

# **FDA Week**

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## **Report Shows Safety, Efficacy Data As Reason For First Cycle Review Failure**

New molecular entities and biologics that fail to get FDA approval in the first cycle but are successful in subsequent reviews often lack sufficient data about the safety or efficacy of the product, according to new findings from a pharmaceutical research consulting firm. The study comes as an FDA official touted a high number of first-cycle approvals last year and as FDA begins implementing product review changes under the Prescription Drug User Fee Act V that will allow for more transparency and communication between the agency and sponsors.

Parexel International, a pharmaceutical clinical research consulting firm, said the lack of safety, efficacy or chemistry manufacturing controls information topped the list of reasons why more than a third of new molecular entities received multiple reviews by FDA's drug center before gaining approval. The firm's study analyzed data from January 2009 to the end of 2012.

Mark Mathieu, Parexel's director of strategic research, said the study was done at the behest of drug companies interested in why applications were stalling in the first review cycle.

"It was something that many companies asked us to do," he said. "Certainly a lot is at stake and I think there is very little evidence of companies bouncing right back after failing to get first cycle approval."

Mathieu also said that because the company only looked at products that failed initially but were later approved, it was able to determine that review issues were due more to the execution of sponsors' applications than the products themselves.

Safety, chemistry manufacturing controls and efficacy concerns led in reasons cited by FDA for not approving new molecular entity applications during the first review. Safety questions were raised in about 80 percent of the cases reviewed, Mathieu said. Dose related issues were also present in about 40 percent of first cycle failures.

Mathieu said FDA often asked companies to show data exploring the full dosing range of the products, reflecting the agency's sensitivity to dosing issues in recent years in light of issues with opioids and other commonly abused drug classes.

Safety issues were also frequently cited in failed biologics applications, but efficacy concerns were less significant, according to the study. Instead, manufacturing controls and product quality issues were identified as key issues in those cases. Concerns about Risk Evaluation and Mitigation Strategies were also prominent in 75 percent of rejected biologics applications.

Mathieu said one interesting finding was that oncology drug sponsors were less likely to resubmit products that failed the first cycle review.

**"I think the cancer angle is very interesting," he said. "No cancer product has ever failed in the first review cycle and then come back to get approval in a subsequent review."**

That could be due to the adept manner in which FDA's oncology review division is able to quickly assess the effectiveness of products and shepherd those deemed most effective through the review process as well as the fact that many oncology companies are small and cannot afford to invest more time and money in conducting the additional clinical trials needed to address the efficacy issues, Mathieu said.

He added that the one exemption was an oncology drug that failed in the first cycle, but was later approved by the agency after the company changed its indication.

Parexel's findings come as FDA says it has increased the number of first-cycle approvals for new molecular entities and begins working toward goals to enhance the review program for drugs and biologics under PDUFA V.

FDA drug center Deputy Director for Regulatory Programs Doug Throckmorton said during a talk at the Biotechnology Industry Organization International Convention last week that 81 percent of all new molecular entities were approved in the first cycle in 2012. That data shows FDA's drug center has improved its process to allow for a transparent, efficient review process to foster development, he said.

In its PDUFA reauthorization goals the agency negotiated with industry for 2013-2017, FDA must enhance review

transparency for new molecular entities and original biologics license applications through a new program that will encourage sponsors to have a presubmission meeting with the agency, have the application completed according to parameters outlined at that presubmission meeting, and provide opportunity for a mid-cycle meeting to update the applicant on the status of their review.

Jay Siegel, chief biotechnology officer at Janssen Research & Development, said the program should help ensure that companies submit complete data in their initial applications.

“The program should help in a couple of regards,” he said at a recent event. “One is there is incentive to ensure that industry submits applications that are more complete. But also there is a lot of focus on efforts to encourage the FDA and create the process to ensure that issues that might delay approval are identified earlier and are communicated to the sponsor earlier in a way that optimizes the opportunity for resolution and approval.”

Mathieu also said the metrics Parexel used support the idea that more interaction between FDA and sponsors during the first cycle review will improve the possibility of approval and that, overall, the company agrees that FDA’s first cycle approvals appear to have increased greatly. — *Stephanie Beasley*