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New bill calls for more data and new development approaches on orphan drug development

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The top line: A bipartisan bill introduced earlier this month in the Senate seeks to make some modest changes to the Orphan Drug Act – and creates the groundwork for substantial changes in the near future.

First, let's talk about the legislation.

- **The bill is S.4071, the Helping Experts Accelerate Rare Treatments Act of 2022,** and is cosponsored by Sens. Robert Casey (D-PA) and Tim Scott (R-SC). The bill is similar to a bill by the same name introduced in 2021 in the House of Representatives by Rep. Paul Tonko (D-NY). While the bill was introduced on April 7th, the text of the legislation was only made public today.
- **The bill would make changes to the current Federal Food, Drug and Cosmetic Act with respect to FDA's ability to consult with stakeholders.** Specifically, 21 USC §360bbb–8(a)(1) would be amended so that the FDA could consult with external stakeholders "at any time" (rather than just at "a time") during the review process, and that such consultations could include

patients and patient groups "impacted by the rare disease or condition," as well as "at least one expert … selected by such groups" as long as they don't have a conflict of interest. FDA would also be able to consult with general experts "in the science of small population studies" in the event that no expert is available due to existing conflict of interest – a common occurrence for ultra-rare diseases or conditions for which the few existing experts are likely involved in clinical development efforts.

- **The bill calls for an annual report on the activities of the FDA's Orphan Drug Program.** Specifically, the annual (or more frequent, if FDA desires – it often releases quarterly reports for similar programs) report would make note of all rare disease drug approvals, the number of applications for approval, and the number of such applications that are rejected or remain pending. Notably, the FDA makes available only limited information on orphan drug approvals, including the number of products approved, the number of drug approvals for New Molecular Entities (a.k.a., novel drugs), and the number of designations granted. The new information would offer additional insights into the state of the orphan drug program.
- **Other information could be helpful as well.** For example, the report would require the FDA to make available "the size of the affected population in the U.S. of each disease or condition addressed by an application" for an orphan drug. This is a critical piece of information that is missing from the current orphan drug designation database and is information that is often missing from Summary Basis of Approval documents as well. Standardized information could be helpful for regulatory research purposes, allowing researchers to see the size of affected populations.

Perhaps the most interesting part of the bill is that it would start a process to potentially make significant changes to the Orphan Drug Act.

- **Compare and contrast: FDA with EMA?** As AgencyIQ has previously explained , the E.U.'s system for categorizing orphan diseases for the purposes of incentives is different from the U.S. system. FDA relies on a flat number of patients to determine eligibility (200,000 or fewer affected persons), while the E.U. relies on a percentage-based approach (1 in 2,000 affected persons) which scales as the population changes. As the result of the U.S. approach, the threshold for meeting the definition of "rare" has become more difficult since the 1984 passage of the Orphan Drug Act. The bill calls for HHS to "enter into an agreement with the National Academies of Sciences, Engineering, and Medicine to examine and report on European Union safety and efficacy reviews of drugs for rare diseases and conditions, the use and sufficiency of existing mechanisms and tools of the Food and Drug Administration in ensuring that patient and physician perspectives are considered throughout such reviews, and opportunities to improve such reviews in the United States."
- **Among the potential points of improvement that NASEM will be charged with reviewing** include "any flexibilities, authorities, or mechanisms available in the European Union," how the European Medicines Agency (EMA) makes use of "supplemental data" during its review of orphan drugs, and FDA's processes for reviewing orphan drug applications (and in particular those intended to treat rare diseases or conditions affecting fewer than 20,000 persons).
- **NASEM's report is also set to make recommendations on how the FDA and Congress could improve the orphan drug**

development process, such as "new tools or mechanisms … to collect and consider external expertise." NASEM is also asked to develop "alternative processes" to resolve potential conflicts of interest that might arise from a reliance on experts in an ultra-rare disease or condition who are also potentially involved in the development of the relevant drug product.