EXHIBIT 9

Beyond borders

Global biotechnology report 2009

Ernst & Young

Quality In Everything We Do

In the wake of a sharp economic downturn and fewer exit options, venture capitalists (VCs) have become increasingly risk-averse and selective. While the year's overall venture funding numbers look relatively strong, the totals mask the deterioration in the fourth quarter and the struggles of many smaller companies trying to raise capital. In addition, VCs themselves face the risk that their limited partners, who have often seen declines in their portfolios, will not be able to honor funding commitments. And VCs looking to raise new funds will face a more challenging environment, many likely finding they cannot raise targeted amounts.

Meanwhile, investors in publicly traded biotech companies, which provided the bulk of the industry's capital in recent years, are unlikely to return in force any time soon. The turmoil in the capital markets has ended the era of easy money and caused a massive deleveraging. There is now simply less capital to go around, leaving biotech companies with less funding for the foreseeable future.

Deals

While rapid changes have radically altered the environment for the biotech industry in recent months, some long-term drivers remain unchanged. In particular, the pipeline challenges confronting big pharma companies continue to become increasingly urgent. Many firms face significant patent expirations in the years ahead and do not have enough in the pipeline to fill the gap. Not surprisingly, big pharma companies remained active buyers of biotech assets in 2008, helping drive deal totals for the year to impressive heights.

The total value of M&A during the year was more than US$28.5 billion – a record high not counting the megadeals of prior years, such as the 2007 acquisition of Medimmune by AstraZeneca. In 2008, although there were no megadeals, there were three large transactions valued at more than US$5 billion each: Millennium Pharmaceuticals' acquisition by Japan's Takeda Pharmaceuticals, ImClone Systems' purchase by Eli Lilly, and the acquisition of Applied Biosystems by Invitrogen (since renamed Life Technologies). Big pharma's interest in successful mid-cap biotech companies remains high, and we could well see more such "mini-megadeals" in 2009.

While no megadeals were completed during 2008, the back-and-forth negotiations for the mother of all megadeals kept the industry transfixed for much of the year. Roche offered in July to buy the minority stake in Genentech that it did not already own, and the two parties finally agreed in March 2009 to a US$46.8 billion purchase price, or US$95 per share.

Deal activity was every bit as heated for strategic alliances, where the potential value of alliances reached an all-time high of almost US$30 billion. This was mostly due to significant growth in the potential value of biotech-biotech deals.

Financial performance

The US industry's financial performance in 2008 was a mixed bag. The revenues of publicly traded US biotech companies grew by 8.4% in 2008, down from the 11.3%

US biotechnology at a glance (US$b)

	Public companies			Industry total		
	2008	2007	% change	2008	2007	% change
Financial						
Product sales	$54.1	$49.9	8.4%	$57.0	$52.7	8.0%
Revenues	66.1	61.0	8.4%	70.1	64.9	8.0%
R&D expense	25.3	21.0	20.5%	30.4	26.1	16.8%
Net income (loss)	0.4	(0.1)	-430.7%	(3.7)	(4.2)	-11.2%
Industry						
Market capitalization	$343.8	$369.2	-6.9%	–	–	–
Total financings	8.6	15.9	-46.3%	13.0	21.4	-39.2%
Number of IPOs	1	22	-95.5%	1	22	-95.5%
Number of companies	371	395	-6.1%	1,754	1,758	-0.2%
Number of employees	128,200	131,300	-2.4%	190,400	192,600	-1.1%

Source: Ernst & Young
Data were generally derived from year-end information (31 December). 2008 data are estimates based on January–September quarterly filings and preliminary annual financial performance data for some companies. 2008 employee data are obtained from 10-Ks at time of publishing and include a combination of 2007 and 2008 employee data. The 2007 estimates have been revised for compatibility with 2008 data. Numbers may appear inconsistent because of rounding.

growth seen in 2007 and significantly below the industry's historical compound annual growth rate (CAGR) of about 15%. As in previous years, the revenues of the industry were diminished to some extent by the acquisitions of a number of larger successful biotechs by companies outside the biotech industry. In particular, the year's three mini-megadeals had a palpable impact on the industry's top line. The acquisitions of ImClone and Millennium by big pharma buyers removed two firms that together accounted for more than US$1 billion in revenues.

The merger of Invitrogen and Applied Biosystems also dampened the industry's total revenues in 2008, even though neither company was acquired by a big pharma firm. Instead, the merger resulted in the formation of Life Technologies. While we include the new company in our biotech industry numbers, one result of the accounting treatment of the merger under US Generally Accepted Accounting Principles (GAAP) is that for 2008, the new company reported the full-year revenues of Invitrogen and only those revenues from Applied Biosystems that were after the acquisition date. In its 2008 annual report, Life Technologies states (on a pro-forma basis) that had the merger occurred on 1 January 2007, the 2008 revenues of the combined entity would have been about US$1.5 billion higher.

If these "lost" 2008 revenues are included in the industry's numbers, the top-line growth rate would have been 12.7% instead of 8.4% – roughly comparable to the industry's historic CAGR.

Revenues were also diminished by slower growth at the industry's largest revenue-generating company – Amgen. This is the second year of slowing revenue growth at the Thousand Oaks, California-based stalwart. Amgen's revenues grew by a CAGR of 27% between 2002 and 2006, but growth slowed to 3.5% in 2007 and declined even further to 1.6% in 2008. For the most part, this slower rate of growth was driven by the negative impact of regulatory and reimbursement developments on sales of the company's erythropoiesis-stimulating agents (ESA) products, including safety-related revisions to product labels and the loss of or significant restrictions on reimbursement. (For additional discussion, refer to the "US year in review: products" article in *Beyond borders 2008*.) As a result of these challenges, the company implemented a restructuring plan that included, among other things, worldwide staff reductions targeting 2,500 positions, a rationalization of its worldwide network of manufacturing facilities and the divestiture of some less significant marketed products.

The most anticipated financial-performance news was somewhat anticlimactic. For several years, Ernst & Young has been forecasting that the US publicly traded biotech industry would reach aggregate profitability before the end of the decade. In 2007, the industry came within a hair's breadth of reaching that milestone, and in last year's *Beyond borders* we were fairly confident the industry would reach aggregate profitability in 2008. Indeed, the US biotech sector was profitable in 2008 – with aggregate net income of US$0.4 billion, a historic, if largely symbolic, accomplishment.

