When Novelty Is Not Enough

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Neither orderly nor fully rational, the current healthcare environment is a mosaic of providers, products, services, and intermediaries delivering healthcare, regulatory, and other government institutions, and consumers. The information required for informed healthcare decisions for novel pharmaceutical interventions varies appreciably with the audience, the therapeutic area, and the stage of product development. In this environment, the viability of new product introductions can be heavily influenced by perceived value as well as by mechanistic novelty. Correspondingly, research and development activities can be influenced profoundly by the use of incentive-based formularies, prior authorization requirements, or systems of reimbursement that mandate a stream of evidence confirming clinical utility in the presence of therapeutic uncertainty (eg, Centers for Medicare & Medicaid Services, Coverage with Evidence Development). The economic impact of innovative technology on the healthcare system, as well as the effects on the individual patient, can become a significant variable that influences the extent of research activities from the bench to the physician–patient–payer interface.

The current explosion in the science that supports discovery platforms and clinical development activities places a particular emphasis on the importance of integrating knowledge across a spectrum of interests and perspectives extending from the laboratory to the pharmacy. These efforts are driven by the increases in prevalence of chronic illnesses, the associated direct and indirect costs, and, for some indications, the rapid infusion/diffusion of innovative therapy into practice. Research and development activities, including the hypotheses addressed and the methods used thus become relevant to benefit design decisions. A critical review that separates overly enthusiastic and premature technology endorsements from initiatives that are likely to yield testable novel hypotheses and compounds is warranted. Innovative devices (eg, nanotechnology), routes of administration (eg, oral versus parenteral), and the joint development of diagnostics bundled with treatment (eg, biomarkers permitting disease fractionation and patient segmentation) represent potentially significant effects on the delivery of care in several clinical categories. Changes in regulatory guidance regarding clinical trial design and the art and science of conducting clinical research likewise facilitate an environment of innovation. These changes accelerate the clinical evaluation of compounds that will enhance therapeutic indices, shape longer-term outcomes, and significantly affect the overall cost burden associated with care.

The Discovery–Development Interface

Novel Targets

Research pipelines in many therapeutic modalities are filled with compounds derived from innovative technology reflecting a scientific environment that has significantly expanded our knowledge of molecular and cellular biology (see commentary, Industry Trends–Clinical, The 2007 Pharmaceutical and Biotech Pipeline Year-End Summary. AHDB. 2008;1[1]:43-45). We now have a vastly better understanding of cellular signals that mediate cell-cycle processes in oncology, for example, as well as the critical role that supporting tissue performs in the maintenance of cell growth and viability. A more sophisticated understanding of molecular oncology currently is facilitating significant advancement in the detection, classification, and treatment of clinical conditions. Newer, and very specific, medications occasionally offer a compelling rationale for use with, rather than instead of, an established regimen to enhance efficacy or mitigate known toxicity issues—a process that adds to the complexity of evaluating the overall utility of new products entering clinical use.

Developments at the interface between devices and

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In addition, studies may be truncated based on 4 as well as typical demographic, sociological, or physician communication factors. Such technology raises the possibility of innovative diagnostics (molecular imaging), or localized cellular reporters of efficacy that can confirm access to the target, and multifunctional therapeutics in which targeting, as well as therapeutic, agents are simultaneously presented.

**Innovation in Clinical Methodology**

In many therapeutic areas, clinical development has been transformed by the research community. As a result, innovative programs yield more data, at more relevant dosing regimens and combinations, in an increasingly segmented but more therapeutically relevant patient population. These initiatives reduce the number of patients exposed unnecessarily to experimental therapy ultimately demonstrated as inferior. They facilitate more extensive exposure to new therapy based upon continually updated efficacy and safety data, and allow clinicians to characterize disease or patient features that will classify and predict response earlier in the drug development process.

