Papers

Riposte: FDA response to 'Yin, yang and the biopharmaceutical industry'

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In his editorial entitled 'Yin, yang, and the biopharmaceutical industry',[1] Henry Miller attributes the three-year decline in biotechnology stocks to two factors: competition among biotechnology firms for a relatively small number of products, and Food and Drug Administration (FDA) regulatory actions. While we too are very concerned about the recent decline, we take issue with both the assertion that the FDA has played a large role in this decline and with the claims made to substantiate this assertion.

In point of fact, the number of new molecular entities (NMEs) submitted to regulatory authorities for marketing has dropped worldwide in recent years[2] (L. Hunt, personal communication) (Figure 1), and the number of Biologics Licence Applications (BLAs) has diminished as well from peak numbers in 1997 (Figure 2). As a result, even though the FDA approved a higher percentage of submitted NME applications during 1993–2000 (65–85 per cent), following enactment of the Prescription Drug User Fee Act (PDUFA), than in 1987–1992 (40–60%),[3] the absolute number of new products has dropped. The biotechnology sector may be particularly affected by these trends.[4] While there has been extensive speculation about the cause of this global decline, we, like most observers, agree that many factors are responsible.[4–6] We should particularly like to emphasise that during this recent time period, few changes in regulatory policies have occurred, and those few that have been implemented (eg heightened interest in evaluating toxicity to the cardiac conduction system), were unlikely to have had an impact on biotechnology drugs.

Dr Miller quotes statistics on drug development times from the Tufts University Center for the Study of Drug Development to bolster his argument that FDA regulation has created excessive barriers to market entry. We appreciate the intense interest in our approval processes and agree that there are many important factors that can affect the pace of product development, and that there are opportunities for improvement. However, while Dr Miller notes that total drug development time increased from 8.1 years in the 1960s to 15.2 years in the late 1990s, he fails to consider that the times required for the clinical and approval phases of drug development — the major times influenced by the FDA — have been steadily declining since 1993, the beginning of the PDUFA era. Tufts reports that FDA approval times dropped by 30 per cent and that clinical development times declined 24 per cent between 1992 and 2001.[7] These findings are not consistent with an increase in regulatory burden in the last few years. Tufts also reported that while FDA review times for biopharmaceuticals have dropped since the 1980s, clinical development times have risen sharply.[8] Current clinical development times for biopharmaceuticals are reported to be about $5\frac{1}{2}$ years, similar to non-biotechnology NMEs. This trend reflects the 'coming of age' of the biotechnology sector, whose product profile and target disease states have changed from those in