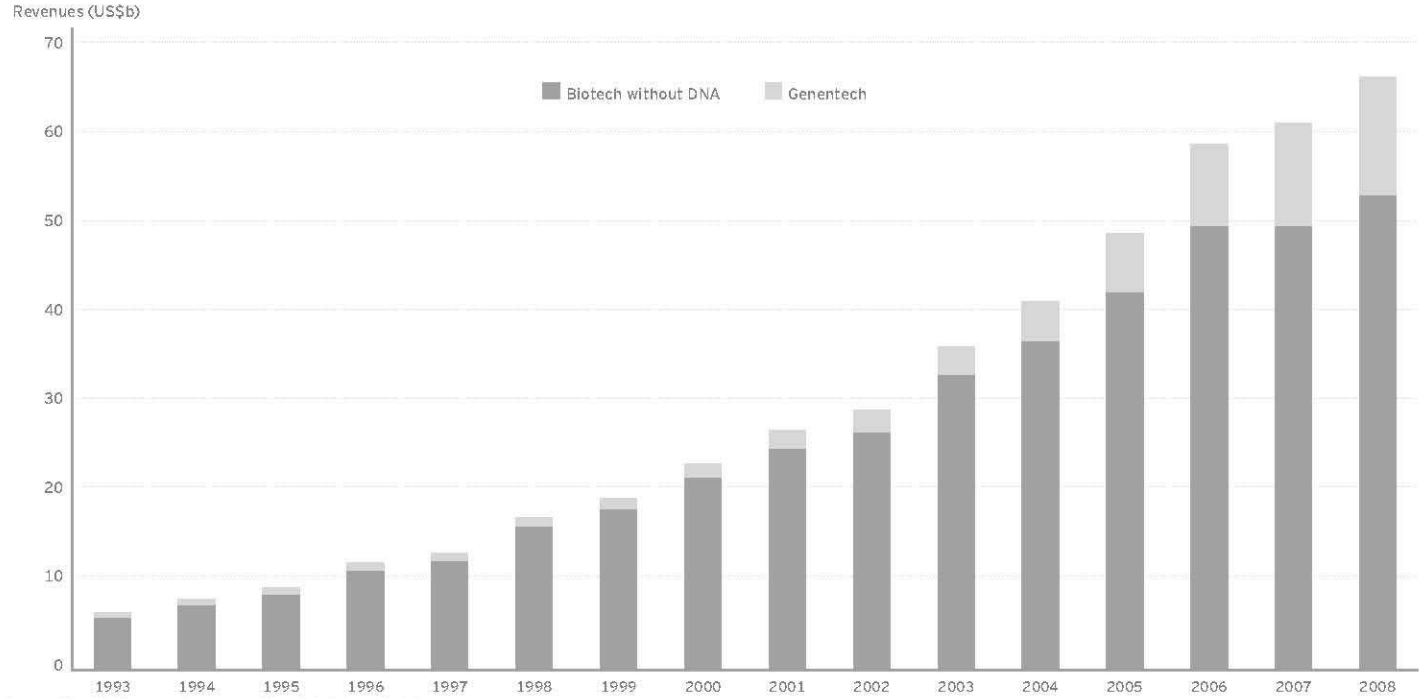
It also turns out that the industry was considerably closer to aggregate profitability in 2007 than we had initially estimated. Our estimate of the industry's net loss for that year included some extrapolation of fourth quarter results for companies that had not filed their quarterly financial reports before our publication was printed. In fact, the industry's 2007 net loss was US$0.1 billion instead of US$0.3 billion.

Biotech without DNA?

If aggregate profitability is a largely symbolic accomplishment, it also turned out to be, in hindsight, a fleeting one. With the acquisition of Genentech by Roche in 2009, it is hard to see how the industry will be profitable in aggregate any time soon. The South San Francisco-based giant had a net profit of US$3.4 billion in 2008, and its departure leaves a sizeable hole that other companies will have to fill for the overall industry to become profitable again.

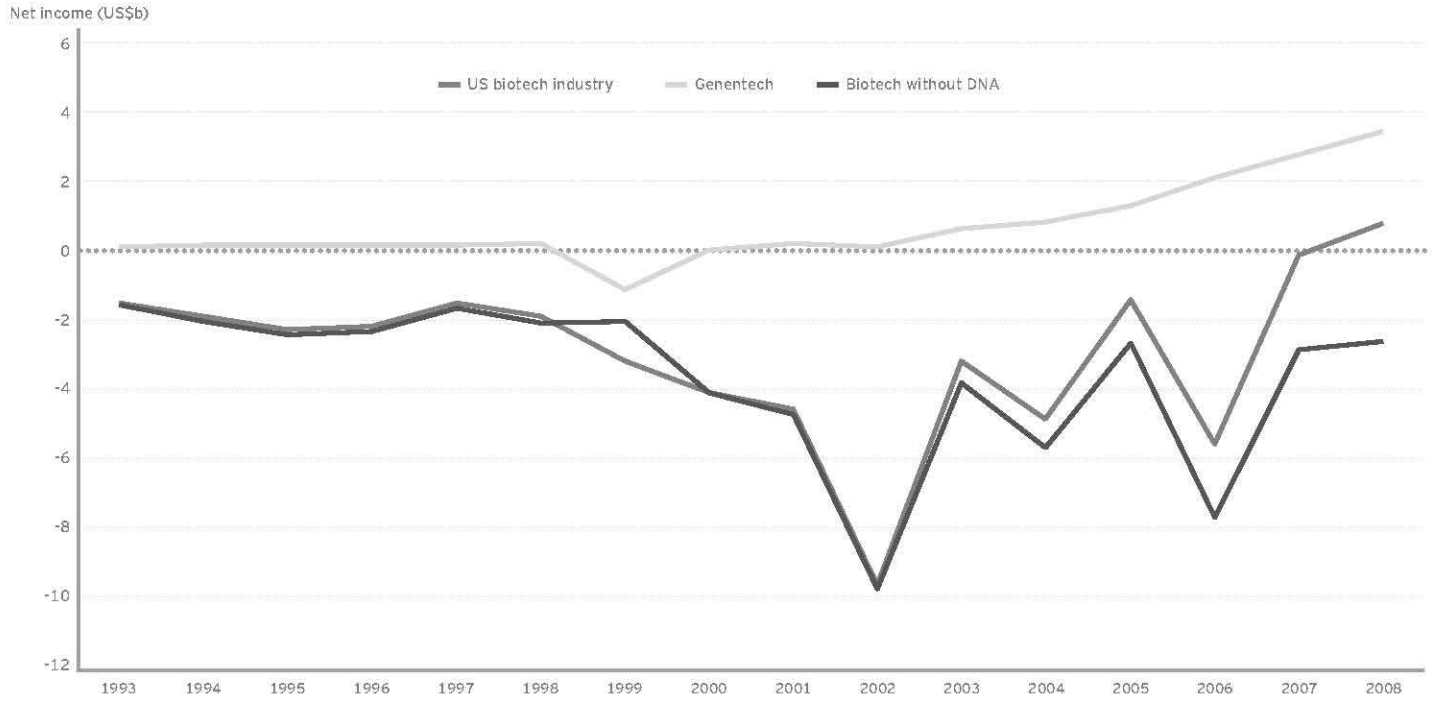
Biotech without DNA?

