

Reprinted with permission from *American Health & Drug Benefits*. Vol 1, No 3, 2008:13-19. Copyright © 2008, AHDB.

Medicare Coverage Policies for Biologics: The Broad Gray Line

Part 2 of an Interview with Joseph Antos, PhD



In October 2007, *American Health & Drug Benefits* asked Dr Joseph Antos to discuss the forces that have shaped Medicare's policies and their impact on the various stakeholders in US healthcare. The first part of the interview appeared in *AHDB* in February 2008. This second part focuses on the impact of the Centers for Medicare & Medicaid Services drug coverage on the future of biologic products. This discussion does not reflect any new developments occurring after October, such as the recent recommendation of the US Food and Drug Administration advisory committee to narrow the indication for erythropoiesis-stimulating agents to patients with cancer.

Robert Henry: *How are decisions being made for conventional pharmaceutical products on the one hand and biologic products on the other? Biologics have a comparative carte blanche—for now. Attempts at cost-containment in biologic treatment have been shown to be counterproductive, punitive, and not cost-effective. How adept are payors in utilizing conventional pharmaceutical products compared with the biotech products?*

Joseph Antos: Clearly, proliferation of unique products that promise benefits not available from conventional pharmaceuticals, and for which there are no substitutes, will be a challenge for insurers, including Medicare. Although some biologics—such as insulin, human growth factor, erythropoiesis-stimulating agents (ESAs)—have been around for a long time, we are already seeing exotic new molecules coming on the market to help narrowly defined patient populations with specific cancers and other serious diseases. These are not the mass-market blockbusters of old; these are

products that will hit the market with laserlike precision. Past experience will provide little guidance to insurers facing a more fragmented, but more intense, market demand from highly motivated groups of patients and their physicians.

Virtually every decision an insurer makes will be more complex. Coverage, which was never an easy decision, will be complicated by the need to also pay for specialized patient testing to determine suitability and dosage strength. Will insurers be willing to pay for expensive tests for all patients presenting with a specific disease, possibly spending substantial sums to screen out patients who would not benefit from the drug? Patient management will take on a new look if there are no close substitutes for an expensive biologic. Moreover, patient monitoring will become even more important for tracking effectiveness of the treatment and possible side effects—both issues of interest to the payor as well as to the patient and the doctor.

Price negotiations will also be perplexing. How does the insurer gauge value and potential demand from its customers, and what is the basis for price negotiations with the manufacturer? Where is the balance between cost and patient value?

Insurers are not alone in this complicated new world. The innovator drug companies themselves must consider the same issues. The ultimate question they must answer at a very early stage of drug development

Dr Antos is the Wilson H. Taylor Scholar in Health Care and Retirement Policy at American Enterprise Institute for Public Policy Research. He is also a member of the Panel of Health Advisors to the Congressional Budget Office, a Commissioner of the Maryland Health Services Cost Review Commission, and Adjunct Professor at the School of Public Health of the University of North Carolina at Chapel Hill.

is: What is the market potential for a product that has great scientific potential but that is not fully proved, a product that will require the investment of time and a very large amount of money before it gets to market?

The search for breakthrough conventional pharmaceuticals has become increasingly difficult. Clearly, the big companies recognize that the next frontier is the biologics area.

Henry: *It is a problem of alignment of stakeholders, and I am sure it fascinates the formulary and drug benefit design decision makers.*

Antos: “Fascinates” is probably too benign a term. “Terrifies” may be closer to the truth. There is big money at stake, and greater uncertainties than in the conventional pharmaceutical market concerning the drug efficacy, the size of the market, willingness to pay, and possible adverse consequences that can only be detected once a drug has gone into general use for the relevant group of patients. The drug may be very effective for most patients with a particular disease, or it may be valuable only to a small subset of patients. There may be hidden factors that cannot be determined through relatively small clinical trials that would dictate which subset of patients should receive the drug. Genetic or other types of patient testing could clarify this issue, but such tests may be difficult to develop and could be expensive.

