The Value of STRATEGIC EPIDEMIOLOGY to Inform Product Development and Commercialization

Contributed by

ADRIAN LEVY, PH.D., *Senior Scientific Advisor, Oxford Outcomes, an ICON plc Company*

NIGEL GREGSON, *Partner, PriceSpective, an ICON plc Company*

Challenges and Changes in the Biopharmaceutical Industry

Every year, the industry is confronted with an increasingly constrained environment in which to invest in research and development. Established blockbuster drugs are reaching the end of their patent lives, facing competition from an increasingly aggressive and buoyant generic and biosimilar industry. The pace of innovation and level of R&D productivity have declined, leaving a dearth of new products to 31replace those coming off patent. And higher developmental costs, coupled with declining R&D budgets, have intensified pressure to maximize returns from the R&D investment.

Adding to the challenge is greater scrutiny by regulators and payers on the questions of comparative effectiveness and benefit-risk, and of value, respectively. This heightened scrutiny is accompanied by seemingly conflicting messages and goals. Speeding access to new products while enhancing patient safety, legislating joint assessment of benefits and risks while leaving the analytic framework unspecified, undertaking comparative effectiveness research while leaving the placebo-controlled regulatory environment intact, fostering innovation while improving value for money, all leave difficult questions about where to focus resources.

In response, the industry is undergoing a fundamental transformation in its approach to drug research and development, moving away from pursuing blockbuster primary care medicines, and toward a targeted approach concentrating on tailored therapeutics prescribed by specialists.

Smaller, more specific patient populations are becoming the focus and the number of products within portfolios is increasing, each seeking to reduce morbidity and/or increase survival, while minimizing potential safety issues.

The common thread running through these changes is the recognition of an increasingly important role for epidemiological studies and reasoning in informing product development and commercialization.

Early Development

If arguing the need for epidemiologic thinking in the early drug development seems abstract, consider that even at the stage of basic and translational research, before the clinical development program is underway, a key strategic question is whether or not to invest in future research.

This is best answered by characterizing the illness, the impact of the disease on quality of life and survival, and the number of patients affected. Doing so involves studies characterizing the natural history of disease at the population (person, place, and time) and clinical (from diagnosis through prognosis to resolution or death) levels, as well as incidence, prevalence, and humanistic burden of illness. Added to this is the need to make sense of advances in molecular pharmacology, nanotechnology, biomarkers, biotherapeutics, and pharmacogenetics in terms of the meaning to patients and payers. Epidemiologic reasoning is essential for these tasks.

Pivotal Clinical Trials

An estimated 40% of the total drug development cost is incurred in exploratory Phase II (and confirmatory) and Phase III (randomized clinical trials). To assess improved health benefits beyond the regulatory hurdles and with an eye to market access, the designers of clinical trials must be sure to incorporate the perspective and requirements of the payer. Payers want manufacturers to design clinical trials that identify patient sub-groups in which the value of the new drug is likely to be concentrated and show endpoints that demonstrate the health benefits of the drug.

Payers want these trials to be of sufficient duration to be able to show the full benefits of the drug. Where required, trial extensions can be useful, provided appropriate endpoints are monitored.

Maximizing the return on investment from the clinical program requires epidemiologic principles and reasoning into both the design of the trial itself and the use of the data in post-approval activities. The development teams designing trials often fail to incorporate sufficient epidemiologic input because the trial is considered conceptually straightforward. Nevertheless, despite the scale of the investment and the consequences of a misstep in the clinical development program, there is ample evidence of design flaws realized too late to make effective modifications.

Post-Marketing and Real World Studies

As Phase III programs are concluding, the value proposition is based on the epidemiological characteristics of the disease and the benefits offered by the new drug. At this stage, the need for different types of epidemiological studies and evidence becomes even more crucial. Descriptive epidemiologic studies of humanistic burden of illness, once considered onerous and time-consuming, are now included as standard components of regulatory and reimbursement submissions.

Once on the market, greater emphasis on drug utilization, lifecycle approaches to benefit risk, harmonization of regulatory and reimbursement review processes between countries, and implementation of patient-centered and comparative effectiveness research have all led to the growing recognition of epidemiologic methods and reasoning.

Phase IIIb and IV studies, which were once done sparingly and seen predominantly as tools for gaining greater information on safety, are now becoming increasingly common as various stakeholders seek, or are obligated, to provide information on special populations and environments, to refine dosing recommendations, to identify less common adverse reactions, and to refine benefit-risk relationships.

Hand in hand with waxing emphasis on drug safety is a trend toward joint benefit–risk assessment. In the European Union, the pharmacovigilance legislation due to come into effect July 2012 requires that evaluation of effectiveness will be required in risk management plans and reported in periodic safety update reports.

Observational Studies and Meta-Analysis

As products move from the clinic to the real world, an important methodological shift occurs, from the randomized trial paradigm to the observational study paradigm. In the randomized trial, the goal is to make an inference as to whether a new medication is more efficacious than placebo — or in some cases, standard of care — through statistical hypothesis testing. In the observational study, the objective shifts to determining the strength of the association. A coherent understanding of the disease process and the drugs' mechanisms of action must be combined when designing pharmacoepidemiologic studies of drug effectiveness. Such studies require refined thinking and extraordinary care at the design, data collection, and interpretation stages to avoid making incorrect inferences, to transparently show the limitations and to correctly contextualize the findings.

Observational studies may complement randomized studies by evaluating safety signals found in the clinical program and evaluating new signals that appear once a drug comes to market, quantifying effectiveness in the real world, identifying new indications and new target populations, and understanding the effectiveness of medications given concurrently. The results of these studies can suggest new hypotheses to be tested in randomized trials. Careful thinking about study design at the outset avoids making spurious inferences, a common occurrence in the peer-reviewed literature. Absence of such thinking can lead to new trials that are ill-conceived; there are active examples of such trials that are underway today.

The use of network meta-analysis is growing as a way to satisfy the needs of regulators in terms of comparative effectiveness research and of payers in terms of synthesizing all available evidence. Careful and nuanced thinking guided by epidemiologic principles is required for correctly assembling and analyzing the network of evidence.

Skate Where the Puck Is Going, Not Where It's Been

The insight of Wayne Gretzky provides an apt metaphor for the biopharmaceutical industry today. As the industry's processes are transformed in response to external and internal challenges, there is growing recognition of the need for strategic epidemiologic thinking at all stages of development in the drug lifecycle: characterizing the humanistic burden of illness, targeting specific patient populations, refining therapeutic product profiles, collecting patient reported outcomes, undertaking pharmacoepidemiologic and comparative effectiveness research for developing insights into real world effectiveness, and assessing iteratively the benefit-risk balance.

Those involved in tailored therapeutics often hear the phrase "using the right medication for the right patient at the right time." Correspondingly, the phrase for those involved in research and development is "answering the right question using the right study design for the right target audience." Epidemiologists have a lot to say about that. PV