Genentech has accounted for an increasingly large share of US industry revenues ...



Source: Ernst & Young and company financial statement data

... and the industry's profitability will likely be very different after Genentech's acquisition



Source: Ernst & Young and company financial statement data

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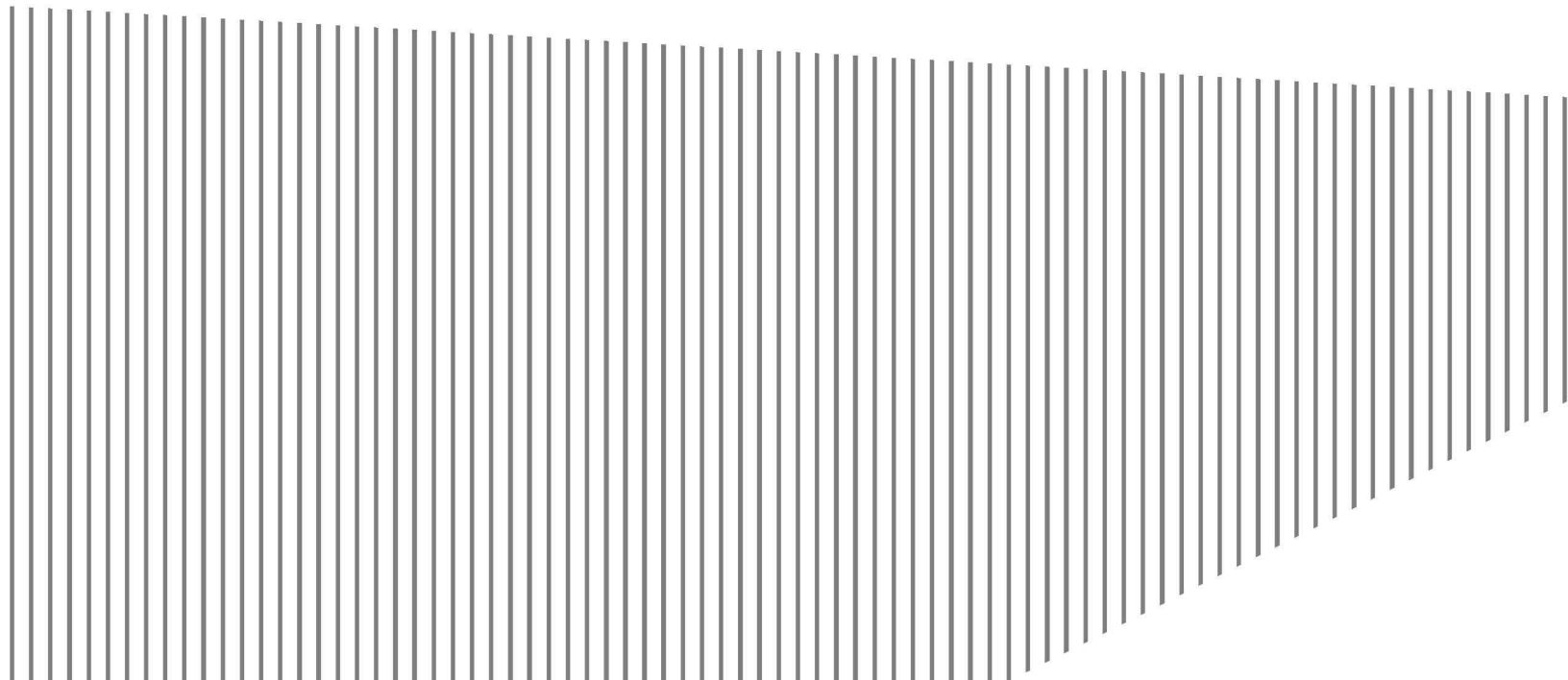

EXHIBIT 10

Nature Reviews Drug Discovery | AOP, published online 12 May 2008; doi:10.1038/nrd2532

PERSPECTIVES

OUTLOOK

Follow-on biologics: data exclusivity and the balance between innovation and competition

Henry Grabowski

Abstract | Legislation to create a regulatory pathway for follow-on biologics is currently being considered by the United States Congress. A critical issue in this respect is the period of data exclusivity for innovator companies before a follow-on competitor can rely in part on data obtained for an original biologic for an abbreviated approval. Given the nature of patents on biologics, the period of data exclusivity is anticipated to have a key role in determining how quickly follow-on competitors emerge, and consequently also on the time available for originator companies to recoup their investment. With this issue in mind, this article discusses factors influencing return on investment on biologic research and development. A break-even analysis for a representative portfolio of biologics provides support for a substantial data exclusivity period.

In the United States, most biologics are regulated through the Public Health Service Act. At present, this does not contain a mechanism for an abbreviated application for 'follow-on' versions of innovator biologics following patent expiry analogous to that which exists for generic chemical drugs under the Hatch–Waxman Act. Motivated by factors such as stimulating price competition with innovator drugs following patent expiry, the United States Congress is currently considering legislation that would create an abbreviated regulatory pathway for follow-on biologics, which are also referred to as biosimilars or biogenerics (for discussion of these acts, see REFS 1–3). As was the case when it created a regulatory pathway for generic chemical drugs through the Hatch–Waxman Act, Congress must balance innovation incentives and price competition. In addition, follow-on biologics raise complex scientific, regulatory and legal issues that differentiate these entities from generic chemical entries[2].