Henry: *Can we conclude that the conventional pharmaceutical products have been overregulated with benefit design hurdles? Might this tend to induce pharmaceutical companies to abandon research and development of conventional products and focus on the higher payback areas in biotech?*

Antos: One could argue that there has been overregulation of conventional pharmaceuticals, but I don’t think that’s the main problem. The US Food and Drug Administration (FDA) vacillates between protecting patients from possible health problems that result from approving a drug too quickly and protecting patients from the potential loss of therapeutic value by not approving a drug quickly enough. The pendulum seems

to be swinging toward greater caution in drug approvals. However, I think the real problem is scientific; the search for breakthrough conventional pharmaceuticals has become increasingly difficult. Consequently, we see mainline pharmaceutical companies spending large sums on mergers and acquisitions of other drug companies—in many cases, to acquire the intellectual property of the smaller company. Clearly, the big companies recognize that the next frontier is the biologics area.

Furthermore, while small innovator companies may have an edge on the science, they have a real disadvantage coping with the regulatory process and marketing. Big pharma has the size and experience to overcome those hurdles to market success. I think we will continue to see a strong synergy between the biologics innovators and big pharma.

Henry: *The utilization of drugs, biotech or otherwise, is supposed to be following evidence-based guidelines. However, recent events show that that evidence-based medicine is a thin veneer easily peeled off in the face of agenda-driven initiatives. When the robust biotech pipeline floods the market with costly drugs, we better have a grasp on evaluating their value. A riveting example of the problem was the events that followed the publication of the rosiglitazone meta-analysis, conducted by Dr Steve Nissen, in the New England Journal of Medicine last year. The publication of the study hot-wired into the professional, public, and government mainframe. Whatever you think of the study itself, it seems hard to justify the degree to which one questionably done meta-analysis affected the entire healthcare landscape. The question is, was the study critical of rosiglitazone in general or only on the branded-name product known as Avandia? For if it was the latter—I think Dr Nissen said something to the effect that he isn’t afraid to take on any of the big pharma companies—then we have some hard reckoning to do here.*

Antos: In politics and in healthcare, the boldly stated accusation trumps careful analysis every time. People remember the simple negatives, and hold on to them even when the more complicated truth finally comes out. That’s human nature, but it is no way to run the health system.

As you indicated, the Avandia meta-analysis was done in by partial analysis. Dr Nissen had access to the preliminary results of several clinical trials and used those results to rush to judgment about the increased risk of heart attacks to patients. His conclusions were dramatic—the odds of having a heart attack increase by 43% for patients who take Avandia compared with those who take other drugs, or a placebo. No need to

ask whether the FDA confirmed the clinical significance of these preliminary findings. The FDA had not made that determination in May 2007, when Dr Nissen's story hit the media, and the FDA maintains that the studies remain inconclusive. No need to ask what may be the absolute risk of adverse consequences for patients taking the drug. Typically in drug studies, a large-percentage increase in the risk of serious side effects is based on a very small absolute risk of incurring the negative health outcome.

Certainly, the industry could have been more forthcoming about potential problems with the drug. And one can legitimately criticize the regulatory process for lapses that could harm some patients. But there has to be a balance. I do not think the industry can get ahead of the Steve Nissens of the world, because there will always be a critic who can claim the company did not reveal information quickly enough or completely enough. There will always be a lawyer ready to take a product-liability case to court, and ultimately money changes hands and scalps are taken. That is part of life today for pharmaceutical companies.

As a society, we should focus on the net impact of this on patients. Once a drug gets a bad reputation (regardless of its usefulness in treating disease), doctors won't prescribe it, and patients won't take it. Vioxx is the best-known example. This drug was vastly superior to other painkillers for patients with severe arthritis who also suffered abdominal pain and complications from other treatments. This drug obviously had risks, like all pharmaceuticals, and it was overprescribed to patients who could safely use less-powerful drugs, but it was clearly the painkiller of choice for some patients. A good outcome would have been to tighten the prescribing standards, limiting the drug to the appropriate class of patients. Nonetheless, the drug was withdrawn from the market under a barrage of negative publicity.

