



U.S. Food and Drug Administration

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Public Workshop on Developing a Consolidated Pediatric Rheumatology Observational Registry May 12-13, 2009

On May 12-13, 2009, FDA's Center for Drug Evaluation and Research (CDER) held a public workshop to seek constructive input from key stakeholders in the pediatric rheumatology community, the pharmaceutical industry and the public to explore the value and feasibility of developing a consolidated pediatric rheumatology observational registry. FDA obtained public comment on issues relating to development of a consolidated pediatric rheumatology observational registry.

Executive Summary. The workshop began at 8:30 on May 12, 2009. Dr. Carolyn Yancey provided introductory remarks. She described juvenile idiopathic arthritis (JIA), its subtypes and categories and the nature of the debilitating disease. Prior to 10 years ago, she said the only drugs available to treat this condition were NSAIDS, corticosteroids and methotrexate.

She said that only within the past 10-15 years has there been a wide selection of drug treatments. Three laws were cited as promoting drug development for JIA: Pediatric Rule (1998) which allowed FDA under certain conditions to require manufacturers to test drugs in pediatric populations; Best Pharmaceuticals for Children Act (2002) which provided marketing exclusivity for manufacturers who voluntarily test drugs in children; and Pediatric Research Equity Act (2003) which requires companies in certain cases to test adult drugs in children where there is a potential for benefit.

Subsequent to enactment of the laws cited above, several additional drugs have been approved for marketing for treatment of JIA: Non-selective NSAIDS /Cox-2 Selective inhibitors; Enbrel (etanercept) - 1999; Celebrex (celecoxib) – 2006; Humira (adalimumab) – 2008; and Orencia (abatacept) – 2008.

Because of the long-term use associated with drugs for chronic conditions originating in childhood, Dr. Yancey cited the need for mechanisms to assess long term safety for both the older JIA drugs and for those newly approved for the condition. Dr. Yancey said that post-marketing registries are often useful in assessing the safety as well as the effectiveness of drugs for chronic conditions such as JIA. Currently, each of the new generation of JIA drugs is included in a separate postmarket observational study, but the product-by-product approach has well-known limitations, including failure to capture data about children who switch from one medication to another, limited enrollment size for a rare disorder such as JIA, and enrollment criteria that may be exclusive. Dr. Yancey said that a consolidated registry could address these limitations.

The purpose of the workshop, said Dr. Yancey was to bring key stakeholders together to discuss the advantages and disadvantages of a consolidated registry, lessons learned from existing registries and the challenges of transitioning to a new model.

Dr. Gerald Dal Pan, Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research gave a general overview of the Food and Drug Administration Amendments Act (FDAAA), with a focus on Title IX of the Act which provided FDA with enhanced authorities to identify potential risks associated with newly approved drugs and to require postmarketing risk evaluation and mitigation strategies (REMS) to actively monitor such risks. The new law also gives the Agency authority to require drug labeling changes based on new safety information. Dr. Dal Pan discussed the FDA's Sentinel System, which is set up in response to section 905 of the law as an active post-market risk identification and analysis system. He also discussed section 901 of the law, which gives the FDA authority to require post-marketing epidemiology studies. Although the FDA has not issued formal guidance on many areas of the law, if Pharmaceutical companies' requirements under the law can be met with a consolidated pediatric rheumatology registry that would be a desirable outcome.

Following Dr. Dal Pan's remarks, a panel of experts convened to hear public speakers. PANEL I. "Introduction to the Issues" featuring panelists Peter Margolis, Cincinnati Children's Hospital; Lawrence Jung, Children's National Medical Center, Washington, D.C.; James O'Dell, American College of Rheumatology; Bernard M. Murphy, Arthritis Foundation; Nicolino Ruperto, Pediatric Rheumatology International Trials; and, Jeffrey Siegel, FDA, Chairperson. There were three speakers.

Dr. Carol Wallace, Professor of Pediatrics at the University of Washington, presented the perspectives of the two main childhood arthritis and rheumatology organizations: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Pediatric Rheumatology Collaborative Study group. Dr. Wallace said that currently 80% of drugs used in children, including for treatment of JIA, have not been tested in children. This leaves important gaps in our understanding of basic questions such as proper dosing, adverse events, and long term effects on patients. There are also critical gaps in our understanding of how JIA medications are actually used and how safe and effective they are in both the short and long term. Better information is needed in order to manage risks, choose between various medications, particularly the newer ones, and improve the overall quality of care. Current methods of collecting information focus on individual medications for JIA are insufficient and a single consolidated disease registry for children with JIA could collect much-needed safety information.

Daniel Solomon, M.D., Brigham and Women's, Harvard Medical School presented on "Methodological Considerations: Lessons Learned from Studies of Biologic in Adults" which examined some of the "real world" challenges of designing a registry, including how to track lifelong medication use beginning in childhood. Current medication based registries are not useful in tracking people who switch medications or who combine medications.

Michael Severino, M.D., Amgen, presented an industry perspective of the challenges and opportunities presented by a disease registry. In a rare disease setting, single medication registries suffer from inherent limits of scale, making it difficult to find statistical significance. Other challenges include sample size, attrition, background rates and comparator selection, and changes in therapeutic options.