One critical decision for legislators relates to the issue of the period of data exclusivity, which represents an important form of intellectual property for innovators. This is the period of time after US Food and Drug Administration (FDA) approval before a follow-on competitor can enter based on an abbreviated regulatory filing that relies in whole or part on the innovator's data on safety and efficacy. Without a data exclusivity period, there would be little incentive to invest in developing and marketing new product candidates with few remaining years of patent protection or with uncertain forms of protection. In addition, newly approved products with substantial commercial sales would be exposed immediately to legal risks associated with patent challenges and early entry of generic versions.

Data exclusivity and patents are complementary forms of intellectual property for new pharmaceuticals and biologics. The importance of patents to research and development (R&D) innovation for new pharmaceutical therapies has been demonstrated in several economic studies[4–6]. Patents are a reward for innovation based on the criteria of novelty, utility and non-obviousness. Innovators generally apply for patents on compounds in the preclinical or early clinical phase of the development process. In the period after a patent is granted, but before a product can be marketed, innovators must generally perform a long, risky and costly investment process to demonstrate a product's safety and efficacy. Data exclusivity recognizes the substantial investment that innovators have to make in the data that demonstrate safety and efficacy to gain FDA regulatory approval. Ideally, data exclusivity would delay abbreviated filings and patent challenges until innovators have had an opportunity to earn a positive return on the new therapeutic candidates that successfully complete the lengthy and costly R&D process.

The Hatch–Waxman Act provides a 5-year data exclusivity period for new chemical entities (NCEs) before an abbreviated new drug application can be submitted (BOX 1, Note 1). By contrast, the European Union (EU) recently harmonized across member states a 10-year data exclusivity period for both NCEs and new biological entities (NBEs) before generic copies or follow-on biologics can be approved (BOX 1, Note 2). In addition, the EU provides for an additional year of data exclusivity for entities with significant new indications that are approved within the first 8 years after approval[7,8].

Current US legislative proposals for follow-on biologics contain widely different provisions regarding data exclusivity. At one extreme, a bill introduced by Representative Henry Waxman (BOX 1, Note 3) would not provide for any data exclusivity for NBEs. On the other hand, the bill introduced by Representatives Jay Inslee, Gene Green and Tammy Baldwin provides for 14 years of data exclusivity (BOX 1, Note 3). A bipartisan Senate bill, co-sponsored by Senators Kennedy, Enzi, Clinton and Hatch, has a 12-year exclusivity provision. Recently, a House bill introduced by Representatives Eshoo and Barton has a 12-year exclusivity provision plus 2 years for a new indication and 6 months for paediatric exclusivity (BOX 1, Note 3).

Data exclusivity assumes particular importance for biological entities as compared with chemical entities because many of these products rely on narrow patents that

Box 1 | **Additional notes**

Note 1. The new chemical entity (NCE) data exclusivity period under the Hatch–Waxman Act affords new molecules a floor of effective exclusivity from generic entry through the abbreviated new drug application (ANDA) process for 5–7.5 years, depending on how long courts take to resolve patent suits. The Act has a stay on generic entry of up to 30 months beyond the 5-year exclusivity period while court cases are in progress[1].

Note 2. Generics firms can submit abbreviated applications to the regulatory authorities 8 years after approval of the original molecule, but the earliest these applications can become effective is when the 10-year exclusivity period expires.

Note 3. Representative Waxman introduced H.R. 1038, The Access to Life-Saving Medicine Act, in the House and Senators Clinton and Schumer introduced an identical companion bill in the Senate, S. 623. Representatives Inslee, Green and Baldwin introduced H.R. 1956, Patient Protection and Innovative Biologic Medicines Act. Senators Kennedy, Enzi, Clinton and Hatch introduced S. 1695, Biologics Price Competition and Innovation Act of 2007. Representatives Eshoo and Barton introduced H.R. 5629, The Pathway for Biosimilars Act, in the House in March 2008. For an analysis of the different features of the alternative Congressional bills on follow-on biologics, see REF. 46.

Note 4. A patent's validity can be challenged on grounds such as obviousness, anticipation by the prior art or double patenting. A court may determine, for example, that a drug invention was "obvious", allowing the generics challenger to enter if the data exclusivity period has expired. The issue of patent type is also relevant from a policy standpoint. Process, method of use, and formulation patents have less breadth than product patents and may be more vulnerable to challenge on the grounds of validity or non-infringement, although each situation must be evaluated on a case by case basis. As of June 2002, the US Federal Trade Commission (FTC) reported that generics firms had won the vast majority of suits, but most of the cases with outcomes at that time involved late-stage process or method patent challenges[47].

Note 5. Most of these patent challenges now occur 4 years after market approval, which is the earliest point in time that a generics firm can submit an ANDA filing with a certification for challenging patents validity or asserting non-infringement[12]. The first generic to successfully file and win its patent suit gets an 180-day exclusivity under the Hatch–Waxman Act.

Note 6. For a general description of the discovery and development pathway for new drugs and biologics, see REF. 48.

Note 7. Janet Woodcock of the US FDA noted that: "Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variants in the manufacturing process. The quality and nature of natural source products can vary depending on the condition of the source material, processes used to extract and purify the product and other factors."[45] Validation of a biological manufacturing process involves many complex activities and even minor changes in this process can affect a product's quality and properties that necessitate additional testing.

Note 8. The starting point is the initiation of Phase I trials by the company performing the clinical investigations, rather than the filing of the investigational new drug application, which is often much earlier in the timeline.

Note 9. For a detailed discussion of the methodology and data issues associated with estimating R&D costs in pharmaceuticals, see REFS 21,49. Since these papers were published, a follow-on paper on this topic was published by FTC economists using alternative data sets, which found comparable estimates for R&D costs to our earlier paper, including significant variability across therapeutic classes[50]. It is worth pointing out that the therapeutic area with the greatest concentration of biological entities — oncology — has significantly higher R&D costs than the mean compound (US$1.016 billion compared with $868 million for the mean compound)[50]. This paper focuses on an earlier period than REF. 16, but is generally consistent with the estimates in that analysis after allowing for time-related adjustments in the growth of R&D costs.

