"Keynote Speaker Dean Kamen was awesome and deeply inspiring!"

DIA 2012: Orphan Drug Development

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The urgent need for developing orphan drugs, challenges to global orphan drug development, strategies to overcome these challenges, and the pending impact of PDUFA V, were critically examined at DIA 2012 through *Orphan Drug Development*: *Global Regulatory Challenges* & *Initiatives* (Session 359). "The experts here really know the orphan space and regulations," enthused Session Chair Kinnari Patel, PharmD, RPh (Bristol-Myers Squibb Company).

She established context for this session by reviewing the FDA's statement of purpose for the 1983 Orphan Drug Act: "To stimulate innovation in developing treatments for patients with rare diseases and conditions and to foster the prompt availability of therapeutically superior drugs." The act primarily provides financial incentives, such as waiving application fees, to accomplish this purpose. For further context, she reminded attendees of the FDA's definition of a rare ("orphan") disease – it affects less than 200,000 people in the US – and that there are more than 7,000 rare diseases known to affect more than 25 million Americans. In 2011, 323 requests for orphan drug designation were filed with the FDA, and 192 designations were granted.

Marlene Haffner, MD, MPH (Haffner Associates, LLC) overviewed *Current Challenges in the Designation & Development of Orphan Products*, while *Regulatory Challenges & Initiatives*: *Strategies for Success* was presented by Jonca C. Bull, MD (Novartis Pharmaceuticals Corporation).

Dr. Haffner first summarized the "rarity paradigm": Rare disease patients have an illness which is poorly understood, is often diagnosed late, and are geographically dispersed because their population is so small. "They don't all live in North America," she explained. "They don't all live in the United States. Rare diseases know no borders."

Dr. Haffner suggested that sponsors interested in developing an orphan drug first check the Office of Orphan Products Development (OOPD) website to see if other products for the same disease are already in development, and also directed attendees to an online FDA "tip sheet" for developing orphan products and submitting your orphan designation application. "You need to clearly define what the disease is," she explained. "What is this drug and why does it treat only this rare disease?"

Dr. Haffner's other suggestions for sponsors included involving the OOPD and your review division early in your application process, collaborating with NORD and patient advocacy groups, and ensuring that you understand the patients' true therapeutic needs. "You will almost always be asked to conduct multi-center if not multi-national trials," she explained. While clinical trials are simply unfeasible for certain conditions, data from registry or natural history studies can sometimes be submitted in these circumstances.

Rare diseases are a highly diverse collection of disorders, Dr. Haffner concluded, and clinical development programs for products to treat them must

reflect the disease and population being studied, and the sponsor's understanding of the proposed intervention and its expected impact on the disease. One size will NOT fit all.

"First and most importantly, there remains a tremendous unmet need," began Dr. Bull. Over 80% of rare diseases seem genetic in origin – research has defined the genetic basis of more than 2,000 rare diseases – which means they can potentially be identified and impacted in their pediatric stages.

Dr. Bull noted that PDUFA V authorizes hiring more CDER and CBER resources to facilitate communication to sponsors during drug development. "You put some dollars behind the research. That's always important," he said.

Dr. Bull turned to development and clinical trial programs for orphan drugs. How can your enterprise translate innovative science into therapies that meet regulatory requirements for marketing? "I think we can all agree that the overall process of drug development is too costly and too long," Dr. Bull continued. "The other thing that has a huge impact is that things are so much more complex."

"The **principle** of orphan drug development is not different: You still need to demonstrate safety and efficacy," said Dr. Bull. "The **process** is different." Dr. Bull noted the importance of the patient and advocacy community in drug development, citing the cystic fibrosis drug developed by Vertex as an example of successful patient community involvement. "Patients are going to have a much greater voice in benefit/risk," he suggested.

Dr. Bull concluded with a sobering reality check: What is the capacity of the US health care system to pay for novel therapies that benefit a relatively small population? "Where is the greater public health need served?" he asked.

Timothy R. Coté, MD, MPH (Coté Orphan Consulting; Keck Graduate Institute) delivered *Good Words from the Orphanage*: *Risks*, *Metrics & PDUFA V*. Dr. Coté itemized three kinds of risk in drug development – scientific, management and execution, and regulatory – and focused primarily on its regulatory aspects. Getting the orphan designation is not easy, he allowed. Regulatory hierarchy and its companion statutes, regulations, policies and practices are not always transparent. FDA likes to approve orphan drugs but still requires substantial evidence of safety and effectiveness. "This business of demonstrating substantial evidence of effectiveness is no joke," he said.

Take advantage of your pre-IND meeting to establish a collaborative relationship with those who, by definition, are always right. "Your pre-IND meeting is your opportunity to take advantage of that invitation – 'let's talk,'" he stressed.

Turning to metrics, Dr. Coté cited data that compared the number of trials, the number of patients in trials, and other statistics for orphan and non-orphan products, and then compared clinical development times for orphan and non-orphan products and found they did not significantly differ: The median time in the clinic for both orphan and non-orphan products was 69 months, and the median FDA review time for both orphan and non-orphan products was 14 months.

"PDUFA is the watchword of this conference," Dr. Coté reminded attendees. "What does PDUFA mean for orphans?" He described PDUFA as the "legislative vehicle" that brings together numerous important, timely initiatives into "a must-pass piece of legislation." He concluded with a summary review of the new "Breakthrough Therapy" provision of Title VIII, "Drug Regulatory Improvement," and other Titles of the legislation. ●