As I said, there has to be a balance, and public scrutiny of the actions of the FDA and the pharmaceutical industry is certainly in order. There is always the need for countervailing pressure to ensure that those who stand to make money from the sale of health services and products do not overstep science or their responsibilities to patients and the broader society. Independent researchers should be able to analyze the data and draw their own conclusions about the safety and efficacy of a treatment. That is positive. The question is, do we have reasonable research standards? Are the data up to speed? Do we have a sensible process of getting that information into the system in a way that doesn't cause panic and precipitous action that does more harm than good? We don't now.

Henry: *The interesting takeaway of the rosiglitazone study is the gaping system-flaw it reveals.*

Antos: And nobody seems to be working on it, either. Clearly, individuals have the right to analyze evidence, draw conclusions, and publicize them. What we cannot seem to find is the line between providing information and hollering "fire!" in the theater. In the case of pharmaceuticals, I think that line is very broad and very gray. Different individuals and organizations will have differing views about when a result is solid enough to call for action on the part of the FDA or the manufacturers. Good judgment is hard to come by, and there will be disagreements about what constitutes good scientific evidence.

Patients rarely have only one medical condition, and the physician must weigh the likely efficacy of alternative treatments for a patient who often differs greatly from the subjects in a clinical trial.

This raises the issue of comparative effectiveness analysis—the latest “silver bullet” that promises to simultaneously improve the quality of care and reduce unnecessary health spending. An oversimplified, but increasingly popular view, is that better data collection on treatments and outcomes can lead to unbiased analysis that produces clear conclusions about the best way to treat diseases. Unfortunately, determining the best course of treatment for actual patients is not that straightforward.

The fundamental problem is that healthcare decisions are not simple yes or no questions. Patients rarely have only one medical condition, and the physician must weigh the likely efficacy of alternative treatments for a patient who often differs greatly from the subjects in a clinical trial or an observational study. Moreover, we are severely limited in our ability to collect adequate data, and methodological challenges in the use of such data abound. Electronic medical records can help here, but we have been talking about health information technology (IT) for several decades and have yet to have a functioning health IT system. Controlled clinical trials are a kind of gold standard for assessing treatment efficacy, but comparative studies would

require much larger, more time-consuming, and more expensive trials than would be practical to implement. Observational data may provide an alternative basis for analysis, but such data also have limitations.

Many politicians are drawn to comparative effectiveness analysis, hoping that evidence-based medicine will allow painless spending cuts in government health programs. If we eliminated coverage for a treatment that does not work, the savings could not be viewed as a sacrifice by patients or a reduction in benefits (although healthcare providers may not take the same benign view of such a policy). In other words, difficult political judgments would become technical decisions, absolving policymakers from having to make hard decisions.

However, someone—the physician—will have to make those hard decisions for patients with multiple conditions and other complications who fall outside the limits of even the most thorough comparative effectiveness study. Insurers and government will have to build in flexibility in their coverage and payment policies to account for patients with exceptional and justifiable needs. Such policies will have to balance the needs of patients, the incentives for innovation, and the cost of healthcare. That's a tall order.

Perhaps the most powerful motivator for constructive change is payment. Financial incentives drive the system, and changing those incentives will change the system.

Over time, we will improve our ability to collect and analyze patient data, and increasingly financial and treatment decisions will be driven by a growing body of hard evidence on efficacy. The alternative is what we have now—a system of coverage and treatment decisions that is only partly informed by what we could, in concept, already know about what works for whom in healthcare. And where there is no systematic application of scientific knowledge that we could already use, even with the inadequacies of our current system. Insurers continue to make coverage decisions by asking a committee of physicians to examine research studies with inherent limitations, applying their judgment and experience in a consensus process. Although such committees typically include well-trained and thoughtful experts, they can only know the slice of the world they

are familiar with. Often, the coverage policy does not reflect the inherent uncertainties of this deliberation.

