FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance to limit orphan drug designations for certain pediatric subpopulations

The finalized guidance makes clear the FDA will no longer grant orphan drug designations for pediatric subpopulations of common diseases and represents the agency's efforts to close a loophole through which drugmakers were exempted from conducting pediatric trials under PREA. The guidance indicates that pediatric-subpopulation designations that have already been granted will not be affected.

The FDA finalized guidance outlining its intention to no longer grant additional orphan drug designations to sponsors of drugs and biological products for pediatric subpopulations of common diseases, defined as those with an overall prevalence of 200,000 or more. The guidance is meant to address what the FDA views as a loophole because securing a pediatric subpopulation designation doesn't mandate that studies be carried out in pediatric populations. This means that sponsors may use the designation to be exempted from the studies the designation was actually meant to incentivize.

Under the Orphan Drug Act, the FDA may grant orphan designation for valid orphan subsets of a common disease, including for pediatric populations for which prevalence is less than 200,000 and for treatments whose use in the adult population would be inappropriate. The FDA may also grant orphan drug designation if the pediatric version of the disease differs from the disease in the adult population and prevalence remains less than 200,000.

Typically, the FDA has also granted pediatric-subpopulation designations to drugs used in pediatric subpopulations of common diseases if the prevalence in the pediatric subpopulation in the U.S. is less than 200,000, which is referred to as a rare pediatric subpopulation. The practice was adopted prior to the enactment of legislation to promote the study of treatments in pediatric populations, as sponsors had often failed

to include pediatric populations in their research and development plans. However, several programs have since been implemented, including the 2003 Pediatric Research Equity Act (PREA), which requires certain marketing applications to include a study in pediatric subpopulations.

According to the guidance, PREA and other legislative efforts have been successful in promoting pediatric evaluation of drugs and biologics, while efforts such as the rare pediatric disease priority review voucher program have incentivized and encouraged efforts to study drugs in rare pediatric diseases. As such, the pediatric subpopulation designation is no longer needed to promote pediatric trials. Instead of its intended purposes, the pediatric subpopulation designation has been used as a means to secure an exemption from pediatric study requirements under PREA for certain applications containing new active ingredients, indications, dosage forms or regimens, or route of administration.

The guidance also notes that while the FDA doesn't intend to grant pediatric subpopulation designation any longer, it will continue to grant orphan drug designation to drugs if:

1. A rare disease includes a rare pediatric subpopulation.
2. A pediatric subpopulation represents a valid orphan subset.
3. A rare disease is actually different in the pediatric population versus the adult population.

FDA drafts guidance on first-in-human expansion cohort trials for accelerated cancer drug development

The draft guidance discusses which treatments may be appropriate for an expedited development plan using an expansion cohort trial, which draws together the traditional three phases of trials into a continuous trial. The guidance is meant to serve as a launch point for future discussions between the FDA and other stakeholders on issues related to clinical trial design.

The FDA issued draft guidance on the design and conduct of first-in-human (FIH) trials to accelerate the development of cancer drugs using expansion cohort designs, which simultaneously accrue patients in multiple cohorts that assess different aspects of the drug. The guidance addresses the characteristics of products suitable for such trials, what information should be included in investigational new drug (IND) applications, when to interact with the agency and what safeguards to implement to protect patients.

FIH multiple expansion cohort trials are designed to accelerate development by seamlessly proceeding through the initial development stage of dosage determination to individual cohorts testing typical Phase 2 objectives, such as anti-tumor activity. These trials have a single protocol and begin with a dose-escalation phase that continues into three or more individual patient cohorts, which can be launched with limited safety assessment and have cohort-specific objectives. Given the risk of exposing patients to drugs with minimally characterized toxicity profiles, however, these trials also present risks and challenges. To offset such risks and challenges, the guidance recommends that sponsors have in place the infrastructure to streamline trial logistics, facilitate data collection, rapidly incorporate plans to address emerging data, and quickly provide interim data to investigators, institutional review boards and regulators.