During this process, the choice of trial end point can materially shape the ability to assess overall value. For example, a composite may facilitate reduction in sample size in aggregate, while obscuring the impact of individual variables, thereby producing a therapeutic profile based on a mosaic of outcomes, none of which individually provides an “index” for response. The choice of a composite facilitates discussion of a net effect but introduces variability into the way in which the value of a therapeutic intervention can be assessed, as a result of the heterogeneity in response or patient importance across components. In addition, studies may be truncated based on “proxies” for clinically relevant outcomes, thereby terminating study assessments before the actual measurement of any health outcomes. Further still, quality-of-life assessments may emerge as an indispensable component of an assessment of product attributes, given the needs of clinicians to explain and justify treatment alternatives. Each study-design option elected during development dictates the extent and type of data acquired, which either enhances or obscures trial interpretation and utility.

Innovative mechanisms of action also invite an exploration of application outside the terms of the product license (ie, off-label use). This activity raises concerns about product safety, with attendant uncertainties regarding the rigor of data collection and confounding variables that may cloud interpretation. These studies, in turn, may be accompanied by the rapid dissemination of results that can transform the standard of care in a given environment and yield a host of ethical, economic, regulatory, legal, and clinical issues. Indeed, enhancements in information technology theoretically enable every physician–patient interaction to become an opportunity for research. Such technology can accelerate product diffusion within the community and provide additional opportunities for generating hypotheses that extend potential clinical applications as mono- or adjunctive therapy.

**The Development–Commercialization Interface**

**Influencing the Decision Process**

The increase in the number of drugs aimed at novel targets, as well as the stratification of patients during the development process along genotypic or phenotypic dimensions, will result in psychosocial challenges as significant as technological challenges during the process of commercialization. Segmentation already exists within every disease population. For example, the experience of the illness (as opposed to its diagnosis) fractionates an otherwise homogenous disease group. At one end of the spectrum are patients who are undiagnosed, unconcerned, and at risk; at the other end are patients who are diagnosed, very motivated, and fully satisfied recipients of care. In the absence of patientspecific outcome measures, increasingly technical data may encumber a healthcare decision model in which patients must be active participants.

The challenge of creating an information package during development is particularly relevant as diseases are transformed from emergent, life-threatening conditions into chronic illnesses where patients and caregivers cooperatively make choices regarding therapeutic options and resulting quality of life. In this therapeutic milieu, the interaction of a healthcare professional with a patient during this decision process provides a key leverage point for the introduction of clinical trial evidence, and qualifying and presenting that information—systematically—becomes an important part of the commercialization process. Potential variables are as intriguing as they are diverse and can include the method of presentation, such as online medical information or physician communication behaviors, as well as typical demographic, sociologic, and personality characteristics. Physician–patient factors that influence healthcare decisions, including qualitative and quantitative interactions between these factors, are not as frequently evaluated using study designs that are comparable in rigor to the randomized clinical trials used to define efficacy and safety in proto-
typical registration programs. In an environment where patient copayments and compliance with therapeutic strategies are required, understanding the interplay of physician–patient variables that modify the decision process can be crucial.

**Defining the Value Proposition**

Medical technology assessments provide a conversion point for data formally collected in the preregistration and in the periapproval environment—an evaluation of clinical data from a multidisciplinary perspective, including economic aspects associated with acquiring the intervention.\(^1\) Weighting methodologic rigor more than funding source, these evaluations identify data considered most relevant clinically and, when fully articulated, can provide direction to a proposed clinical development program that must consider potential reimbursement as a factor in a therapeutic agent’s ultimate commercial success. For example, identifying the population that is most likely to use the product, as opposed to the population where the agent might have been formally evaluated, influences how evidence may be weighted and how processes can be developed to ensure appropriate patient support. Although regulatory acceptance provides a platform for this review, information from peer-reviewed journals can also be considered, and a mix of case series, cohort studies, and registries are complementary to randomized studies if impractical.\(^2\) The impact of therapy and alternative interventions, used alone or in combination, on overall health outcomes and the totality of the cost burden associated with a new treatment provides key metrics. It is the impact of a therapeutic modality on the healthcare system rather than an isolated clinical measure that provides focus.