Henry: *Would you say that right now we are at a shrill level, where the healthcare debate is waged in very adversarial terms?*

Antos: Adversarial, and likely to get worse, given the rising political tensions over healthcare as demonstrated in the presidential campaign. The shrillness may soon be at a frequency that only dogs can hear, but it will still be painful for patients, physicians, insurers, and suppliers. We must quit looking for scapegoats, because all of us have some responsibility for unnecessary spending and poor decisions. We need to begin to collect the information that already exists on treatments, outcomes, and cost so that we can understand the pattern of our decision-making at all levels.

The scientific facts only take you a part of the way to a sensible health system. We must also look at the financial incentives and other factors that drive decision-making. What motivates physicians? Partly a sense of professionalism, partly medical school training that the doctor may have received 15 or 20 years ago, and partly new information the doctor could be getting through electronic means that may prompt a better treatment decision. Technology can help. For example, electronic prescribing systems can be designed to give the physician important clinical information as well as identify what the drug will cost the patient, and whether there are possible substitutes. This may lower cost for the patient and may also prompt busy physicians to look more closely at the patient's condition, and whether they are prescribing the best course of treatment.

Perhaps the most powerful motivator for constructive change is payment. Financial incentives drive the system, and changing those incentives will change the system. We saw this in the mid-1980s, when Medicare shifted from cost reimbursement to prospective payment for hospitals. Private insurers quickly followed suit. The result was a substantial increase in efficiency and an improvement in the delivery of inpatient care. We went almost overnight from long hospital stays that kept beds filled and money flowing under cost reimbursement to shorter stays and a shift to preadmission testing on an outpatient basis. The orientation of hospitals went from holding on to patients to treating them expeditiously and discharging them as soon as possible, since under prospective payment a hospital no longer received additional payment for another day's stay. Smart payment systems breed smart healthcare

delivery, but it can be difficult to devise payment systems that work well.

Payment also drives medical innovation, including the development of new pharmaceuticals, an area that has proved challenging for Medicare. The patent system grants a period of marketing exclusivity—in other words, a monopoly—to successful drug innovators. That gives the innovator an opportunity to recoup the typically large costs of bringing a new drug to market, particularly if the drug is the first in its class and faces little or no competition. Medicare has long covered physician-administered drugs through its Part B plan, substantially overpaying physicians for those products based on a formula. Recent changes in the formula have brought the extent of overpayment down, but the new formula also has flaws.

With that background, the recent controversy over ESAs begins to make sense. ESAs represent the largest single-drug spending category for Medicare Part B. ESAs improve the ability of very sick patients to function normally, relieving them of the chronic fatigue brought on by a low red blood cell count. If ESAs were not available, the only alternative would be blood transfusions for many of these patients. There are concerns about the potential for overdosing, and there is scientific debate over which patients, with which conditions, would benefit from treatment with ESAs. There are also concerns that financial considerations may have prompted overuse and inappropriate use of this drug class.

In my view, the line between the FDA and the Centers for Medicare & Medicaid Services (CMS) in their respective responsibilities to regulate the pharmaceutical market blurred in the recent ruling affecting the use of ESAs. The FDA is responsible for ensuring the safety and efficacy of pharmaceuticals; CMS, through Medicare, is responsible for ensuring that appropriate payment is made for appropriate medical treatment. However, payment drives medical practice. Medicare's recent coverage decision effectively dictates the clinical circumstances under which ESAs will be used for Medicare patients, and private insurers were quick to adapt similar policies.

The chronology of events is interesting. Faced with new preliminary findings suggesting that dosing standards should be lowered, the FDA convened an advisory panel that met in March 2007 but failed to draw clear conclusions about the appropriate dosage. Subsequently, warning language that had been on the label was elevated to a “black box” status, without strengthening the language.