Note 10. A real cost of capital adjusts for the effects of inflation. Assuming a historical rate of inflation of 3–3.5%, the corresponding nominal cost of capital would be approximately 15%. Our cost of capital estimate is based on a capital asset pricing model analysis for a small set of biotechnology firms with a history of profitability based on multiple marketed products. These companies also had an extensive portfolio of new biological product candidates over the period 1990–2003 (REF. 16).

make them more vulnerable to challenges from follow-on competitors. Although biologics typically have multiple patents on various elements of the active agent[9], several scientific and legal developments have operated over time to constrain the scope of recent biological patents[10,11]. Data exclusivity provides an important back-up to the patent system in those cases in which follow-on competitors could circumvent narrowly drawn patent claims and gain early entry through abbreviated applications. As follow-on biologics will be comparable but not identical to the innovator's molecule — and may also use different methods of formulation and manufacture — they may avoid infringing the innovator's core patents, while still being able to gain regulatory approval through an abbreviated pathway. Each situation must be examined on a case by case basis in this respect.

Generics firms have strong incentives to challenge patents early in a product's life cycle in order to gain first-mover or early-mover competitive advantages[12] (BOX 1, Note 4). Multiple lawsuits involving infringement have become the rule under the Hatch–Waxman Act for commercially important drugs early in the brand product's life cycle (BOX 1, Note 5). As a percentage of abbreviated new drug application filings, they have increased from 2% during the period 1984–1989, to 12% from 1990 to 1997, and to 20% from 1998 to 2000 (REF. 13). While all patent litigations are costly and introduce additional risks to innovators, patent challenges in the early stages of marketing have especially adverse consequences because they occur many years before break-even returns for new medicines. This prospect can be especially troublesome for early stage biopharmaceutical firms, because funding is typically supplied by venture capital firms that are very sensitive to uncertainties and risks about intellectual property protection.

With these issues in mind, this paper presents some of the key factors that influence the optimal length of the data exclusivity period from an economic perspective, and provides a break-even analysis for a representative biologic portfolio. This analysis is used as a basis to discuss the implications for ongoing policy discussions about follow-on biologics.

Optimal exclusivity times

Beginning with the pioneering work of William Nordhaus[14], economists have developed conceptual models to determine the socially optimal exclusivity time. Exclusivity can originate from patents and

Box 2 | **R&D timelines for bevacizumab (Avastin)**

The long timelines for the introduction of new biological entities are illustrated by the discovery and development process for bevacizumab (Avastin; Genentech/Roche), the first of a new class of drugs to treat colorectal cancer[36,55]. In 1989, Napoleone Ferrara, a scientist working for Genentech, isolated vascular endothelial growth factor (VEGF). Then, in 1993, Ferrara and his team published a key study demonstrating that an anti-VEGF antibody can suppress angiogenesis and tumour growth in preclinical models. However, it was not until 1996 that Genentech scientists were able to humanize an anti-VEGF antibody, and Genentech submitted an investigational new drug application for this antibody, now known as bevacizumab, to the US Food and Drug Administration in 1997. The first Phase I trial for bevacizumab began that same year and was followed by a Phase II trial in 1998. In 2000, a Phase III trial began to evaluate the use of bevacizumab to treat first-line metastatic colorectal cancer, which took 3 years. Finally, in February 2004, 15 years after the isolation of VEGF by Ferrara, the FDA approved bevacizumab as the first anti-angiogenic drug for treating cancer.

from complementary forms of intellectual property protection such as data exclusivity. The basic trade-off is between incentives for new product development versus more intensive price competition after exclusivity expires. In particular, longer exclusivity times encourage increased development of NBEs and NCEs as well as additional research on new indications for established products. However, longer periods can also postpone the onset of competition from generics. When the additional benefits from expected development of more new medicines are just equal to the additional costs of postponing the onset of competition from generics, the exclusivity time is considered optimal from an economic perspective.

While this theoretical modelling has not yielded a specific value for the optimal exclusivity time for biopharmaceuticals (or any other industry), it does provide a framework to assess which industry characteristics are relevant to current policymakers' decisions in this regard. In particular, for industries in which the R&D process is costly and risky, longer exclusivity periods to realize innovation benefits are needed in comparison with those industries in which innovation is easier and less costly. Similarly, when the output of innovation has important external benefits to society — as in the case of new medicines and new indications for existing medicines — this also supports a longer exclusivity period[15]. The next two sections review what is known about the basic characteristics of innovative activities for new biologics.

Characteristics of R&D activity for NBEs

Sources of risk for candidate NBEs. The R&D process for NBEs is fraught with many risks. It is common for the development of an NBE to originate in a start-up company financed through venture capital financing. At the initial stages of development, there is a high degree of scientific risk associated with proof of concept. Preclinical data are used to gain insights into expected efficacy, toxicity and pharmacological effects once a lead agent is identified. Even when animal studies indicate promise, they imperfectly predict human response concerning safety and efficacy. This is one important reason for high attrition in clinical trials (BOX 1, Note 6).

As a candidate NBE moves through the clinical-trial process, there are additional risks of failure due to difficulties involving formulation, manufacturing scale-up or inconvenient dosing regimens. As biologics are complex molecules produced from cultures of living cells, manufacturing and engineering process issues at the R&D stage can pose greater challenges than for chemically synthesized compounds. Process specifications and manufacturing know-how are critical elements for NBEs (BOX 1, Note 7).

Several economic studies confirm that the R&D process for NBEs is subject to large risks from scientific, regulatory and economic factors. An analysis of the probability of success of 522 biological candidates at various stages in the clinical development process found that the overall probability of success in clinical development was 30% (that is, the success rate of candidates that make it as far as trials in humans)[16]. While biologics had higher overall success rates than chemical drugs, they have had lower success rates in the most expensive Phase III trials, indicating that biologics that fail in clinical trials often do so only after high development costs have been incurred. A recent study by Goldman–Sachs[17] also found that Phase III success rates of biologics from 1995 to 2003 are lower than those of pharmaceuticals, and have exhibited a significant downward trend over time. This downward trend is consistent with the fact that the complexity of biological products under development has increased, a phenomenon that is also reflected in longer development times.

