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Watching The Clock Stop: US/EU Regulatory Review Time Parity In Sight, Study Suggests

by Bridget Silverman

European Union reform proposals could reduce 'clock stop' time in drug reviews, which a new study identified as the primary driver of longer review times at the EMA compared with the US FDA.

"Clock stop" time in European Medicines Agency drug reviews accounts for the biggest difference between US and European review duration, according to a recent study published in the Annals of Internal Medicine.

The findings provide support for European Union reform proposals that could reduce the "clock stop" periods when drug evaluation is stopped while the applicant prepares answers to questions from the regulatory agency, the 17 October 2023 publication indicates.

"A proposed policy change in the EU that would enable the EMA to provide scientific support to applicants before submission could align the EU with the United States and could expedite the review process in the EU," the authors stated, led by Kerstin Vokinger (University of Zurich and Harvard Medical School) and Miquel Serra-Burriel (University of Zurich).

"When focusing on the time during which the agencies are actually reviewing the application, we found similar review durations across the three agencies," the authors reported. "By contrast, when clock stop durations are included in the review times, our study results are aligned with the finding in previous studies that the US drug review is substantially faster than that in Europe."

"Thus, the differences in review times between the United States and Europe can be explained by the implementation of different review systems," they concluded.

The European Commission's proposals for modernizing the medicines regulatory framework were released on 26 April 2023 and kicked off what is expected to be a lengthy legislative process

with a 20 September presentation to a European Parliament committee. (Also see "*Lawmakers Finally Kick Off Debate On EU Pharma Overhaul*" - Pink Sheet, 18 Sep, 2023.)

The draft regulation would reduce regulatory review time at the EMA from 210 days to 180 days, a would shorten the time the commission has to make a decision on marketing authorization following an EMA recommendation from 67 days to 46 days. The package includes earlier regulatory and scientific support for "promising" new medicines to facilitate their rapid approval. (Also see "*EU Pharma Reform Proposes Cuts In Regulatory Protections & Faster Drug Approval Times*" - Pink Sheet, 26 Apr, 2023.)

"Before the submission of the application, the EMA will provide scientific support to the applicants so that less information will be missing in the initial application and clock stop delays will be reduced," the authors said.

In the US, they noted, "applicants typically have a meeting with the FDA before the application, when the FDA has an opportunity to provide feedback about some of the issues that are likely to be encountered."

Quantifying Differences

For the study, Vokinger, Serra-Burriel et al. calculated the regulatory review duration of all new drugs, including both first and supplemental indications, approved between January 2011 and December 2020 in the EU and US. (The study also included data from Swissmedic for new active substances.)

The primary outcome of the study was "review duration subtracting clock stop duration," and on this measure the EMA was on average only 6% slower compared with the FDA.

However, when the clock stop duration was included, the difference increased markedly. The EMA was 29% slower than the FDA on for the secondary outcome of total review time. Swissmedic was 39% slower.

"Further statistical analyses showed that clock stop time and total review time were strongly associated, explaining approximately 74% of the variation in total review time," the authors said.

The primary analysis cohort included 241 drugs approved in the US, EU and Switzerland. Of those drugs, 128 earned supplemental indications in the US, for a total of 331 supplemental indications; in the EU, 87 drugs had supplemental indications for a total of 205.

"The overall median review duration from submission to approval for drugs submitted to all 3 authorities and subtracting the clock stop period was 39 weeks in the US, 44 weeks in the US, and 44 weeks in Switzerland," the study reports.

The authors also compared review times within each drug, finding that the EMA took a median of 3.7 weeks longer than the FDA.

Cancer And Other Priorities

The analysis published in Annals of Internal Medicine went beyond prior studies comparing US and European review times, which were limited to cancer drugs or first indications of older drugs, the authors noted.

Cancer therapies still stand out from the rest of the pipeline in the analysis. Most of the supplementary indications identified were in oncology. And in the US and Switzerland, "the fastest median review durations were for antineoplastics," the study reports.

In the EU, anti-infective drugs were fastest.

The study also found "similar" differences in submission times compared with past studies of cancer drugs showing that FDA received drugs earlier. However, "our estimated differences in submission times of new applications between the United States and Europe were only marginal," the authors said.

"International cooperation may have helped reduce these differences across countries," they continued. The study highlights the FDA's Project Orbis, a collaborative review program launched in 2019 to speed access to new cancer therapies by establishing concurrent submission and review between regulatory agencies. The health authorities of Australia, Brazil, Canada, Israel, Singapore, Switzerland, and the UK are participants in Project Orbis.

Across indications, review duration was shorter for drugs that used at least one expedited pathway, the study reported: reviews were 45% faster in the US, 44% faster in the US, and 42% faster in Switzerland. Such drugs made up a majority (66%) of the FDA approved new drugs in the sample, but only 21% of EMA and 34% of Swissmedic approvals.

The FDA and EMA also saw similar effects on review performance for supplemental indications, where the FDA was 26% faster for supplemental than for first indications and the EMA was 27% faster for supplements. However, the median total review duration for supplemental indications was 26 weeks in the US and 40 weeks in the EU.

"The proportion and probability of approved supplemental indications rated as having high therapeutic value have been substantially lower than those of first indications," the authors reported.