

U.S. View on the Role of PK/PD in Drug Approval-Discussion on the Basis of Examples. Bob Powell, Joga Gobburu, and Peter Lee. FDA, Silver Spring, MD

PK/PD, or as people have begun to speak more broadly, model based drug development, is being woven into the fabric of FDA work in the form of more quantitatively based decisions. The original focus on dose-response has expanded in a variety of directions described in this talk. One can view the primary work products of the FDA as it relates to drugs, devices and diagnostics as regulatory decisions, advice/consulting, and knowledge sharing. Regulatory decisions include approval of initial human drug dosing (IND), protocol design usually at the end of phase 2 (i.e., special protocol assessment), ability to market the product (NDA), pediatric exclusivity written request, public warning for safety issues (e.g., black box label warnings), and product withdrawal from the market. There are approximately 2100 meetings each year of an advising nature across the 15 CDER (Center for Drug Evaluation and Research) divisions (e.g., Oncology, Cardio-Renal). The topics range from clarification/negotiation of disease primary endpoints for drug approval, trial design, dosage regimen selection, safety and labeling. Sharing knowledge occurs in the form of drug development guidances, summary bases of approval for new drugs, and safety warnings. Critical Path¹ initiatives are designed to influence each of these activities.

Case studies will be presented to demonstrate how PK/PD principles influence:

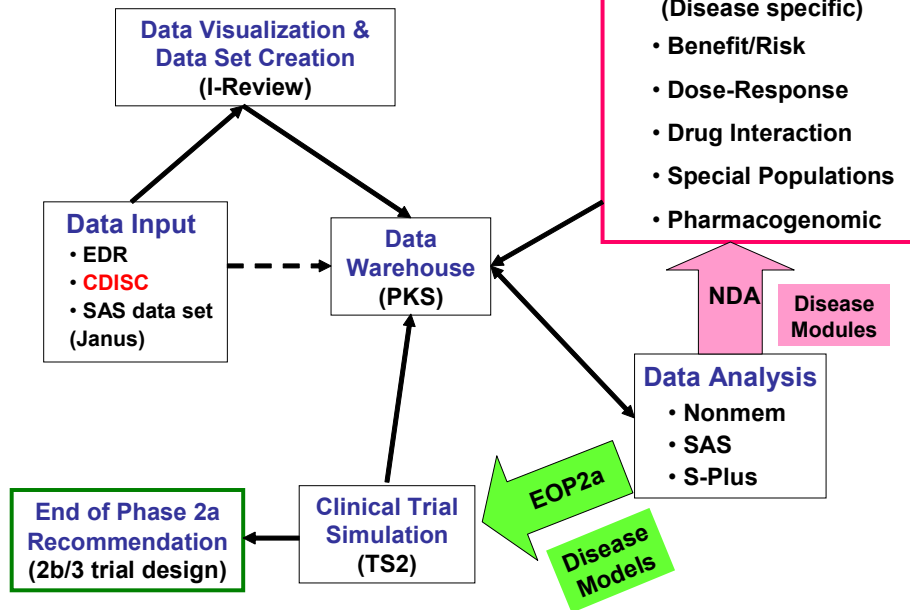
- Decisions
 - NDA
 - Pediatric Exclusivity
- Advising
 - End of Phase 2a Meeting

Prior successful work² is allowing increased work-scope and personnel commitment. A CDER wide centralized consulting group employing PK/PD principles is being formed for QT trials (trial design, completed trial analysis). A similar concept is being considered for pediatric exclusivity trial design and completed trial analysis. We hope this change will result in greater consistency, understanding and scientific quality in these areas.

The Office of Clinical Pharmacology (OCP) has created a centralized 'Pharmacometric Division' to facilitate PK/PD applications along in partnership with primary reviewers. This has resulted in:

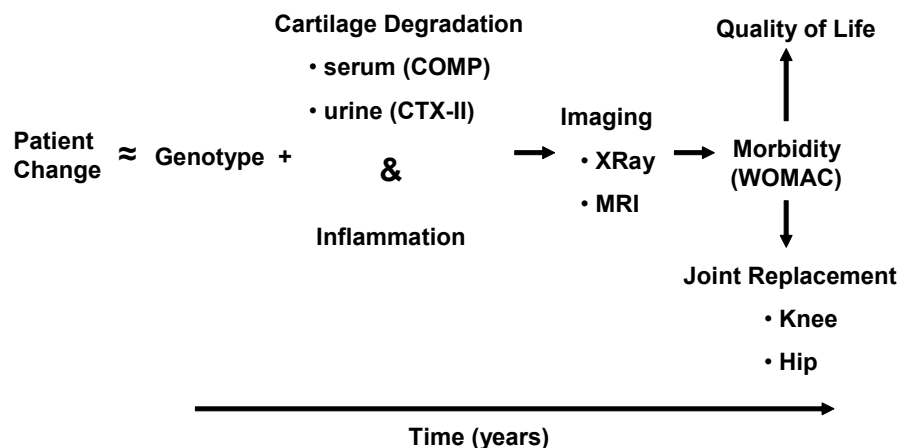
- **Groups focused on consulting services in IND and NDA review, and software development**
- **Internal process improvement to increase value of PK/PD** (e.g., NDA front-loading questions)
- **Information management architecture design and implementation.** Clinical trial information is not currently received using a common format or library of terms so that analysis data sets can be readily created for review and analysis. We have completed and published the clinical pharmacology module of the Clinical Data Interchange Standards Consortium (www.cdisc.org). CDISC will enable OCP to create a modern data acquisition, review, analysis, report, and warehouse system to support our work.

IND/NDA Data Review & Analysis
FDA Clinical Pharmacology Work Plan



- **Disease model and clinical trial information library.** Disease models (mechanistic, empirical) are being adopted from the literature or created internally for approximately 10 diseases over the past year. One example under development is osteoarthritis:

Osteoarthritis Model Development



When this information is used to make clinical trial design recommendations, we have created baseline, placebo and dropout models from prior clinical trials to use in simulations. We are exploring the feasibility of creating a public space

where this information can be shared and grown along with academic and industry colleagues.

- **Personalized medicine.** Application of disease models as described above to clinical trial data allow FDA scientists to understand the value in viewing benefit and safety for specific patient subcategories (e.g., genotype, gender, and ethnicity). Likewise, biomarkers are being evaluated as tools to help clinicians dose patients according to their need. These scientific debates are facilitated by quantitative analysis of the PK/PD style.
- **Fellowship and sabbatical development opportunities.** Pharmacometric and statistician scientists who can perform the above work are in short global supply. FDA is an ideal environment to train pharmacometric scientists because a critical mass of talented scientists have been created, a high concentration of drug and disease development issues is available as in few places, and there is a short cycle time for problems (months versus years in industry).

We encourage company or consulting scientists to contact us prior to engaging FDA in meetings where PK/PD principles will be a central focus to a regulatory consultation or decision making meeting. A common complaint from sponsors is that the meeting did not meet their needs in part because the right people were not present to evaluate the question or the data. It is reasonable and common practice within FDA to facilitate sponsor requests in this manner.

Application of PK/PD principles and data analysis has become a routine aspect of FDA work in the form of decisions regarding efficacy, safety and dosing. These quantitative assessments influence decisions on market access, labeling, trial design, and pediatric exclusivity. This demand has influenced the need to develop a data information system and train new scientists. Influence and negotiation skills have become more important. The FDA has been and continues to be a leverage point for change in this area.

1. The Critical Path to New Medicinal Products. <http://www.fda.gov/oc/initiatives/criticalpath/>
2. Bhattaram VA, Booth BP, Ramchandani RP, Beasley BN, Wang W, Tandon V, Duan JZ, Baweja RK, Marroum PJ, Uppoor RS, Rahman NA, Sahajwalla CG, Powell JR, Mehta MU, Gobburu JVS. Impact of Pharmacometrics on Drug Approval and Labeling Decisions - A Survey of 42 New Drug Applications. *AAPS J.* 7(3):E503-12, 2005