Development times. The development process for an NBE is lengthy and typically spans more than a decade. The discovery and preclinical process is subject to considerable uncertainty and variability, especially when a new class of drug or new target receptor site is being investigated. This is illustrated by the example of bevacizumab (Avastin; Genentech/Roche; BOX 2).

FIGURE 1 shows the mean clinical development time to FDA approval for NCEs and NBEs from REF. 16, which found that the average development time for an NBE was 97.7 months, compared with 90.3 months for small-molecule or chemical drugs (BOX 1, Note 8). And, as shown in FIG. 2, development times for NBEs have increased steadily since the early 1980s. At the beginning of the 1980s, the majority of NBEs receiving marketing approval were proteins with well-understood functions. As this initial group was exhausted, the industry has turned to more complicated, less well-understood targets, and development times have steadily increased. This is true despite the fact that average FDA review times have decreased significantly since the 1980s for NCEs and NBEs as a result of the Prescription Drug User Fee Act[18].

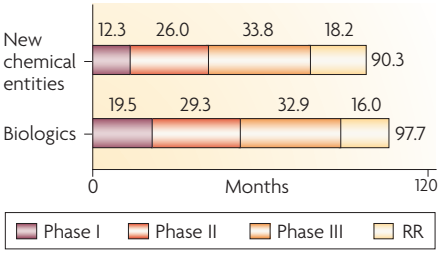

Figure 1 | **Clinical development and approval times for chemical drugs and biologics.** The average development time for a new biological entity was 97.7 months compared with 90.3 months for small-molecule or chemical drugs. A significant part of the difference is associated with a lengthier Phase I process for biological entities. After a new pharmaceutical or biologic is approved, there is frequently substantial additional research and development activity involving investigations for new indications or formulations. In addition, the US Food and Drug Administration may require post-approval Phase IV studies as a condition of approval. Development times include only clinical phases and regulatory review (RR) periods; preclinical times are not included.

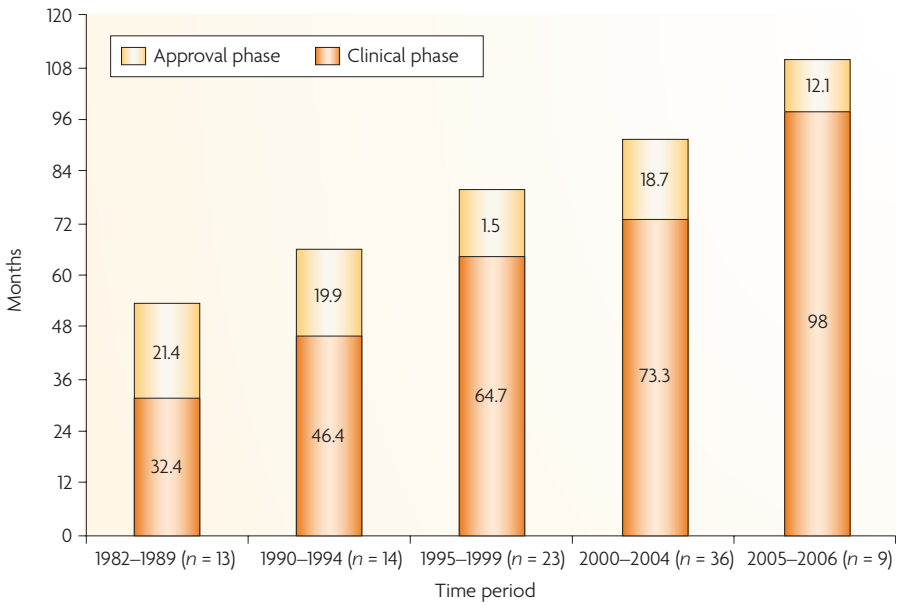

Figure 2 | **Development times for new protein therapeutics.** Development times for new biological entities (defined here as new protein therapeutics, including new recombinant proteins, monoclonal antibodies and non-recombinant proteins) have increased steadily since the early 1980s. This figure is based on data collected by the Tufts University's Center for the Study of Drug Development from several time cohorts of US Food and Drug Administration approvals.

Development costs. R&D costs for new biologic introductions have also been analysed[16] (BOX 1, Note 9). Data were collected to estimate the expected costs at each phase of the cycle, and were then risk-adjusted for the expected probability of success at each stage of the development life cycle. Using this approach, it was found that total out-of-pocket costs for the preclinical and clinical periods exceed US$500 million. Time costs were also taken into account by capitalizing out-of-pocket costs to the date of marketing approval. This study found that the capitalized R&D costs for a representative NBE range from $1.24 billion to $1.33 billion when the real cost of capital is 11.5–12.5% (BOX 1, Note 10). As discussed below, the average cost of capital for NBEs in early stage companies will be much larger than this 11.5–12.5% range that is estimated for a small set of established biopharmaceutical firms[19,20] (BOX 3, Note 1).

It was found that R&D costs for NBEs are comparable in magnitude to earlier estimates involving chemical drugs[21] when the latter estimates are time-adjusted to take into account differences in the time periods analysed. However, the underlying cost components differed significantly. As noted, biologics have higher probabilities of clinical success overall, but lower probability of success in the more expensive Phase III trials. Biologics also have higher discovery and preclinical expenditures and longer mean clinical development times. It was also found that the development of biologics involve higher development costs associated with process engineering and manufacturing than is true for chemical drugs. This reflects the need to resolve novel manufacturing challenges at the R&D stage. By contrast, manufacturing process issues in R&D are typically more straightforward for drugs based on chemical synthesis (BOX 3, Note 2).

Market structure and skewed sales distribution. The sales of NBEs that do make it to the market exhibit tremendous variability, which represents another source of risk. As is the case for chemical drugs, the sales distribution for NBEs is highly skewed, with relatively few compounds accounting for a disproportionate share of sales and profits. An analysis of 30 NBEs introduced from 1982 to 1994 indicated that the top one-fifth ranked entities accounted for roughly 70% of the total 2002 sales[22,23]. Biologics that rank in the top few deciles of the sales distribution are frequently 'best in class' or 'first in class' therapies. In addition to direct competition from new molecules in the same class, they also would be the primary targets of generic biologic firms.