Per the guidance, FIH multiple expansion cohort trials should be restricted to investigational drugs for indications and patient populations in which the potential benefits merit increased risks. In addition, the patient population should be restricted to patients with a serious disease for which no curative therapies are presently available. The FDA notes that drug formulations that contain drug substances with attributes to permit relatively straightforward bridging between early drug formulations and

marketing formulations – such as Class I designated biopharmaceuticals, nonliposomal injections and immediate-release oral drugs – may be better suited to such accelerated trial protocols. The guidance notes that the FDA anticipates the investigational drugs tested in FIH multiple expansion cohort trials will have the potential to meet the criteria for breakthrough therapy designation as development progresses, supporting the accelerated development pathway.

The guidance indicates that FIH multiple expansion cohort trials need to be supported by scientific rationale and carefully designed. Information should be provided in clinical protocols identifying key elements for each cohort, such as endpoints, eligibility and statistical considerations to support the sample size. Per the guidance, protocols should include all the elements for clinical protocols, and sponsors should consider whether additional details may be warranted to allow the FDA to ensure the risks to patients aren't unreasonable and the goals of the trial can be achieved. The FDA cautions that failure to provide an adequate level of detail in the protocol (and any amendments) on the goals and conduct of the clinical protocol in a well-defined population in which risks may be acceptable could result in a clinical hold.

In terms of safety, the guidance notes that a systematic approach should be implemented to ensure sponsors can rapidly communicate serious safety issues and INDs should include a plan for submitting a cumulative safety summary on a periodic basis. It also notes that an independent safety assessment committee or independent data monitoring committee should be established for all FIH multiple expansion cohort protocols. The guidance also recommends that a central institutional review board be implemented. The guidance also recommends that sponsors request a pre-IND meeting with the FDA to discuss development plans that include an FIH multiple expansion cohort trial. If altering protocols in a way that would substantively affect the safety or scope of the protocol, sponsors should alert the FDA.

FDA lays out expected user fees for FY2019 as Senate approves spending bill

The FDA issued its annual list of user fees for the upcoming fiscal year, with most programs experiencing an uptick but biosimilars slated to see a slight decline. The fee schedules come amid a Senate vote approving a funding bill that will see the CDER receive $1.72 billion in funding.

The FDA published the user fee amounts it expects to collect in FY2019 for pharmaceuticals, biosimilars, medical devices, generics and outsourcing facilities producing compounded drugs. Following the publication of the user fees, the Senate voted to approve a funding bill that will grant the FDA $5.4 billion in funding in FY2019, authorizing the agency to spend $960.6 million in prescription user fees, along with $501.4 million in generic user fees, $40.9 million in biosimilar user fees and $196.7 million in medical device user fees. Of note, the amounts approved in the Senate bill don't align with the target revenues the FDA used in calculating its user fee rates for the year.

For user fees under the Prescription Drug User Fee Amendments of 2017 (PDUFA VI), program fees will increase slightly in FY2019, to $309,915. Application fees will also see a jump, with fees for applications requiring clinical data rising to $2.59 million from $2.41 million, and the fee for those not requiring clinical data set at $1.29 million, up from $1.21 million in FY2018. Notably, supplement fees have been removed under PDUFA VI. After adjustments, per the statute, the FDA expects revenue for PDUFA VI user fees to be $1.01 billion. Application fees will account for 20% of the revenue, with a target of $202 million. The FDA anticipates that 2,683 program fees will be invoiced in FY2019, with an estimated 75 waivers and reductions granted.

Under Medical Device User Fee Amendments of 2017 (MDUFA IV), the FDA expects to raise $207 million. As with the prescription drug fees, the user fees for medical devices are slated to increase in FY2019,

though reduced fees are available for small businesses with gross receipts or sales of less than $100 million. The fee for a premarket application, including BLA, premarket report or BLA efficacy supplement, is set at $322,147, a slight increase over $310,764 in FY2018. Fees for de novo classification requests are set to be $96,644, while fees for 510(k)s are set to be $10,953. In addition, the FDA has set a $4,884 establishment registration fee for FY2019.

For fees under the Biosimilar User Fee Amendments of 2017 (BsUFA II), the agency expects to generate revenue of $38 million. As part of its commitment to reduce the BsUFA II carryover reserve, the FDA applied an adjustment to lower the target revenue by $2.1 million. Unlike medical devices and pharmaceuticals, the user fees for biosimilars won't increase in FY2019. The agency decided to maintain the same application fee level from FY2018, at $1.75 million, providing about $15.7 million and accounting for 40% of the target revenue. Program fees will also stay the same, at $304,162. The FDA expects that 23 program fees will be invoiced in the upcoming year, bringing in $6.9 million and accounting for 18% of target revenue. With expectations that a total of 87 participants will be involved in the biosimilar biological product development (BPD) program in FY2019, the FDA expects to raise $16.1 million from BPD fees. The initial and annual BPD fees are slated to be $185,409, dropping from $227,213 in FY2018.