Within 2 months of that meeting, CMS issued a

proposed national coverage decision affecting cancer patients whose physicians prescribed ESAs. It offered a detailed explanation for limiting ESA dosing regimens and the range of conditions Medicare would cover. The proposed decision eliminated payment for ESAs for a variety of cancers and cancer-related conditions, and it effectively prescribed the course of treatment for patients who were covered, by requiring that hemoglobin levels be maintained within tight boundaries. This ran counter to long-established (20 years) successful medical practice with ESAs. Oncologists rose up in a fury over this; patients protested; but the final coverage decision was made only slightly more flexible.

With that background, the recent controversy over ESAs begins to make sense. ESAs represent the largest single-drug spending category for Medicare Part B. ESAs improve the ability of very sick patients to function normally.

Henry: *The American Society of Hematology (ASH) issued a formal declaration opposing this. They had been consulted before the decision was made and were aghast that their official guidelines were roundly ignored. So here we have this intersection of the FDA, CMS, and ASH.*

Antos: Yes, and each of those entities has a potential conflict of interest. ASH advocates for patients, but its members also gain financially by a favorable Medicare coverage decision. CMS is charged with paying for appropriate care, but they also worry about the bottom line. The FDA regulates the introduction of new drugs to ensure safety and efficacy, and it has been under increasing political pressure that has pushed toward the safety side of the equation. When he was FDA commissioner, Dr Mark McClellan emphasized the parallel risks that the FDA must balance: the risk of harming patients from approving a new drug, and the risk of harming patients from withholding approval of a drug that offers therapeutic benefits. So, there is a balancing of risks in the FDA's approval process.

Henry: *The eternal yin and yang. The FDA is going to emphasize that drugs are safe or effective, but it cannot guarantee that drugs will be perfectly safe and perfectly efficacious.*

Antos: Exactly. The regulatory pendulum swings between the goals of safety and efficacy, but lately it seems to be moving more toward safety. CMS has its own yin and yang challenge. By law, Medicare cannot dictate the practice of medicine, but dictating the payment for medicine does dictate the practice of medicine to a large extent. Obviously, CMS would like to avoid causing their patients great difficulties. They do not want to have to answer to Congress because a politically sensitive group of patients is not getting access to necessary treatment. But CMS is also under pressure from Congress about cost. Healthcare providers have the same problem. They want to do what they think is right for their patients, but they also profit from the services they deliver.

The regulatory pendulum swings between the goals of safety and efficacy, but lately it seems to be moving more toward safety. CMS has its own yin and yang challenge.

And patients in the Internet era are much more informed than they have been, but most patients are not in a good position to make clinical judgments. With certain diseases, the patient will know immediately if something has gone wrong. For example, a patient being given an ESA will know when his energy level has dropped, an indication that he might need an increased or an additional dose. But a patient's impression may be misleading, and there are many factors that determine how a patient reacts to a drug. Moreover, patients generally cannot know whether a treatment is putting them at increased risk for serious complications. That is a judgment call based on the clinical evidence but tempered by the unknowns posed by the specific patient who may be far from average in the way his body reacts to the therapy. What is the right course of treatment for me, not for some statistical average, is the important question, which is often difficult to answer with any certainty.

Henry: *It is that gray line again, especially as ESAs do not increase longevity but rather quality of life.*

Antos: What has been proved is that ESAs do what they are supposed to do. They enable the patient to make it through the day. And patients with more energy are more likely to adhere to their treatment regimen,

more likely to do what is necessary to stay alive. Medicare pays for many treatments that do not extend life but improve quality of life.

Another aspect of this controversy is how good were the studies used as evidence? And how reliable was CMS's interpretation of those studies? Again, it goes back to this gray area of healthcare. It is unlikely that a single study or group of studies could give us clear evidence of how a treatment should be used without any uncertainty, or without the need to make exceptions based on the specific patient.