Establishing a pathway for actionable information from the clinical development process has a number of generic characteristics that can be monitored during the course of product development and before its commercial introduction. For example, will the clinical development program incorporate hypotheses generated through claims data (laboratory, pharmacy, and administrative), thereby acknowledging and addressing the importance of questions generated within the system of healthcare as well as for the patient in treatment? Will the clinical development program include patients with concurrent illnesses and concomitant medications representative of the community in which the new therapy will be introduced, in addition to the index indication that can significantly modify the overall cost of care? For planned adjunctive therapy in which quality of life is of appreciable importance, will a proposed clinical development program evaluate patients across a spectrum of disease severity, incorporating patient-specific outcomes contingent upon the severity of illness and facilitating their introduction into clinical research and practice? Bringing the full weight of state-of-the-art technology and trial methodology to address each of these questions will ensure optimal therapy and best choices for patients.

**A Redefinition of Translational Research**

Effective drug benefit design requires sufficient lead time for healthcare providers to assess the implications of innovative technology and its potential impact on a system of healthcare, and to influence the direction of clinical research and development to ensure that questions of relevance are adequately addressed before commercial introduction. Clinical trialists, in contrast, are experts at formulating and addressing testable hypotheses based upon these questions, and are in an optimal position in the discovery/development process to generate information facilitating those assessments. The opportunity for collaborative research at every phase of discovery, development, and commercialization appears to be self-evident based upon the participation of multiple stakeholders in this process.

The research and development perspective within this publication operates under the assumption that systematic reviews of new drugs or devices, in discovery or development, by leading experts within the field, will enable informed decisions about health benefits because they can influence the scope and detail of planned clinical research programs. The decision process concerning methods of disease detection, classification and segmentation of affected patients, and treatment will effectively transform the meaning of translational research from its traditional bench-to-bedside venue to a wider spectrum of patient-oriented research. That spectrum will include epidemiologic evaluation, health outcomes research, or educational interventions that are tailored to the needs of a changing and dynamic healthcare environment.

**References**


**AHDB Stakeholder Perspective**

Dr. Murphy’s opening statement about the importance of “integrating knowledge across a spectrum of interests and perspectives” to new drug development captures the essence of the challenge to align the interests of manufacturer and customer. Research and development (R&D) represents the capability of science to heal; it is a progressive field. The provider, payor, and regulatory stakeholder sectors are inherently conservative, delaying or outright limiting acceptance of new drug innovation. That is as it should be. The question remains—Are all stakeholders aligning their activities in a way that can be considered progressive and efficient for making available the use of important new therapies?

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R&D are providing important new therapies faster than healthcare plans can pay for them. This is putting pressures on payors and health plan sponsors to impede branded drug utilization. Several financial factors are behind this payor dynamic, and they must be addressed if healthcare is to receive the full potential of innovative research. The first is the demographic/epidemiologic reality of the graying of the baby boom generation, which has resulted in an increase in chronic diseases that, in turn, caused an increase in drug utilization. A second factor is the increased cost of launching a new drug, now approaching an average of $800 million. A third factor is a rise in litigation in the wake of a new drug’s side effects.

However, payors also have an incentive to take advantage of new drug development if they are at risk for overall healthcare resource allocation and not just the drug benefit. A healed patient is preferable financially to a patient taking inexpensive, older drugs that fail to heal.

Meanwhile, the demand for evidence-based formulary/benefit design models is countered by an incomplete consensus on the ability of different categories of evidence to determine drug safety, efficacy, and above all, value, including randomized controlled trials, observational data, meta-analyses, and adaptive clinical trial designs. In addition, much remains to be understood about the application of population-based research findings in the clinical setting.

Pharmaceutical and biotech companies are attempting to collaborate with payors at the early stages of drug development to identify which drugs will resonate with the plan. Much work remains to be done to align interests, as manufacturers still need to protect trade secrets and payors cannot agree to use a drug that will be launched several years hence in a changed market. The advantages of aligning stakeholder interests outweigh the traditional boundaries that historically have kept new drug development the best-kept secret. Cost pressures are too great to expect the stakeholders to resist collaboration.