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Current trends in the cardiovascular clinical trial arena (I)

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Abstract

The existence of effective therapies for most cardiovascular disease states, coupled with increased requirements that potential benefits of new drugs be evaluated on clinical rather than surrogate endpoints, makes it increasingly difficult to substantiate any incremental improvements in efficacy that these new drugs might offer. Compounding the problem is the highly controversial issue of comparing new agents with placebos rather than active pharmaceuticals in drug efficacy trials. Despite the recent consensus that placebos may be used ethically in well-defined, justifiable circumstances, the problem persists, in part because of increased scrutiny by ethics committees but also because of considerable lingering disagreement regarding the propriety and scientific value of placebo-controlled trials (and trials of antihypertensive drugs in particular).

The disagreement also substantially affects the most viable alternative to placebo-controlled trials: actively controlled equivalence/noninferiority trials. To a great extent, this situation was prompted by numerous previous trials of this type that were marked by fundamental methodological flaws and consequent false claims, inconsistencies, and potential harm to patients.

As the development and use of generic drugs continue to escalate, along with concurrent pressure to control medical costs by substituting less-expensive therapies for established ones, any claim that a new drug, intervention, or therapy is "equivalent" to another should not be accepted without close scrutiny. Adherence to proper methods in conducting studies of equivalence will help investigators to avoid false claims and inconsistencies. These matters will be addressed in the third article of this three-part series.

The Magnitude and Scope of the Background Problem

The cardiovascular therapeutic area

The cardiovascular indication has been the largest or second-largest focus of clinical trials for the past decade (the central nervous system has occupied first place since 1999), making up 15.5% of all clinical investigator contracts[1] Correspondingly, the cardiovascular therapeutic area commands the largest market for prescription drugs – nearly one fourth of branded prescription drug sales – as the dominant indication for branded medicines sold commercially during the past few years. The total worldwide cardiovascular market is expected to show revenues of $91.2 billion in 2008, an increase of 6.9% compared with 2003 [2]

The WHO ICD-9 coding system specifies 46 cardiovascular diseases within this therapeutic area; however, 65% of all cardiovascular trials address the top six of these subindications. Essential hypertension is in first place (27.1% of trials), followed by congestive heart failure (13.1%) and cerebrovascular disease (9.9%).

The public health impact

The above mentioned figures are more than justified by the impressive ranking identifying cardiovascular disease as the dominant cause of death and disability worldwide [3] Cardiovascular disease remains a massive public health problem in the developed world, not only in terms of survival, but also with regard to work capacity [4] In the US alone, more than 10 million individuals have symptomatic coronary heart disease, and up to 70% of older adults have hypertension [5] resulting each year in approximately 1.5 million myocardial infarctions, nearly 1 million deaths, and an economic burden of $12 billion. According to WHO figures, [6] cardiovascular disease kills an estimated 17 million people worldwide each year, and it will remain the primary cause of overall mortality for the foreseeable future.

Demographic changes

This latter trend is at least in part a reflection of a worldwide demographic explosion – a huge increase in the number of older adults as a result of unprecedented gains in life expectancy. Globally, the population of people over 65 years of age is increasing by 750,000 each month. The older population is expected to triple in many developing countries within the next 30 years [7]

The aging of the population is beginning to transform health care and social systems, as new public policies in health and social care are being widely adopted throughout the world. [8-11] Public interest and discussions of healthcare issues are at an all-time high. Because the cost of health care is continually escalating in both developed in developing countries, the trend is toward structural reform of healthcare systems.

Spending on prescription drugs

Maintaining a balance between healthcare costs and income is the biggest challenge faced by the majority of markets worldwide. The discrepancy between what is possible today in the provision modern healthcare and what is affordable within limited budgets continues to grow. Politicians, healthcare authorities, hospital administrators, and providers are all looking for cost-containment strategies and additional sources of financing in an effort to curb rising healthcare debts and costs at a time when the proportion of gross domestic product (GDP) allocated to healthcare spending has remained static or is about to fall in many countries.

