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Registries Rising: FDA Looking At TNF Inhibitors; AHRQ Updates Standards

The FDA Amendments Act of 2007 gave the agency many new safety powers and the potential for promotional restrictions and post-marketing fines have understandably received much industry attention. But FDA also appears to be drawing upon its beefed-up authority to increase use of a much older, low-tech safety effort: the patient registry.

Patient registries lack the dramatic impact that restricted distribution or a huge clinical trial can have in the minds of executives. Nevertheless, FDA sees them as critical tools to help answer key product safety questions.

The agency has used to its new authorities to compel registries for Forest's *Savella*, Amgen's *NPlate*, GSK's *Promacta*, and, most recently, Lilly's *Forteo*. Because registries are categorized as "studies" as opposed to "trials," FDA even has a lower regulatory threshold to meet when decide to make one a post-marketing requirement ("The Pink Sheet" DAILY, July 15, 2009).

But the agency may take a bigger step in this area – requiring a class-wide registry for TNF inhibitors. FDA recently updated the products' boxed warnings to highlight the risk of cancer in children, but is also "is working with manufacturers to explore new ways to further define the risk."

"One avenue under consideration is to establish a consolidated registry for children with rheumatic disease to collect more information on the risk of cancer among larger numbers of children than have been studied previously and among patients followed for a longer time," an FDA spokesperson said. "In addition, there will be continued pharmacovigilance. Additional studies or trials could be post-marketing requirements under FDAAA."

FDA laid some of the ground work for such a registry in a public workshop convened May 12-13 to discuss the concept of a "consolidated pediatric rheumatology observational registry."

In an interview, FDA's Lisa Mathis, the Office of New Drugs' associate director of pediatric and maternal health staff, declined to discuss the agency's specific thinking on whether to require a consolidated registry and what one might look like. But she did say, "If you look at some of the disease-based registries for pregnancy, most of those are actually run by outside groups who have expertise in doing disease-based registries with some support from industry."

"Those are usually public-private partnerships," Mathis noted.

Asked now long disease-based registries usually run, Mathis said, "There would be no time when you would want to stop that. You would have patients coming out of the registry in kind of a rotating basis. And every so often you would do interim analyses to pull out data and possibly apply it to a given product."

For an industry concerned about expanding FDA requirements, that may be particularly disheartening. Essentially, an FDA request for a registry produces what amounts to a perpetual user fee for safety efforts – albeit a rather small one and one that is not paid to FDA.

Registries are considered less onerous alternatives to clinical trials, and in certain populations such as children and pregnant women, seem to have a better chance of producing meaningful data.

The Best Way To Conduct A Registry

With registries increasing, so too will industry’s desire for clearer guidance on how to design and conduct them. FDA already has a guidance on pregnancy registries, and formally encourages their use in the proposed rule on pregnancy and lactation labeling (“The Pink Sheet,” Sept. 28, 2009).

“Within the Office of New Drugs, the pediatric and maternal health staff covers both pregnancy and pediatrics,” Mathis notes. “So we do try to coordinate our efforts and have actually worked with each other when we’re working with the divisions in order to provide some guidance for industry. But as of today there’s no formal guidance for industry in establishing a pediatric registry. And that may be something that in the future would be helpful.”

One issue to critical designing a good registry, Mathis noted, is ensuring good recruitment and retention, especially for long-term studies.

Other government agencies have more general guidance. The Agency for Healthcare Research and Quality issued a “User’s Guide to Registries Evaluating Patient Outcomes” in 2007, and due to its popularity it is the process of updating the handbook (*see chart*).

Still, industry may wonder about the long-term utility of registries, given promising initiatives such as data mining and the Sentinel surveillance project.

Mathis noted, “I think the registries can certainly focus on specific populations and specific adverse events that we will be looking at. I suspect as we move forward in the development of the Sentinel project we may see that there is some overlap.”

However, Nancy Dreyer, chief of scientific affairs at Outcome Sciences in Cambridge, Mass., said that registries are unlikely to be replaced in the foreseeable future.

