments (MDUFA IV) and Outsourcing Facility Fees.

The base revenue for FY2020 PDUFA VI fees is $1 billion prior to adjustments, with a final target revenue of $1,001,479,592. The agency says application fees will be set to generate 20% of the total target revenue amount, or $214.9 million, in FY2020. It estimates 2,740 program fees will be invoiced in FY2020, with 54 waivers and refunds granted and 44 exemptions based on orphan drug exemptions. The fee rates for applications requiring clinical data will be $2,942,965, up from $2,588,478 in FY2019, while those for applications not requiring clinical data will be $1,471,483, up from $1,294,239 in FY2019.

For GDUFA II, the FDA says user fees should total $493.6 million annually, adjusted for inflation. The base revenue amount for FY2020 is $501.7 million, or $513,223,000 after factoring inflation. Abbreviated new drug application (ANDA) fees will make up

33% of that amount, or $169,363,590. For FY2020, the FDA expects approximately 953 original ANDAs will be submitted and incur filing fees. The agency also estimates 444 fee-paying drug master files (DMFs) for FY2020, or about $25.7 million. The fee for a facility located outside the U.S. will be $15,000 higher than the amount for a facility located in the U.S. in order to cover the extra cost of conducting an inspection. Finished dosage form (FDF) and contract manufacturing organization (CMO) facility fee revenue will make up 20%, or $102,644,600. For FY2020, the FDA expects 192 FDF domestic, 248 FDF foreign, 75 CMO domestic and 99 CMO foreign facilities. Active pharmaceutical ingredient (API) facility fees will account for 7%, or $35,925,610. The FDA identified 624 API facilities, including 76 domestic and 548 foreign. The GDUFA II program fee will make up 35% of fee revenue, or $179,628,050. The FDA estimates there will be 199 applicants in the small-business tier, 63 applicants in the midsize tier and 63 applicants in the large-size tier.

For FY2020, the base revenue amount for BsUFA II is the FY2019 inflation-adjusted fee revenue amount of $40,947,463. The FDA estimates receiving 10 biosimilar biological product applications requiring clinical data for approval in FY2020, providing a total of $17,467,450 in revenue, or 42% of the FY2020 target revenue amount. It also anticipates 42 biosimilar biological product program fees will be invoiced, providing an estimated $12,774,804, or 30% of the FY2020 target revenue amount. Further, the agency expects a total of 99 biosimilar biological product development (BPD) fees to be assessed in FY2020, representing $11,680,746, or 28% of target revenue.

For MDUFA IV, the Federal Food, Drug, and Cosmetic Act (FDCA) establishes a base fee of $4,760, with no reduction in the registration fee for small businesses. The total revenue amount for FY2020 is $221,603,174 after inflation. The premarket application fee will be $340,995, up from $322,147 in FY2019, while the de novo classification request fee will be $102,299, up from $96,644 in FY2019. The 180-day supplement fee is set at $51,149, up from $48,322 in FY2019, and the 510(k) premarket notification submission fee will be $11,594, up from $10,953 in FY2019.

For outsourcing facilities, the FDCA establishes the FY2020 rates for the small-business establishment fee at $5,599, the nonsmall-business establishment fee at $18,288 and the reinspection fee at $16,798 for outsourcing facilities. The FDA expects 14 entities will qualify for small-business exemptions and pay the reduced fee for FY2020, and it expects 85 outsourcing facilities, including 14 small businesses, to be registered with the FDA in FY2020.

Program	FY2020
PDUFA VI	
Applications:	
Requiring clinical data	$2,942,965
Not requiring clinical data	$1,471,483
Program fee	$325,424
GDUFA II	
Applications:	
ANDA	$176,237
DMF	$57,795
Facilities:	
API – Domestic	$44,400
API – Foreign	$59,400
FDF – Domestic	$195,662
FDF – Foreign	$210,662
CMO – Domestic	$65,221
CMO – Foreign	$80,221
GDUFA program:	
Large-size operation generic drug applicant	$1,661,684
Midsize operation generic drug applicant	$664,674
Small-business operation generic drug applicant	$166,168