The percent increase in annual spending for prescription drugs has reached double-digits for the past several years, making drugs increasingly unaffordable. These expenditures represent the fastest-growing component of health care, accounting for 10% to 30% of total healthcare spending in most countries (10% in the US, equalling a 15% increase per year over the past several years,[12] to 30% in Slovakia and Bulgaria[13]). It is estimated that prescription drug expenditures will continue to rise faster than any other service medical sector in most countries over the next decade and to represent 15% of total national health spending in the US by the year 2010 [12]

From January to June 2003, the number of prescriptions issued in the UK was 631.7 million, an increase of 21.6% since 1999–2000; this increase in prescriptions was associated with a 45.9% increase in drug costs to £7,182.2 million over the same 3-year period. Between June 2002 and June 2003, prescription costs increased by 11.1%, whereas the number of prescription items increased by 5.4% [14] This trend has already had an impact on public insurance programs and triggered considerable political attention in recent years, as healthcare cost containment has become a priority on the political agenda of governments seeking to curb the spiralling debt.

The profile of spending/sales

Of the 9,532 registered drugs on the US market, the bulk of the 1-year spending growth of $22.5 billion in 2001 was largely attributable to increased spending on a rather small number of individual drugs and categories of drugs[15]:

• Just over half (50.6%) of the growth in spending occurred in just nine categories of drugs – those used for treating depression, high cholesterol, diabetes, arthritis, high blood pressure, pain, allergies, and ulcers and other gastrointestinal ailments.

• Among the 50 drugs that contributed most to the 1-year increase in spending, sales rose by 43.3%. Sales of all other drugs (9,482 in the retail market) rose by 6.7%. The numbers of prescriptions written for the top 50 drugs rose by 31.7%; by comparison, the increase was 2.2% for all other drugs.

The paradigm shift of drug discovery

Against this background comes an explosion of potential new therapies. Over the next decade, combinatorial chemistry, genomics, and proteomics[16] will likely unleash an exponentially greater number of therapeutics into the development pipeline. These new agents will have the potential to further increase the complexity of today's drug expenditures and, no doubt, considerably increase the cost of drug-development programs.

For the time being, however, spending by the pharmaceutical industry on research and development (R&D) is driven by several factors [17] The first is the increasing cost of bringing a new chemical entity to the market, approximately $500 to $800 million by current estimates. This

rising cost is generated not by inflation alone, but primarily, by the increased complexity of current drug development. In contrast to the situation in past decades, a growing proportion of modern drugs are intended to be used for an extended or even an indefinite period (i.e., they will be taken daily to treat such chronic conditions as hypertension, hypercholesterolemia, diabetes, and neuropsychiatric diseases). Because these drugs are supposedly free of, or almost, free of side effects they are advantageous for use by the elderly, many of whom take several different drugs simultaneously, thereby increasing the risk of harmful drug interactions.

The main challenge faced by pharmaceutical companies – to reduce time to market and time to peak sales – is accomplished by three measures:

• Increasing the number of new molecular entities in the pipelines of the pharmaceutical industry's R&D departments (The number of compounds under development by the US pharmaceutical industry between 1995 and 1999 increased by 35%, to 7,434; however, the number of product launches declined 22%, to 56, during the same period.)

• Productivity advances with the potential to generate new and better leads in a range of therapeutic areas (The ability to conduct high-throughput screening of compounds increased from approximately 3 to 4 million data points in 1998, to 150 million data points in 2002.)

• Aggressive and relentless marketing of new products to physicians and consumers alike.

The Problems

Drug safety issues

According to estimates, the drugs that are most commonly used are effective in only 30% to 60% of patients with the same disease. Additionally, a subset of these patients may encounter severe side effects. Adverse drug reactions were reported to be the 4th to 6th leading cause of death in the US in 1994, resulting in 106,000 fatalities and having a $100 billion financial impact that year [18] In 1998, 108,000 Americans died from adverse reactions to FDA-approved drugs, properly administered by licensed medical professionals. In the same year, 2.2 million Americans had adverse reactions to approved drugs [19-22]

The pro-patient and public health expectations

One of the most visible organizations in the broad coalition of pro-patient groups is the Medicines in Europe Forum,[23] a Paris-based group of scientists and political activists. As a counterpoint to industry views on how EU rules should be changed, the forum has been calling loudly for "a policy of medicines that puts patients first." Among the forum's most strongly expressed complaints is that "many new medicines are sold without having been compared to the most appropriate drugs for the same disease already available on the market." The remedy, it argues, is for independent information to be compiled and disseminated. "Health authorities must be able to supply comparative information on the added therapeutic value of new medicines – or on the lack of it," it says, and "this information can be obtained only if the appropriate clinical trials are carried out."

The UK charitable foundation known as the King's Fund[24] has published a new report expressing the following views with reference to the UK government's relationship with the pharmaceutical industry: "We want to see a relationship develop between government and the pharmaceutical industry that is geared towards the promotion of health, not just the promotion of wealth. For too long, the pharmaceutical industry has been in the driving seat of this relationship, with the government acting as a passive purchaser of drugs."