The FDA also set user fees for generic drugs under the Generic Drug User Fee Amendments of 2017 (GDUFA II) and outsourcing facilities. Application fees for abbreviated new drug applications are slated to go up slightly, from $171,823 to $178,799. Fees for outsourcing facilities include a qualified small-business establishment fee of $5,461, an establishment fee for non-small businesses of $18,375 and a reinspection fee of $16,382.

Table: Select fees for prescription drugs, medical devices and biosimilars

Program	FY2018	FY2019
PDUFA VI		
Applications requiring clinical data	$2,421,495	$2,588,478
Applications not requiring clinical data	$1,210,748	$1,294,239
Program Fees	$304,162	$309,915
MDUFA IV (Small-Business Fee)		
Premarket application and premarket report	$310,764 ($77,691)	$322,147 ($80,537)
De novo classification	$93,229 ($23,307)	$96,644 ($24,161)
510(k) premarket notification	$10,566 ($2,642)	$10,953 ($2,738)
Annual fee for periodic reporting (Class III device)	$10,877 ($2,719)	$11,275 ($2,819)
Annual establishment registration	$4,624 ($4,624)	$4,884 ($4,884)
BsUFA II		
Initial and annual BPD	$227,213	$185,409
Applications requiring clinical data	$1,746,745	$1,746,745
Applications not requiring clinical data	$873,373	$873,373
Program fees	$304,162	$304,162

OIG report points to some inconsistencies, inaccuracies in Open Payments data

The review looked at 11.9 million records and found instances of data inconsistencies, inaccuracies and inconsistent information, including issues with drug and device names. The OIG provided recommendations to improve the accuracy and consistency of the data, including improved validation rules to ensure the proper drug and device names are reported.

The Department of Health and Human Services' Office of Inspector General (OIG) published a review of Open Payments data, which makes public the financial relationships between health-care practitioners and industry. The Open Payments program is meant to encourage transparency by highlighting the nature and extent of these financial relationships – which may take the form of consulting fees, research payments, and investment or ownership interests – while discouraging the development of inappropriate relationships. However, achieving such goals requires that accurate and complete data be reported. As such, the OIG reviewed data published on the Open Payments database in 2015 to ascertain whether data were complete, accurate and consistent.

The OIG found that 11.9 million records were published on the website in 2015, of which less than 1% (11,463) were missing data elements. The most common missing data element from records related to physicians' financial interests was the physician specialty, the OIG found. Generally, the information missing wouldn't stymie a consumer's ability to secure information about the financial relationship between a provider and industry, the OIG determined.

The OIG further found a small percentage of records included inaccurate, imprecise or inconsistent data, including imprecise or inaccurate product names, national drug codes (NDCs) not contained in the FDA's database and payment dates beyond the reporting year. Among the issues identified were at least 10,000 records in which drug and device names weren't specific enough to identify the products. In 6,630 records, the OIG noted that the record indicated a payment was related to a covered drug or device, but the drug-name or device-name field indicated "no product." The OIG also noted many instances of records citing overly broad therapeutic areas and product categories, observing that about 6% of device-related records included the name of a body part rather than an actual device name. The report notes that such a practice makes it difficult to determine whether devices used in consumers' care may be associated with payment received by their practitioners.

Overall, the office noted that about 9% of records (1.1 million) contained NDCs that weren't found in FDA databases or other drug information sources – records linked to $302 million in payments. The OIG noted that while the system validates that the NDC provided for a given payment is in the correct format, it doesn't validate the code. The OIG noted that 1,265 NDCs were associated with payments, 110 of which weren't in the databases or other resources.

Based on its findings, the OIG recommends that CMS:

- Review its validation processes to ascertain why records missing data were accepted.
- Bolster its validation rules and revise data element definitions to ensure that actual drug and device names be reported.
- Refine the definition of the device-name data element to prevent records from claiming broad therapeutic areas and product categories.
- Implement a validation procedure to ensure NDCs are valid.