***The 21st Century Cures Act and Approving New Drugs, 15 March 2017***

**What changes does the 21st Century Cures Act suggest for clinical trials?**

The 21st Century Cures Act was passed in December 2016. Among other things, it directs the Secretary of Health and Human Services to develop tools to speed-up the approval of new drugs and devices. But new regulations are not out as yet; FDA Commissioner just nominated last week, Scott Gottlieb, but not confirmed as yet.

In the meantime, some views already have been published on the Cures Act: Kesselheim, A.S. and Avron, J. *“New 21st Century Cures” Legislation: Speed and Ease vs. Science,* Jama, online, January 5, 2017. And they are expressed here.

Among other things, Kesselheim and Avron are concerned that the Cures Act may lead to biological and other biomarkers becoming a basis for drug approval without rigorous validation. If so in the new FDA regulations, biomarkers would serve much more as surrogate endpoints in clinical trials.

Moreover, they are concerned that observational data arising from routine clinical use may take the place of prospectively collected data from randomized clinical trials. If so in the new FDA regulations, the use of observational data would represent a monumental change in the approval process for new drugs.

**What are the key measures used in the drug development process**?

Key measures in the process of developing new drugs are defined in the following sources:

**Sullivan, E.J., Clinical Trial Endpoints, Course for the FDA, 2013;**

**Center for Health Policy, the Brookings Institution, Workshop *on Facilitating Biomarker Development,* October 27, 2015; and**

**Baker, S.G. and Kramer, BS, *Evaluating Surrogate Endpoints, Prognostic Markers, and Predictive Markers: Some Simple Themes*, Clinical Trials, August 2015.**

They define three important measures for drug development:

*1*. *Primary endpoints* are detectable benefits to patients---including lengthened survival, improved symptoms, enhanced functional capacity, and decreased chances of developing a disease complication. They are the preferred basis for approving a drug from a clinical trial.

There are two FDA-acceptable types of primary endpoints: (1) Objective measures: survival, disease exacerbation, clinical event; and (2) Subjective measures: Symptom score and a tested and validated “health related quality of life” survey. To be a useful primary endpoint, both types need to closely track patient baseline differences and condition changes.

An example of a primary endpoint for APBD is the six-minute walking test that was used in the C7 Phase 2 clinical trial for this disease.

*2. Biological Biomarkers* are by definition an objective, quantifiable characteristic of biological processes. They are often used in clinical practice to diagnose a disease, predict/monitor response to therapy, or explore the effects of an investigational drug.

An example of a biological biomarker for APBD is the metabolites of creatinine and methionine that were used to monitor the response to therapy in the C7 Phase 1 trial for this disease.

*3. Surrogate endpoints* are indicators or signs used in place of a primary endpoint to tell if a treatment works. Today, the FDA says that surrogate endpoints must demonstrate a close connection to the primary endpoint or clinical benefit. The connection between surrogate and primary endpoints must be shown based on epidemiologic, therapeutic, path-physiologic, and similar evidence. Simple correlations between surrogate and primary endpoint data are not sufficient to establish a close connection.

Surrogate endpoints usually involve behavioral or cognitive scores; such tests as MRIs, mammograms, and electrocardiograms, but rarely biological biomarkers.

An example of a potential surrogate endpoint for APBD might be certain brain and spine magnetic resonance images.

**Why do some rare disease investigators want to advance the use of biological biomarkers as endpoints?**

In 2015, Dr. Emil Khakis ***(now president and CEO of Ultrangenyx)*** advanced the idea of qualifying biological biomarkers to serve as endpoints in rare disease clinical trials (source: Kakkis, E. and others*, Recommendations for the Development of Rare Disease Drugs Using the Accelerated Approval Pathway and for Qualifying Bio-markers as Primary Endpoints,* Orphanet Journal of Diseases, 2015.)

He advanced this idea because rare disease treatments/cures are hampered by “small heterogeneous patient populations, long time-frames for disease progression, a poor understanding of disease natural history, and a lack of prior clinical studies. But recent advance in medical science has enhanced the understanding of these rare disorders at the biochemical level, offering more therapeutic options.” However, if prior clinical data is lacking to support the predictive value of a biological biomarker, then that biomarker most likely would not qualify as an endpoint (a surrogate endpoint according to current FDA definitions).

Dr, Khakis cites the case of a biological biomarker that was successfully approved as a surrogate endpoint for alpha-1-antitrypsin deficiency disease. And those investigators demonstrated the reasonable restoration of blood levels even without direct proof of affecting the tissue level.