

'The Pink Sheet' DAILY

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

Printed By Jennifer Jeng Firm:() on [April 29, 2009]

FDA's New Interest: Identifying Latent Risks

April 28, 2009

Volume 21 | Issue 80 | Number 002

BOSTON - FDA is taking a closer look at how to identify risks that present spontaneously but modestly.

"There is new and growing interest in this kind of event," said Bob Temple, Associate Director for Medical Policy, CDER. "A real change in focus."

Temple spoke April 28 at the Post Approval Summit in a session titled, "Risk Assessment in the XXI Century," and noted the four most common ways a serious risk is identified: (1) when it is a common and severe reaction that obviously is drug-related; (2) when it is a rare and severe reaction that obviously is drug-related. (3) when it occurs spontaneously and is not obviously drug-related, but is increased greatly in rate by the drug; (4) when it occurs spontaneously, but only modestly (less than two-fold) increased by the drug.

The last type, he said, is the one on which FDA plans to focus much of its attention.

"There is little doubt that there is a new interest in possible modest adverse effects of (mainly) chronic-use drugs that has spread from cardiovascular drugs (where it has long been present because of experience with anti-arrhythmics and various inotropes) to other chronic-use drugs, including anti-diabetics, NSAIDs and chronic-use asthma drugs," said Temple.

Typically, these adverse events are cardiovascular-related, but they also could include tumors or adverse outcomes of the disease. (In fact, FDA just decided to add warnings on internal bleeding and liver damage to over-the-counter pain relievers.)

Challenges in identifying these risks

The challenge comes in pinpointing these hard to identify risks. Many safety problems are identified in epidemiological studies. But where an increased risk is low and where population characteristics would be difficult to match in an epidemiologic or historically controlled setting, the only reliable source of information is a randomized trial or a meta-analysis of multiple trials, argued Temple.

Even most of the randomized clinical trials that have shown adverse effects in cardiovascular disease or cardiovascular effects in a non-cardiovascular disease came about either by accident when a company was attempting to show a clinical benefit, or when there was an existing concern about a drug considered valuable, Temple said.

The UGDP trial in the 1960s sought to show the value of improved glucose control, but instead revealed an adverse effect of cardiovascular death; the CAST study intended to show

improved survival, but instead showed a two-fold increase in mortality.

"We have had such experiences in the past, but several recent situations, both pre- and post-market, have greatly increased interest," he said. Some of those include the COX-2 selective NSAID, rosiglitazone and other diabetic treatments, erythropoietin problems, and results with long-acting beta agonists, to name just a few.

The value and cost-benefit of such trials could be a challenge as well, Temple said. "How likely, absent an animal or human signal, is a bad outcome?" Temple asked. "If these are very hard to detect, and detection is uncertain, how worthwhile is it compared to other important questions?"

The interaction of this new interest and FDAAA authority, Temple said, will be "worth watching."

-Lauren Smith (lauren.smith@elsevier.com)

Printed By Jennifer Jeng Firm:() on [April 29, 2009]

Contents copyrighted © F-D-C Reports, Inc. 2004; protected by U.S. Copyright Law.

Reproduction, photocopying, storage or transmission by magnetic or electronic means is strictly prohibited by law. Authorization to photocopy items for internal or personal use is granted by F-D-C Reports, Inc., when the fee of \$25.00 per copy of each page is paid directly to Copyright Clearance Center, 222 Rosewood Dr., Danvers, MA 01923, (978) 750-8400.

The Transaction Reporting Service fee code is: 1530-1214/04 \$0.00 + \$25.00. Violation of copyright will result in legal action, including civil and/or criminal penalties, and suspension of service. For more information contact: Michael Magoulias F-D-C Reports, Inc., at 301-657-9830.