I find it particularly concerning that CMS's decision is different from the FDA's label. The label states clearly that dosing should seek to maintain a patient's hemoglobin level between 10 and 12 g/dL, yet the CMS coverage decision permits payment when the level is below 10 g/dL.

Despite official denials, this looks like a disagreement between the 2 agencies on the science, and it raises questions about their respective roles. To what extent should the latest scientific judgments drive Medicare coverage policy, and vice versa? Is CMS operating on the medical science or on cost-containment grounds here? This is likely to be a continuing controversy, given the inherent scientific uncertainties associated with any medical treatment.

Henry: *And meanwhile patients are in limbo?*

Antos: They are not in limbo, since the coverage decision is binding. Given the cost of the drug and the difficulty of challenging such decisions for a single patient, the vast majority of physicians will conform their treatment protocols to fit the CMS ruling. That means patients will be taken off ESAs once their hemoglobin level exceeds 10 g/dL. Some patients will be put on a biological rollercoaster, going on and off the treatment as their blood levels change. Obviously, hemoglobin levels fluctuate, but the payment standard is perfectly rigid. Some patients who previously would have had continuous treatment with ESAs will now be required to go on and off, with the inevitable consequence of periods of extreme fatigue. That won't be good for their quality of life, and it may have an impact on their overall health status.

Henry: *While the private insurers and employers may have differing views on where to set coverage, with Aetna deciding that 10 g/dL is appropriate but SIGMA deciding on a different level, CMS is a monolithic purchaser of healthcare. This could be loosely called the "California effect," where the*

trends all start in California and drift East, and the trends that started with CMS drift over to the private industry.

Antos: Yes, but it is more powerful than that. Medicare is probably the dominant payor for this class of patients, thus Medicare policy will be even more important for cancer patients than for the average person. And what Medicare decides to do will greatly influence what Aetna, Humana, Prudential, and other insurers decide to do. One can expect private insurers to line up behind the Medicare coverage decision, since that decision may seem more conservative medically, and tighter coverage limits can save money. And let's not forget that the new coverage decision could open up a basis for malpractice liability. One could imagine litigation over a patient suffering adverse consequences, where the first piece of evidence in the case is the fact that the insurer covered ESA treatment for patients with hemoglobin levels above 10 g/dL.

Henry: *The litigation threat is one of the other drivers of utilization.*

Antos: Yes, and in this case, less utilization.

Henry: *So less utilization is legally, not necessarily medically, safer?*

Antos: I'm not a physician, but that appears to be the case. The implication is that Medicare coverage and payment policy will have a very powerful impact on the pharmaceutical industry, more so than we have seen in the past.

Henry: *In the biologics area?*

Antos: Yes, although Medicare will probably move carefully here because of the newness of such products and the targeting of small patient populations. That may mean that Medicare will take a wait-and-see attitude. The traditional approach to coverage is wait to see whether a new, expensive biotech drug becomes an essential part of the community's standard of practice. Medicare may use the Coverage with Evidence Development (CED) process for these drugs. There will be political, as well as clinical, reasons to do that. But whereas CED is a way CMS has adopted to allow limited coverage for expensive treatments, it is unclear that coverage could be withdrawn if the drug proves to be only modestly efficacious; that remains to be seen. Given the high financial and political stakes, Medicare

will be loath to rush into anything and will want the private insurers and the medical community at the local level to lead the way.

The new biotech drugs will pose a harder problem for CMS. Medicare will exert more pressure on manufacturers for supporting evidence, genetic testing or protein markers, or other ways of identifying the patient population who would most benefit from an expensive new biotech drug.

The implication is that Medicare coverage and payment policy will have a very powerful impact on the pharmaceutical industry, more so than we have seen in the past.

Henry: *So that is the only true cost-containment tool that has any practical utility for biologics.*

Antos: If there are reliable ways of distinguishing among patients. I suspect that we have a long way to go before tools such as genomic testing are widely available, and even longer before they are used routinely as part of Medicare or a private insurer's decision about payment.