Intellectual property and the financing of biotechnology R&D projects. Intellectual property is a key dimension of the decision to invest in life-science companies that have little other tangible or intangible assets and a lengthy period of clinical trials before marketing approval. If an abbreviated application process is created by the United States Congress for follow-on biologics, data exclusivity will become an important aspect of the calculation of risks and rewards by private and public markets.

Given the characteristics of the R&D process, some important implications follow for the financing of R&D investment in an innovative entrepreneurial industry like biopharmaceuticals. First, in the early stages of development, it is crucial to have the support of financial institutions such as venture capital firms that can take a relatively long view and a portfolio approach to such risky investments[24]. Second, if the relatively few large successes experience increased uncertainty due to patent challenges and the potential for early entry of generic versions, higher risk-adjusted rates of return will be demanded by venture capital firms as well as in initial public offerings and secondary offerings in public markets, yielding fewer candidates that meet this standard. Early stage R&D in start-up firms will be the most likely affected segment. Such a prospect is a particularly unfavourable outcome for firms and industries whose products contribute to important long-term advancements in public health.

For NBEs that are developed internally by large, established biotechnology or pharmaceutical firms, similar considerations must also be confronted in portfolio decisions. Product candidates with significant uncertainty from expected legal challenges soon after marketing launch would have diminished economic prospects relative to other investment-stage candidates.

Importance of biologic innovation

When innovation has important benefits for overall social welfare, this provides support for a longer exclusivity period. There is accumulating empirical evidence that new medicines and therapies have played an important role in increased longevity, enhanced quality of life and improved labour-force productivity[25–27]. Furthermore, recent studies have found that consumers have appropriated significantly more of the societal benefits than innovators in the case of new therapies for HIV/AIDS, as well as several other new technologies[28,29].

The biotechnology industry is a relatively new source of medical innovation; it had its first new drug product approvals in the early 1980s. However, it has become a major source of novel drug introductions and overall industry growth in recent years. A recent paper examining the quantity and quality of worldwide new drug introductions between 1982 and 2003 found that biotechnology drugs are the fastest growing segment of new therapeutics: they accounted for 4% of new drug introductions in the 1982 to 1992 period, which grew to 16% in the 1993 to 2003 period[30]. In addition, US firms are the dominant source of drugs from biotechnology companies, originating more than half of all worldwide biopharmaceutical introductions from 1982 to 2003.

Although not the only measure considered in this analysis, one of the key indicators of drug quality or novelty was first-in-class introductions, and NBEs had a significantly higher likelihood of being a first-in-class or novel therapy compared with NCEs. NBEs have been particularly focused on oncology and immunological areas in recent years. Given the increased knowledge of the molecular bases for cancer, the oncology class has been characterized in recent years by the introduction of breakthrough monoclonal antibodies and other targeted biological agents. These include rituximab (Rituxan; Genentech/Biogen Idec), trastuzumab (Herceptin; Genentech/Roche) and bevacizumab (Avastin; Genentech/Roche).

Several NBEs have had rapid uptake and are among the leading drug therapies in their class from a therapeutic perspective. Furthermore, these products are being investigated for a number of new indications at present. Substantial improvements in survival, morbidity and patients' quality of life have been documented in diseases previously resistant to successful treatment, including cancers such as aggressive HER2 (also known as ERBB2)-positive breast cancer[31] and gastrointestinal stromal tumour[32], as well as in preventing the disease progression, functional decline, joint destruction and disability associated with rheumatoid arthritis[33].

The prospects of future advances are further enhanced by a strong pipeline of more than 400 biotechnology drugs under development in various therapeutic areas[34]. These include novel approaches to conditions with large disease burdens, including 200 biotechnology drugs for cancer alone. Early stage R&D of a novel drug is fraught, of course, with high risks, but can also yield both high potential rewards to investors as

Box 3 | **Additional notes**

Note 1. Grossman[19] estimates that biotechnology firms without a marketed product but with one or more drug candidates in Phase II or III trials have an average nominal cost of capital of 27.4%. He also estimates a nominal cost of capital for biotechnology firms with at least one drug approved of 18.7%. Myers and Shyum-Sunder[20] estimated a 14% real cost of capital for a group of publicly traded biotechnology firms for an earlier period. As noted, our 11.5% real cost of capital is based on a smaller group of biotechnology firms that have multiple products and a history of positive operating profits over the past decade.

Note 2. It is important to note that the costs of constructing a new manufacturing facility or retrofitting an existing plant for large-scale commercial production are not included in the R&D cost estimate. The cost of a new multi-product manufacturing plant is substantial in the case of biologics. In particular, it has been estimated that a new manufacturing plant can take 3–5 years to build, and cost US$250 million or more[51]. Even retrofitting an existing plant can cost between $50–100 million.

Note 3. While generics typically capture the dominant share of the market within a short time after entry for commercially successful pharmaceuticals, innovative firms can retain some of the market in the post-patent expiration period through authorized generics (albeit at significantly reduced prices and margins)[13]. Another strategy that is sometimes successfully used by innovators is to develop an improved formulation (for example, an extended-release product) before the patent expiration of the basic molecule. These new formulations must be submitted to the US FDA for approval with new clinical-trial data demonstrating efficacy and safety. They are then eligible for a 3-year exclusivity period. Companies may also be able to obtain additional patent protection for new formulations, but formulation patents are more susceptible to challenges on the grounds of obviousness and other points, and also easier to invent around by generics firms. The recent Supreme Court ruling in KSR versus Teleflex raises the bar on the non-obviousness criterion for patents, and makes improvement patents more vulnerable to challenges on the grounds of obviousness[52].

Note 4. These trends were examined in REF. 12 along with the case for longer data exclusivity periods under the Hatch–Waxman Act. This could be patterned along the lines of current European Union (EU) policies. Since this paper was published, these adverse trends have intensified. Doug Long, Vice President of IMS, in a recent presentation provided data that demonstrated the growth in total prescriptions for generic products since 2001 has significantly exceeded that for branded pharmaceutical products[53]. Generics currently account for 67% of all prescriptions dispensed in the United States. The fastest growing segments of the pharmaceutical industry are now generics and biologics.

