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# On Site: Does Industry Need a Preclinical Database? Robert Califf Says Yes

FDA Commissioner Robert M. Califf, M.D., has suggested that establishing a government-sponsored database of preclinical studies could improve transparency in drug development and the ability of researchers to reproduce study results.

Califf, who made his comments at an event co-sponsored by the National Library of Medicine, said that data from preclinical studies, including work that both succeeded and failed, could be made publicly available on a website similar to ClinicalTrials.gov, a federally mandated registry and results database of clinical research trials conducted in the U.S. and around the world.

The proposal for an official preclinical database in the U.S. would likely face many obstacles if Congress or government officials decided to pursue the idea. Yet there is growing recognition that creating mechanisms that allow sponsor companies and academic researchers to share preclinical data could result in faster, more efficient drug development by helping researchers eliminate false leads and avoid replicating risky or unpromising research.

"Establishing a preclinical database is a good idea. It's novel. I haven't seen anything like this yet," said noted bioethicist Arthur L. Caplan, Ph.D., director of the Division of Medical Ethics at New York University Langone Medical Center. "Sharing information, especially about what hasn't worked, would be useful to the scientific community. It would be important to see the large-scale animal studies that don't go anywhere. People would be able to save time, money and effort."

The results of some preclinical studies are published as a short summary for compounds that reach the market. However, most preclinical data is not published or shared in public databases since the results from successful studies become trade secrets, while those from failed studies are often shelved. Yet Califf believes that disclosing preclinical data could help the industry address the long-standing challenge of reproducing major research results.

Sponsor companies are often unable to reproduce the published studies they relied on to identify new targets for drug development. Three years ago, for example, a former Amgen researcher reported trying to confirm findings published in 53 top journals before pursuing a particular line of cancer research, yet scientific findings were confirmed in only six cases. Other researchers reported similar difficulties. In 2011, a team at Bayer reported that only about 25% of published preclinical studies could be validated with enough evidence to justify further investment in the project. In some cases, clinical trials have been conducted based on preclinical study results that were not replicated in advance, and the studies subsequently failed. Peer-reviewed articles have estimated that at least 50% of published research cannot be reproduced.

Elizabeth Iorns, Ph.D., founder and CEO of the Science Exchange, a company that provides outsourced research services and promotes cooperation among scientists, said a preclinical database could be a valuable tool, particularly for validation studies. Iorns suggested that the initiative could include a preclinical database of replication studies, which would create a set of validated targets that pharmaceutical and biotechnology companies could use to develop drugs. Iorns noted, however, that federal funding would be needed for conducting replication studies that validated the exploratory results.

"At the moment, it's estimated that about 80% of results that are published from exploratory studies are never reproduced. No one really knows what results are real. A federally funded database of preclinical replication would prevent failed later-stage results built on initial findings that were presumed to be correct but later showed to be not reproducible," said Iorns, whose company's platform is used to publish major replication studies conducted in biomedical science. "It would be much more successful than individually trying to validate these results with very high failure rates."

Katharine A. Briggs, a research leader at the U.K.-based Lhasa Limited, a nonprofit that facilitates collaborative data sharing projects in the pharmaceutical industry, sees that preclinical data sharing has become more commonplace in recent years. Yet it has not become standard practice and is typically limited to special projects. The proprietary nature of this data, she said, means that initiatives to share preclinical data tend to be restricted to the scientific community or closed groups and often rely on an independent third party or "honest broker" to coordinate activities.

Lhasa Limited serves as the "honest broker" for several data-sharing initiatives, including the eTox consortium, which has compiled a database of preclinical toxicity data for drug compounds or candidates from 13 pharmaceutical companies and the public domain. The database, which is the cornerstone of a public-private partnership within the framework of the European Innovative Medicines Initiative, includes data from more than 7,200 preclinical repeat-dose studies on more than 1,800 drug candidates.

"For the industry, the benefits [of sharing preclinical data] include reduced attrition as a result of knowledge gained, potential improvements in in-silico predication of toxicity, plus reduced time and cost associated with getting a new drug to market as a result of pooling data, reducing animal usage and more informed testing strategies," Briggs said.

Establishing a federally mandated preclinical database equivalent to ClinicalTrials.gov in the U.S., however, would likely face many hurdles. Researchers at Duke University have found poor compliance with ClinicalTrials.gov reporting requirements, and questions have been raised about the accuracy of the data posted. Duke researchers also found a lack of enforcement when companies failed to meet reporting obligations. If a federal preclinical database was established, many believe that significant investments would be needed to upgrade both databases.

Another potential problem with the idea, according to Caplan, involves the fact that a larger number of animal studies are conducted compared to those conducted in humans, which means there would be a sizable amount of data to audit, monitor and transcribe into an accurate form for posting on a preclinical database. In addition, animal data is not 100% generalizable to humans.

"Animal studies are notorious for not being predictive," said Caplan. "You might have a big animal study where nothing happened, but that doesn't mean that it was a false lead. Researchers will hopefully understand that and still pursue leads that looked good in a lab."

Questions about proprietary issues also may be raised by sponsor companies if they were required to post results to a public website when preclinical studies showed early promise.

"A preclinical database similar to ClinicalTrials.gov is a good idea where the benefits of the data sharing outweigh the risks, as in the case of failed drug candidates. It is unlikely that industry would agree to share data on drug candidates still in development, as this would reveal proprietary information and, in the case of marketed drugs, I believe there would be concerns around data re-interpretation," said Briggs.

An FDA spokesperson said Califf's remarks reflected his own personal views, and there are no formal plans to establish a preclinical database at the FDA.

*— Karyn Korieth*

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