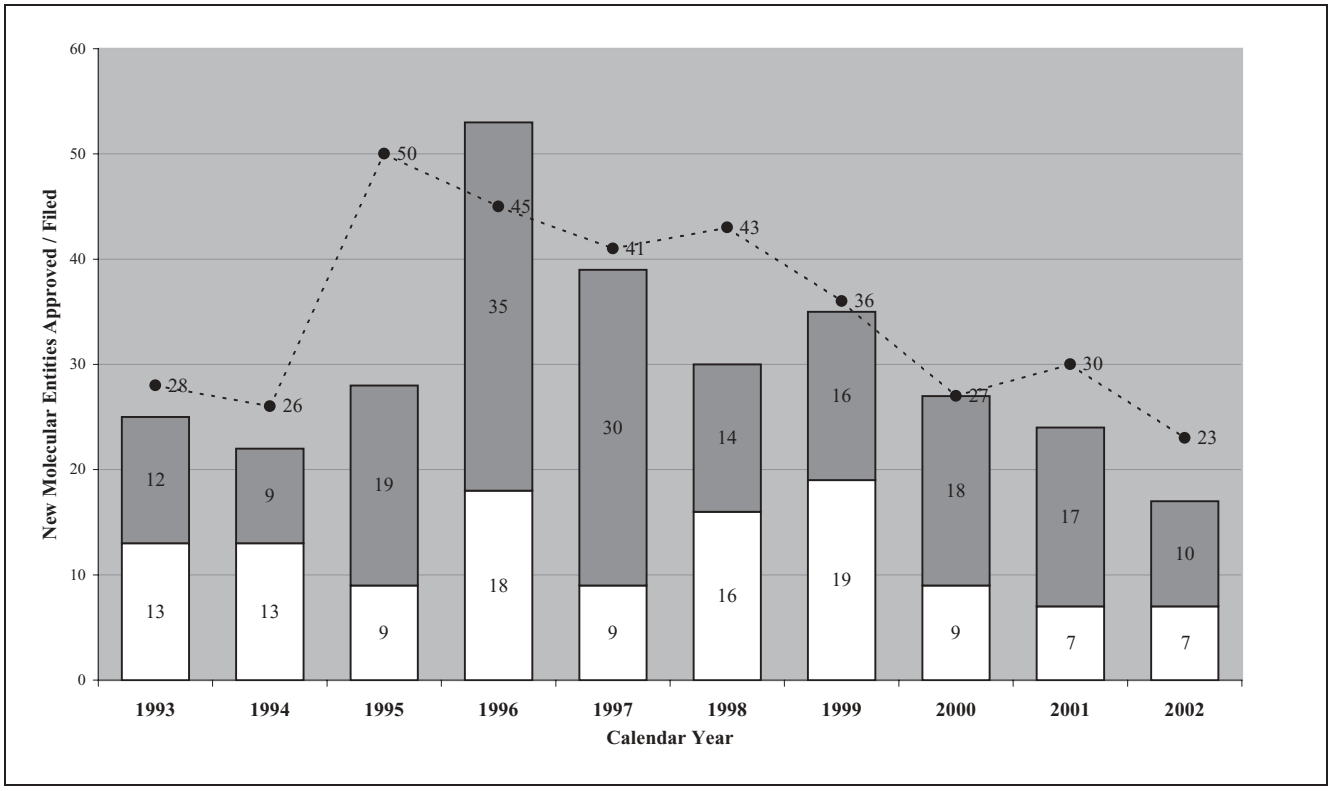

Figure 1: New Molecular Entity filings (NMEs) and approvals by calendar year. The number of NMEs filed by the Center for Drug Evaluation and Research (CDER) per calendar year is shown in the dotted line. The number of NMEs approved under standard review time frames are shown in dark bars and those approved under priority review are shown in white bars. The NMEs filed in a given year do not directly correspond to those approved in the same year and may include applications that have not yet received FDA approval. NMEs are new compounds that have not previously been approved by the FDA and multiple applications submitted for the same new compound are counted only once

previous decades: product profiles have changed from predominantly replacement therapies, whose mechanisms of action and anticipated toxicities were well understood, to therapeutic interventional molecules, whose modes of action and toxicities are less well understood; and greater interest is currently focused on chronic disease states, for which durability of clinical response is an important issue. Although such therapeutics take longer to develop, this successful transition represents a largely unsung triumph for the new industry.

The similarity in clinical development times between biopharmaceuticals and small molecular entities is perhaps not surprising, in view of the highly similar challenges and issues in their clinical development. However, one area in which they differ critically is that of immunogenicity, the potential to develop immune responses to the agent. This is of particular concern for products that are recombinant versions of endogenous molecules subserving unique biological functions. A recent example of the devasting clinical nature of such immune responses has been witnessed in Europe, where, in some patients, immune responses to Eprex (epoietin-alpha) have neutralised not only the recombinant molecule, but also its endogenous counterpart, rendering them transfusion dependent for extensive periods of time.[9,10] Thus, while we appreciate the need for efficiency in clinical development, caution in clinical trials and vigilance post-marketing cannot be viewed simply as 'regulatory barriers'. The safety of human subjects must remain paramount.