Program	FY2020
BSUFA II	
Initial BPD	$117,987
Annual BPD	$235,975
Reactivation	$235,975
Applications:	
Requiring clinical data	$1,746,745
Not requiring clinical data	$873,373
Program	$304,162
MDUFA IV	**Standard Fee (Small-Business Fee)**
Premarket application, a product development protocol submitted under Section 515(f) of the FDCA or a Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act	$340,995 ($85,249)
Premarket report (submitted under section 515(c)(2) of the FDCA)	$340,995 ($85,249)
Efficacy supplement (to an approved BLA)	340,995 ($85,249)
Panel-track supplement	$255,747 ($63,937)
De novo classification request	$102,299 ($25,575)
180-day supplement	$51,149 ($12,787)
Real-time supplement	$23,870 ($5,968)
510(k) premarket notification submission	$11,594 ($2,899)
30-day notice	$5,456 ($2,728)
513(g) request for classification information	$4,603 ($2,302)
Annual fee type:	
Annual fee for periodic reporting on a class III device	$11,935 ($2,984)
Annual establishment registration fee	$5,236 ($5,236)
Outsourcing Facility Fees	
Qualified small-business establishment fee	$5,599
Nonsmall-business establishment fee	$18,288
Reinspection fee	$16,798

FDA final guidance details recommendations on child-resistant packaging statements in drug labeling

The final guidance addresses the information applicants, manufacturers, packagers and distributors should include in child-resistant packaging (CRP) statements if they choose to include such statements in product labeling for prescription and over-the-counter (OTC) drug products.

The FDA published final guidance outlining which information should be included to support child-resistant packaging statements in drug product labeling for new drug applications (NDAs), abbreviated NDAs (ANDAs), Biologics License Applications (BLAs) and application supplements. The guidance includes labeling recommendations for nonprescription drug products approved under NDAs or ANDAs, as well as those marketed under the OTC drug review. The final guidance comes two years after a draft version was released, and the FDA says it considered comments submitted on the public docket to clarify the document.

In general, the guidance notes that if an applicant, manufacturer, packager or distributor (collectively referred to as firms) decides to include labeling statements to indicate a product is packaged using CRP, the CRP should be described with words rather than abbreviations or symbols, which may be misunderstood. Given that CRP statements address how a product is supplied from a manufacturer, rather than dispensed by a pharmacist, the FDA prefers the term “supplied” rather than “available.” To ensure CRP statements are not deemed false or misleading, which may render a product misbranded, the FDA notes they should be used only when drug product packaging has been shown to comply with U.S. Consumer Product Safety Commission (CPSC) regulatory standards and test procedures for CRP.

This guidance aims to help ensure that drug product labeling is clear, useful, informative and, to the extent possible, consistent in content and format.

The guidance outlines several specific recommendations for prescription and nonprescription products, including:

- **Prescription drug products:** CRP information should be provided in the section of labeling that addresses how to supply, store and handle the product and should be clearly linked to a particular package, especially in instances in which multiple packages are supplied and not all have been shown to be child-resistant. If a commercial container with a CRP is meant to be dispensed directly to patients, the CRP should be included in the patent labeling under the heading "How should I store Drug X?" and should be consistent with the CRP in the full prescribing information.
- **Nonprescription drug products:** Although FDA regulations do not specify where CRP statements should be placed on labeling for nonprescription drugs, the guidance recommends it be included under the subheading "Other information" within the storage statement.

For both prescription and nonprescription drugs, the FDA notes that a CRP—such as "this package is child-resistant" or "child-resistant package"—may be provided on carton labeling or container labels as long as there is enough space to include it alongside required information. If space allows, a firm may include a storage statement in tandem with the CRP statement to recommend the package be kept out of reach of children. Per the guidance, CRP statements for prescription drugs are best displayed on the side panels of carton labeling and container labels, near the storage information. For nonprescription drugs, the text is best placed on the principal display panels.

The guidance notes that firms should provide written verification that the CRP meets CPSC requirements and recommends they retain the data used to support CPSC standard requirements. For products approved under an NDA, a BLA or an ANDA, verification that the CRP meets CPSC standards should be provided in the container closure section of the Electronic Common Technical Document. If a firm decides to make changes to the package or labeling after approval, submissions for changes to add CRP statements on labeling should also provide written verification that the CRP meets CSPC standards. While there is no established process for submission of a written verification that nonprescription drug products under an OTC monograph adhere to CSPC standards, the FDA recommends that firms that opt to include a CRP statement retain the data demonstrating the packaging meets applicable standards and follow the labeling recommendations provided.

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