Panelist Dr. Ruperto encouraged widespread international collaboration in the effort to develop a registry that can provide statistically robust results. He recommended that a single registry be developed for all biologics used in JIA, and that participation be a regulatory requirement.

Panelist Mr. Murphy expressed the AF's firm support for a "fully funded" registry. He recommended that a representative of the patient community be included in designing and running the registry.

Panelist Dr. O'Dell expressed the ACR's support of a registry and remarked that pediatric rheumatologists are in short supply and great demand is placed on their time. Data entry process for physicians needs to be user friendly and efficient.

Panelist Margolis endorsed the proposed disease registry and urged the group to think about creating incentives and opportunities for patients and their families to participate in the registry. Patient-reported outcomes such as those involving pain, fatigue, and emotional distress are important factors to capture in the registry. He also urged the group to design studies within the registry to improve patient care.

PANEL II. “Lessons Learned from Current Integrated Registries” featuring panelists Christina Chambers, Organization of Teratology Information Specialists; Murray Passo, ACR and Susan Cummins, FDA. There were three public speakers.

Joel Kremer, Albany, NY, founder of the CORRONA Database spoke on “Creating A Registry” which focused on the practical issues surrounding getting a registry started. He said that the person in charge will need to work fulltime with a working group including experts in biostatistics (half-time), epidemiology, legal and support. The total cost of getting the registry up and running is likely to be in 7 figures. Data collection needs to be simple and incentives are needed if doctors are to participate. If doctors receive automatic feedback that impacts the quality of patient care, they are more likely to participate. Housing and ownership of registry data are issues that need to be addressed up front to avoid debilitating problems later.

Taunton Southwood, Univ. of Birmingham, UK, spoke to the group concerning “lessons learned” in running the BSPAR Biologics and New Drugs Registry in the UK. He pointed out the need for agreement on the types of data to be collected in the registry. What comprises a “significant adverse event (SAE)” must be agreed to in advance. Data entry needs to be simple and intuitive. Patient/family data should be encouraged and appropriately used. Industry and others remain concerned about the difficulty involved in assigning causality for a SAE.

Femke H.M. Prince, M.D., Rotterdam, The Netherlands, described some of the challenges that have been faced in running the Dutch National Register on Arthritis and Biologics in Children. She described the challenges of maintaining funding for the register. She also mentioned the difficulty involved in incentivizing physicians to participate and recommended that ease of data entry and useful feedback are helpful.

BREAKOUT SESSIONS. Following lunch the workshop divided into four breakout sessions. The session chairs summarized their findings on the morning of May 13, 2009.

Session I: “Challenges to be Considered for Transition to a Consolidated Registry for Juvenile Idiopathic Arthritis (JIA)”. The group endorsed the proposed registry and recommended that the long-term goal be standardized care for JIA patients. Participation by doctors and patients will require a culture change. The registry design must ease this transformation. There are important challenges that need to be addressed. These are related to data access and ownership, the risk of “false discoveries”, integration of existing registries. The breakout raised the question of whether the registry data could be part of the FDA regulatory requirements.

Session II: “Structure of Clinical Registry and Data Elements”. The group endorsed the registry and reported their finding that safety should be the primary focus of the registry. Drug effectiveness issues are important but secondary to safety. The group discussed and made recommendations on baseline data elements, safety parameters, and effectiveness parameters. The group also discussed and made recommendations about the structure of the registry. Issues that were not discussed by the group included strategies to incorporate existing registries, quality control and monitoring, and recruitment and retention of patients. Central adjudication of SAE’s and their causality need to be a central feature of the new registry. The group recommended creation of a working group to develop detailed specifications for the initial phase of a consolidated registry.

Session III: “Potential for Research Initiatives within a Consolidated Pediatric Rheumatology Registry”. This group recommended that clinical, translational, and health outcomes research be a critical component of the registry. They discussed and presented some specific research opportunities arising from such a database and addressed some practical issues arising from its implementation. The group raised a number of significant questions about the funding and maintenance of the research efforts involving the database, as well as about where the research registry data will be housed and how it will be accessed.

Session IV: “Analysis of Data to Identify Safety Signals”. This group focused on practical issues regarding capturing the best data available in terms of patient behavior and disease progression for inclusion in the registry. Family and patient-reported data should be encouraged and considered carefully. There is a need for careful monitoring of the registry and judicious use of the validated data.

Final Wrap-Up and Closing: Dr. Jeffrey Siegel, Director of FDA’s Rheumatology Division (DAARP) thanked the workshop attendees for their participation. He noted that there is broad agreement in government and the JIA community about the value of a consolidated disease registry. He said he thought that FDA would be able to use the registry to address many or most of the regulatory issues concerning safety of new products for JIA. Crucial questions remain about funding and operation of the registry but we are off to a good start he said. He said that members of CARRA had volunteered to form a working group to move ahead with next steps and that other members of CARRA had volunteered to write a paper for publication describing this meeting. Dr. Siegel promised to continue to dialog with the JIA community as we work to fill in the details of the registry.