Frankly, we are puzzled by Dr Miller's use of the development and licensing of

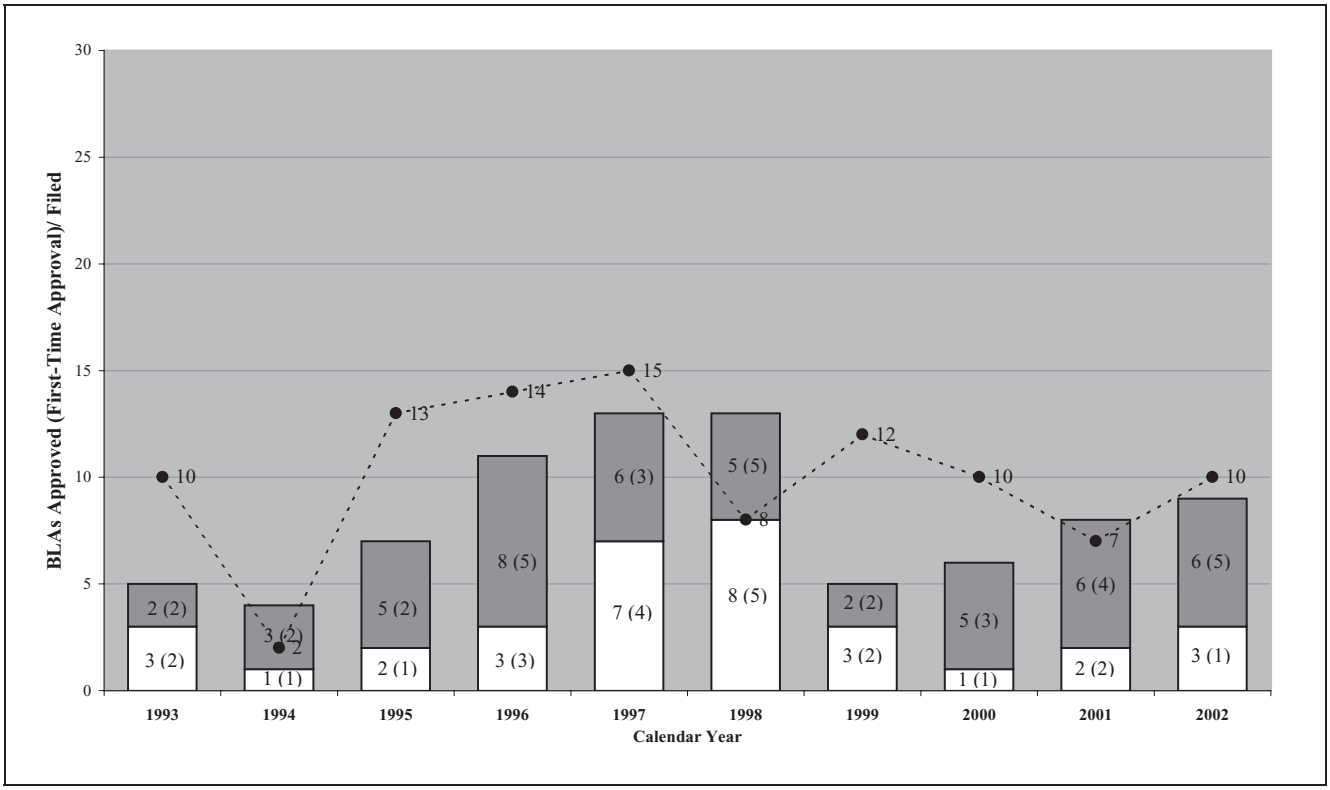

Figure 2: Biologics Licence Application filings (BLAs) and approvals by calendar year. The number of BLAs submitted per year is shown in the dotted line. This figure includes all BLAs submitted to the Center for Biologics Evaluation and Research (excepting allergenic products, test kits, blood grouping reagents and blood banking products) and includes new applications for biological products that have previously received FDA approval. The number of BLAs approved under standard review time frames are shown in dark bars and those approved under priority review are shown in white bars. The number of first time approvals (a biological product never before approved by the FDA) for products in each review category is shown by numbers in parentheses

the recombinant hepatitis B vaccine (RecombivaxHB®, licensed by Merck in 1986) as a primary example of the FDA's purported 'unreasonableness'. This seems a poor 'example', not only in view of the fact that this action was pre-PDUFA, and therefore irrelevant to current review time frames and issues, but also when one considers that the entire development time for this product was rapid, even by current standards. Thus, the first clinical trial of the recombinant hepatitis B vaccine was started in July 1983,[11] the product licence application submitted to the FDA in 1985, and approval issued within one year: hardly a long, drawn-out process for the licensing of the first recombinant DNA vaccine in the USA! The rapidity of the approval for this product was in good measure based on the FDA's willingness to use surrogate markers of clinical efficacy, namely serum antibody levels and seroconversion rates, as assessed in a subset of the trial population (594 healthy individuals in various age groups and 53 dialysis patients), except for one small study in infants which measured a clinical outcome. Thus, we do not believe that these clinical trials were unwarranted or unduly burdensome and they clearly illustrate the fact that the FDA did not adopt the most risk-averse course to product approval.

Dr Miller further refers to FDA-imposed barriers to antibiotic development. His comments fail to acknowledge the complexities of antimicrobial drug development and the continuing efforts that the FDA is making

in this area. Over the past year, the FDA has held multiple public Advisory Committee meetings as well as a two-day workshop co-sponsored by the Infectious Disease Society of America (IDSA) and Pharmaceutical Research and Manufacturers of America (PhRMA), focused on both the issue of antimicrobial resistance and on reevaluation of the current paradigm of antimicrobial drug development.

The mission of the FDA includes facilitating the availability of safe and effective new products, as well as protecting the public from unsafe or ineffective therapeutics. The current slowdown in applications for innovative therapies prompted the Agency in February, 2003, to announce a new initiative, conceived in 2002, entitled 'Improving Innovation in Medical Technology: Beyond 2002'. This initiative seeks to ensure that the FDA is doing everything possible to help make medical product development as efficient as possible, and, whenever possible, to define and smooth the regulatory pathway for new technologies.

Successful drug regulation involves a difficult balance among the competing needs of the stakeholders. While the regulatory process should be (and is) open to critique, the public is best served by an open and factual dialogue about its strengths and weaknesses, including any potential shortcomings, and the need for improvement.

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