“I have a long career in data mining and I really appreciate what it can do,” Dreyer noted. “What it can’t do is provide rich clinical detail, or even much clinical detail. Most of the data that people use for mining are billing systems which whether they are right or not – and holding aside whether people bill accurately – they just describe an encounter, even when they are right, so those aren’t too detailed. And electronic health records are too sparse and too inconsistent in the way data are collected and coded.”

– M. Nielsen Hobbs (n.hobbs@elsevier.com)

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"Registry of Registries": AHRQ Has Ambitious Plans For Update Of Handbook For Designing And Using Registries

The Agency for Healthcare Research and Quality is in the process of updating its 2007 "User's Guide to Registries Evaluating Patient Outcomes." The entire handbook will be posted for review in the coming months, but AHRQ has already posted five white papers on how to expand the scope of its efforts. Comments are due Sept. 15.

| Topic | Lead And Other Notable Authors |
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| <p>Developing a Registry of Patient Registries: The draft report considers how best to build a registry of registries – especially whether it should be a “de novo” service, a clinicaltrials.gov “add-on” or a “hybrid approach that leverages the capabilities” of clinicaltrials.gov and AHRQ. “There is a clear need among stakeholders for a registry of patient registries, but the lack of incentives or pressures for registry owners to participate is a critical barrier to a successful program,” the report states. “Given the participation risks, the most practical approach may be one that begins with the core functionality of listing and search and builds other components over time.”</p> | <p>The Outcome DEcIDE Center</p> |
| <p>When Should a Patient Registry End?: “For registries focused on safety or effectiveness outcomes, there is little reason to support a registry continuing indefinitely,” this white paper argues. To make a decision to stop easier, registries should from the outset include data-driven goals such as a minimum number of specific adverse events, or “until the upper bound of a confidence interval for the rate or risk of the key outcome falls below some threshold.” Funding, as well as the question of whether the registry “is unable to fulfill its purpose” should also be considered. But a registry should continue if “the potential safety concerns are so grave that they must continue to be monitored [and] essential long-term follow-up can only be secured in the context of the registry.”</p> | <p>Kenneth Rothman (RTI Health Solutions)</p> <p>Joanna Haas (Genzyme Corporation)</p> |
| <p>Interfacing Registries with Electronic Health Records: “While we remain a long way from full semantic interoperability, a great deal of useful work has and is being done,” the white paper states. In the meantime “functional interoperability” – matching “whatever content has been rigorously defined” in the EHR that is also “usable and acceptable” to the registry – “provides a goal that can be achieved in the near term with significant gains in improving workflow and reducing duplication of effort for providers and patients participating in registries.”</p> | <p>Dan Levy and Richard Gliklich (Outcome)</p> <p>Landen Bain (Clinical Data Interchange Standards Consortium)</p> |
| <p>Linking Registry Data – Technical and Legal Considerations: The technical feasibility of linking a registry with other data must be “equally weighted” with its legal permissibility, the white paper states, with the feasibility governed by the types of data available and the permissibility governed by the “terms and conditions that applied to the original compilations of each data set.” Among the questions that should be considered: “Are the individuals performing the linkage permitted access to identifiers or restricted set of identifiers? Are they an honest broker or the source of one of the datasets to be linked?” The paper cautions that “linkage of de-identified data may result in accidental re-identification.”</p> | <p>Stephen Fienberg (Carnegie Mellon University)</p> <p>Sara Rosenbaum (George Washington University)</p> <p>Susan Adams (Dartmouth College)</p> |
| <p>Use of Registries in Product Safety Assessment: Registries are “well suited to identify effects that can only be observed in a large and diverse population over an extended period of time.” But technical challenges surrounding the definition of exposure and risk windows, off-label use, “understanding the representativeness of the registry population,” concomitant medication, dose effects, delayed effects and patient compliance need special attention. “Registries not designed to evaluate safety, particularly those that are not sponsored by a regulated manufacturer raise additional questions regarding what their appropriate role should be in both detection and reporting on potential safety concerns,” the paper notes.</p> | <p>Kathryn Starzyk and Nancy Dreyer (Outcome)</p> <p>Stella Blackburn (EMEA)</p> |