How do we square the circle between rising healthcare costs and scientific uncertainties? We must recognize that resources are finite, and eventually we will have to make hard decisions about how we want to divide those finite resources between healthcare and other forms of consumption. That will require a change in the unrealistic but common view that health insurance should pay for every medical intervention that might confer some benefit on the patient. This problem cannot be solved solely by technical judgments about the comparative effectiveness of alternative treatments, since the resource constraint is an absolute limit on consumption. Consequently, we must discard the hope that science will solve the health financing crisis in a way that is totally painless, with unnecessary treatments eliminated and everyone getting all the care that could provide some benefit, regardless of cost. Even with good information on the efficacy of alternative treatment, we will not be able to avoid the value judgments that will be forced on us by resource limitations.

Henry: *You said that the FDA has safety advocates and efficacy advocates. Is there a similar division within CMS: cost-containment versus quality advocates?*

Antos: Yes, but I would characterize the safety/efficacy debate as one that is weighed by decision makers in both agencies rather than between advocates. Of course, experts can disagree about the relative importance of safety and efficacy in considering a specific case, but both issues are considered. There has been a rising consciousness in CMS about the importance of quality and access to treatment as well as cost. A similar evolu-

tion in thinking has occurred among private insurers. Responsible CMS officials worry about the balance between cost and efficacy in every decision they make. And reasonable people can disagree about how well they maintain that balance in Medicare policy. ■

For inquiries or comments, please contact editorial@AHDBonline.com.

AHDB Stakeholder Perspective

CMS Coverage Policies for Biologics: Defining a Lagrangian Point for Cost, Quality, and Access

Biopharmaceuticals—including such diverse entities as antibodies, recombinant proteins, and vaccines—provide a convergence point for the interests of all stakeholders in healthcare delivery.

These agents are characterized by remarkably diverse and innovative mechanisms of action that create a compelling rationale for therapeutic use in life-threatening or chronic, debilitating disorders, while simultaneously challenging all traditional management mechanisms about cost and access, such as tier placement, patient copays, and prior authorization. Because the molecular basis for activity can preclude application across all patients with a given clinical phenotype, prudent use may require evaluation of genetic and phenotypic hallmarks to identify patients with optimal prospects for response; that is, fractionating a hitherto-homogeneous medical condition into multiple “orphan” indications, by restricting the therapeutic target and creating a portfolio of recommendations where therapeutic substitutions are neither possible nor appropriate.

Similarly, the molecular basis of activity of many biopharmaceuticals invites (mandates) exploratory evaluations of efficacy and safety in other therapeu-

tic areas, where pathophysiologic mechanisms share common features (tumor necrosis factor inhibitors in rheumatoid arthritis vs ulcerative colitis). Structuring evaluations to maximize the value of repetitive “N of 1” experiments in which every physician-patient transaction seemingly becomes an opportunity for research is a burgeoning area of interest, where all stakeholders can contribute.

Because therapeutic value is weighted differently by different stakeholders, development programs also must incorporate measures that resonate with multiple audiences as a condition of commercialization. Expressed methodologically, this imperative results in prospective evaluation of subgroups, accelerates the use of patient preference and quality-of-life assessments, and extends the length of formal observation before and beyond the time of registration, to assess long-term safety and inform adjustments in dose or regimen due to concomitant medication or illnesses (“researchers worship at the mean, clinicians use the standard deviation”). Biotechnology products have biological properties, routes of administration, and therapeutic targets that challenge conventional research, regulatory, and commercialization processes. Defining a Lagrangian point that balances cost, quality, and access provides a template for pharmaceutical product development in the 21st century.

Michael F. Murphy, MD, PhD
Chief Medical Scientific Officer
Worldwide Clinical Trials

SUBSCRIBE TO

AMERICAN HEALTH & DRUG BENEFITS™

at www.AHDBonline.com

Engage Healthcare Communications, LLC • PO Box 423 • Long Valley, New Jersey 07853