Physicians' behaviour

Better decision-making by physicians has been long considered a means of materially improving the balance between benefits and harm in health care, while saving billions of dollars. However, the much-anticipated changes in the behavior patterns of physicians have never taken place, at least not in the desired direction. Physicians today operate under increasing political and economic pressure, while they process ever-increasing amounts of evolving evidence in the context of their own unique micro- and macro-sociology, where the economic incentives are not infrequently perverse. They must individualize therapy and consider combinations of drugs for which randomized evidence may be limited. In parallel, third-party payers are pressing for drug cost containment, patients' expectations are increasing rapidly, and medico-legal pitfalls are omnipresent [25]

The fiscal intermediaries

A tiny light, however, is visible at the end of the tunnel. Sooner or later, pharmacogenetics will make possible the tailoring of drug prescribing to the individual patient's biology, aligning at last the great diversity of desires among the many stakeholders in the healthcare business. Until that evolutionary point is achieved, however, different solutions have been implemented, or are about to be implemented, in the US and many European countries.

The most radical and highly controversial of these solutions, applied on both sides of the Atlantic, is *generic substitution*, or therapeutic substitution of drugs. This term refers to the dispensing of an alternate chemical entity from the same general therapeutic class as that of the orig-

inal drug prescribed by the physician. The act of substitution dispensing is carried out by a group of, so far, relatively neutral stakeholders in the business – the pharmacy benefit managers, who act as fiscal intermediaries that administer pharmacy benefits for employers, health insurers, and health maintenance organizations [26,27]

The American Heart Association and the American College of Cardiology have formally and vigorously opposed therapeutic substitution, arguing that integration of the medical history, physical status, and the disease process relevant to a particular patient is the province and responsibility of that patient's physician [28] Furthermore, therapeutic substitution may result in the patient's receiving a drug that might not be effective, might produce life-threatening toxicity, and might interact adversely with other drugs the patient is receiving. [29-32] Therapeutic substitution is also opposed by the American Medical Association, the World Medical Association, and the American Academy of Family Physician.

The rationale behind the widespread practice of generic substitution is the *class effect* concept. The term has never been defined scientifically, clinically, or from a regulatory perspective [33] Its oversimplified and inappropriate use is a dangerous practice that is incompatible with evidence-based medicine.

Objectives of drug assessment

Regulatory agencies such as the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) have instituted extensive, stringent requirements for drug development. These requirements include multilevel premarketing reviews and approval processes, as well as postmarketing programs to gather data on, and assess risks related to the use of drugs in the general population. Quality, efficacy, and safety are *sine qua non* conditions for the approval of a new drug for marketing [34] A relevant FDA document[31] emphasizes that "A *safe medical product* is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available." That is, when a new drug is released, its efficacy is supposed to have been well quantified as comparable to that of "alternatives available" (i.e., to drugs in the same class, with the same indications, that are already on the market).

In reality, however, when new drugs are released, little information exists on how they compare with drugs already used for the same indications [35] With the current regulatory requirement of evidence from two placebo-controlled trials for licensing purposes (sometimes from one trial),[36,37] the evidence available for the new drug is limited to its performance in specified experimental conditions (i.e., *relative efficacy*), while and in most cases, evidence regarding its comparability with existing drugs is nil.

The saying "better than nothing is better than no treatment," derived from placebo-based studies, might be an acceptable compromise in many cases. However, the full evaluation of placebo-controlled drugs requires clear answers to a number of questions. If the new drug is not better than the old one, then what are its obvious advantages? Is it considerably cheaper, better tolerated, safer, or easier to administer?[38] These sorts of questions have focused increased attention to the use of cost-effectiveness evaluations from early clinical trial stages [38] Unfortunately, this type of evidence is lacking in most cases at the time of marketing approval. This, together with the, sometimes, questionable efficacy demonstrated through "statistically significant difference from placebo," [39-42] leaves the prescribing physicians with a difficult task when attempting to make informed choices.

The potential solution

This longstanding problem persists despite numerous guidelines, including the E10 document[44] stipulating that new medicines should be tested versus existing alternative drugs rather than compared to placebos. In this context, equivalence/noninferiority trials may be valuable in future marketing authorizations, at least in carefully selected circumstances. Despite raising complex and troublesome issues, such trials may provide prescribing physicians with valuable information to assist them in minimizing drug-related risks.

Competing interests

None declared.

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