Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products: An Institute of Medicine Workshop

FDA Case Studies: Background Information

Tysabri and the Risk of Progressive Multifocal Leukoencephalopathy (PML)
In February 2005, four months after its initial approval to treat patients with multiple sclerosis, Tysabri (natalizumab) was withdrawn from the market because of concern about the risk of a life-threatening, frequently fatal, brain infection, PML. At the time, there was considerable uncertainty about the magnitude of the risk of PML to patients exposed to Tysabri and whether there were any identifiable risk factors that could be reliably used to identify patients at greater risk. In making its decision on whether to allow re-marketing of the drug, FDA considered whether the risk (and uncertainty about the risk) of PML outweighed the drug's recognized substantial benefit.

Relevant information on Tysabri (natalizumab), including historical information and regulatory and labeling information, is available at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm

Anoro Ellipta and Uncertainty about CV Risk Associated with LAMA drugs for COPD
In December 2013, FDA approved a novel combination product, Anoro Ellipta (umeclidinium and vilanterol inhalation powder), as a long-term maintenance treatment for patients with chronic obstructive pulmonary disease (COPD). One of its agents, umeclidinium, is a member of a class of long-acting antimuscarinic agents (LAMAs), which has been the subject of concern since 2007, when pooled analyses suggested an increased risk of stroke, cardiovascular death, and myocardial infarction (MI) associated with tiotropium, one drug in this class. Since that time, various meta-analyses and randomized clinical trials have drawn conflicting conclusions about the cardiovascular (CV) risk of inhaled antimuscarinic agents, and this uncertainty has influenced FDA's decision-making regarding other drugs in the class. The low numbers of major adverse cardiac events (MACE) observed in the Anoro Ellipta pre-market clinical trials made it difficult to draw definitive conclusions about CV risk for this specific product. Therefore, an important question in the Anoro Ellipta approval decision was whether to require a post-market study to further assess potential CV risk. This case highlights the impact uncertainty can have on decisions regarding a class of drugs, as well as the issues presented by conflicting evidence from multiple sources.

Relevant Links:

- FDA's decision memo on Anoro Ellipta (umeclidinium and vilanterol inhalation powder): http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203975Orig1s000ODMemo.pdf
- Information on a related drug, tiotropium marketed as Spiriva HandiHaler http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107272.htm

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm