PAREXEL® CONSULTING INTERVIEW:
RICHARD WILLKE, PHD / PFIZER INC.

EARLY COST-EFFECTIVENESS MODELING WITH PK/PD DATA

Richard J. Willke, Ph.D., Vice President, Outcomes & Evidence, Global Health & Value, Pfizer Inc. talks with John Posnett, Vice President, HERON™ Commercialization.

Q: JOHN POSNETT **Dick, thank you for spending time with us today. You have been with health economics and outcomes research at Pfizer for many years now. Recently, you have taken an interest in early-stage economic modeling on the basis of pharmacokinetic/pharmacodynamic (PK/PD) data. I am sure this is at the forefront of what people are doing in terms of early-stage economic modeling, and I wonder if you would talk to us about what you have done and what you think is the potential for this type of modeling.**

A: DICK WILLKE John, it's a pleasure. Let me give you the background. As at other pharma and biotech companies, our teams have been trying to model the cost effectiveness of drugs in development as early and as well as we can. As you know, this is something that is done with variable degrees of success between different companies, indications, and compounds. But of course, a good early model of efficacy versus cost effectiveness can inform the target product profile and go/no-go decisions, and tell us where the product's best proof of value might lie. This is especially useful if we can get it by Phase II, when we make major buy-up and planning decisions for Phase III trials.

A few years ago, I began to be intrigued by the possibility of building an early economic model on the basis of PK/PD data. For at least a decade now, our clinical pharmacology colleagues have gathered PK/PD data from the literature and in-house clinical trials to predict safety and efficacy and to help determine dosage for subsequent studies. They almost always have pharmacometric meta-analyses that are based on published data, in-house data or both. These are often on dosing criteria that elicit a surrogate-marker response in the compound and/or related ones. I thought that if we could take a pharmacometric model of how a drug works at the basic physiological level, and marry that with an economic model, we might have a better early picture of cost-effectiveness. We might also be able to link dosage with probability of response and with economic outcome.

POSNETT **How did an opportunity to build a model arise?**

WILLKE We had a treatment for gout in an early stage of development. Like most other medications that treat and manage gout, it controls serum uric acid (sUA) levels in the bloodstream. Our pharmacometrics team had already determined the probability of response and nonresponse from a network meta-analysis of published literature on chronic-gout treatments. That response was defined in terms of sUA levels. The biggest challenge in this case was to link that marker response to the things payers care about: that is, patient quality of life—as measured by what we call "utility"—and healthcare resource use. While reductions in sUA do reduce the probability of flares—the intermittent bouts of severe inflammation that plague gout sufferers—those flares are infrequent and not always costly or debilitating. That means a cost-effectiveness argument based on flare reduction

alone may not be very strong, so we also included a direct relationship between sUA and utility as in prior reimbursement-agency submissions.

POSNETT **How did you determine the range of prices to include in the analysis?**

WILLKE There is a standard of care in the market that most payers are likely to compare against, but it will be off patent by the time our drug would be released, so we estimated its generic price and used that. Since it is not clear that any payer would accept either the resource linkage or the utility linkage, we modeled the cost/QALYs for all four combinations of resource on/off and utility on/off. This showed very clearly that the determining factor is utility and that the drug would likely clear the cost-effectiveness hurdle only if the link to utility were accepted by payers. That made it clear how important it would be to show that connection in clinical trials. That, of course, told us the only way to proceed with development was to design a trial that could show that connection strongly enough to convince some key payers.

POSNETT **That is a useful insight to have at an early clinical stage. Do you think this is a technique you can use for other drugs in development?**

WILLKE I do. These days, the PK/PD group always gathers data and models the physiological effects of compounds early in the cycle. They gather data from the literature and from Phase I research, for instance, to make early determinations of efficacy and safety for planning purposes. So that data almost always exists. And in some disease areas, the linkages are well established—the correlation between blood pressure and the likelihood of a stroke, for example. So I can foresee instances where the modeling would actually be a lot easier than it was for this first one in gout. And I am sure it will always give us more insight than we would have without it. In the gout case, for instance, there was no significant issue with side effects worth modeling at this stage. But for other drugs, there is a real trade-off between efficacy and side effects. So part of the early PK/PD analysis is about finding the right dose from a clinical perspective. With a linked economic model, you have the information you need to at least try to tune it for cost effectiveness, too.

POSNETT **So you think this is something you will be doing more of?**

WILLKE Certainly. As you know, the diversity of data required by all the regulators and reimbursement agencies a new drug has to confront make it impossible to gather everything you will need in Phase III trials. So modeling has become an important way to fill gaps in the data. Early modeling helps us make decisions that can save us a lot of money in trials later on. And economic modeling is key to anticipating how strong a case we will have, or will need, for payers. So I have no doubt that early economic models closely linked to PK/PD data will have a big and increasing role to play in early decision making. They are one of the many tools that we can use to make smarter decisions about what to develop, and how to develop it.

ABOUT THE AUTHORS

RICHARD J. WILLKE, PHD, received a Ph.D. in economics from Johns Hopkins University in 1982, concentrating in econometrics and labor economics. He first joined one of Pfizer's legacy companies, Upjohn, in 1991, and today he is Vice President, Outcomes & Evidence, Global Health & Value, at Pfizer, based in New York City. Dr. Willke was a member of the Health Outcomes Committee of PhRMA from 1998-2009, having been its chair from 2002-2004. He was co-chair of the ISPOR Good Research Practices Task Force on Cost-Effectiveness Analysis in Randomized Clinical Trials in 2003-2005, served on the ISPOR board of directors (2007-2009), and was chair of the ISPOR Institutional Council in 2010.

JOHN POSNETT, PHD, is vice president, HERON™ Commercialization, at PAREXEL Consulting. Dr. Posnett is responsible for managing the Health Economic Modeling Unit (HEMU), providing cost-effectiveness and budget-impact modeling and data-analysis services. Prior to joining HERON, he was vice president of Health Economics at Smith & Nephew, director of the MSc program in Health Economics at the University of York (1988-94), and later professor of Health Economics and director of a specialist health economics consultancy at the university (1994-2001).

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