Note 5. It is important to include post-approval R&D costs in the break-even analysis, given that sales values in the analysis include revenues from new indications and formulations as well as the original indication. To take account of post-launch R&D expenditures, I assume they will be 35% of the out-of-pocket expenditures for pre-approval R&D costs. This yields total cash outlays of $195.6 million spread evenly over the first 8 years after launch ($24.5 million per year). These assumptions are consistent with our analysis of new drug introductions[40]. It is reasonable to assume that expenditures on new indications and formulations for biotechnology drugs are proportionately as large as for new drug introductions, given R&D pipeline data and the analysis of Calfee[27].

Note 6. Based on prior work, here it is assumed that there will be $25 million in plant validation costs per product introduction ($12.5 million per year), as these costs are not captured in our R&D cost estimates.

Note 7. Alternatively, this approach is akin to assuming production is outsourced with a contract manufacturing charge equal to book depreciation charges. This also would be a conservative assumption as contractors would have to obtain a margin above depreciation costs to be a viable business.

Note 8. Contribution margins are defined as sales minus the costs of goods sold (including depreciation charges for plant and equipment), marketing, promotion and administrative costs in the numerator. This is expressed as a percentage of sales in the denominator.

Note 9. It is assumed here that total expenses exceed sales by 30% in year 1, and the contribution margin in year 2 is equal to 20%. In addition, in the 2 years before market introduction, it is assumed that there are launch-related expenditures equal to 10% and 20% of the first year's sales. These values are based on information collected in conjunction with new drug introductions[40].

Note 10. Even if therapeutic equivalence is not granted by the FDA, managed care organizations can be expected to use various incentives to facilitate the use of follow-on biologics as therapeutic alternatives. Formulary decisions and other actions will be used by managed care organizations to encourage the usage of follow-on biologics after their pharmacy and therapeutics committees ascertain their comparability to the relevant branded product. In this regard, an Avalere Health study[54] projects a market share for biosimilars of 60% of the total units of the molecule 3 years after their launch onto the market, assuming they compete as therapeutic alternatives rather than substitutes. This compares to market penetration of generics in the range of 90% for the largest selling chemical molecules over shorter time intervals[12].

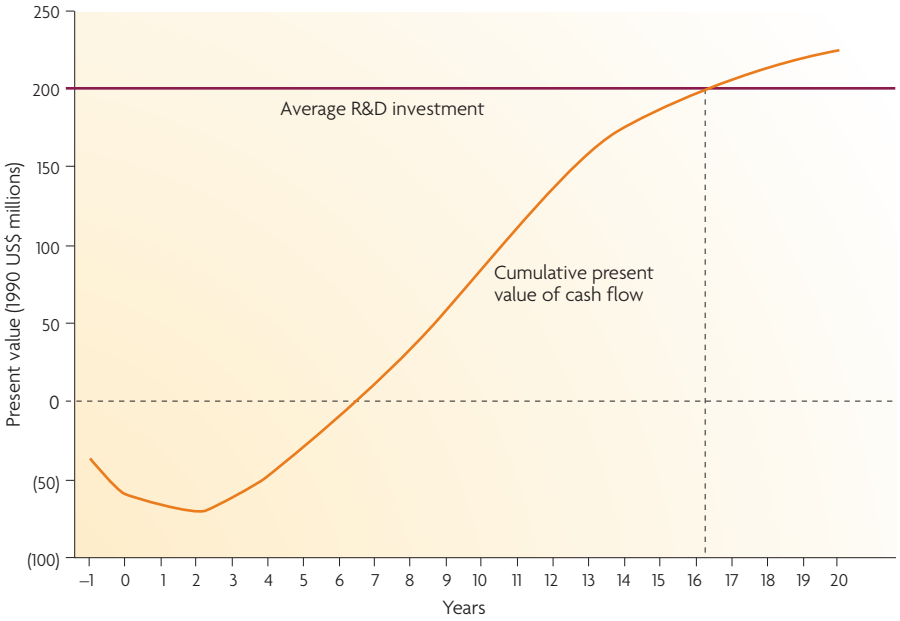

Figure 3 | **Cumulative present value of cash flow versus R&D investment for the mean new chemical drug introduced between 1980 and 1984.** The analysis combines data from analysis of research and development (R&D) costs and cash flows from this cohort of 1980–1984 introductions. The break-even lifetime for the mean drug in this portfolio is just over 16 years. In particular, this is where the present value of cumulative after-tax cash flows just intersects the present value of after-tax R&D investment (all measured in 1990s US dollars), signifying the fact that the firm has recouped its investment plus a return equal to the industry's average cost of capital for that period. Data from REF. 38.

well as large therapeutic benefits to patients. It is important that such high-risk endeavours have sufficient economic prospects for returns to undertake the long, costly and risky investment process.

In a recent paper, Calfee and DuPre pointed out two important features of competition involving NBEs[35]. First, after proof of principle has been established for a new biologic, multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (for example, a particular receptor or dysfunctional enzyme). For example, in the case of trastuzumab there are more than ten targeted drugs currently in Phase II or III for breast cancer targeting the HER2 receptor, other members of the HER family, or one of the other proteins downstream from HER2. The tumour-necrosis factor (TNF) inhibitors for rheumatoid arthritis and anti-vascular endothelial growth factor (VEGF) drugs for cancer are also experiencing similar forms of competition involving the same targeted pathways, but with different modes of action.

A second important feature of competition for NBEs involves new indications associated with the same or related pathways. For example, drugs that were initially approved for rheumatoid arthritis are being investigated for a number of anti-inflammatory conditions that may be related to the same dysfunctional pathway. For example, two of the leading anti-TNF drugs for rheumatoid arthritis, etanercept (Enbrel; Amgen/Wyeth) and infliximab (Remicade; Centocor), have received subsequent approval for psoriasis and Crohn's disease, respectively, and more than 20 clinical trials are in progress for bevacizumab in different types of cancer and different stages of cancer[36].

The development of new indications for established biologics would be particularly vulnerable to early patent challenges by generics firms seeking to enter based on an abbreviated pathway. This is because obtaining approval for a new indication post-approval can take several years and involve large-scale patient trials and significant costs. The uncertainty surrounding early patent challenges may tilt the risk–return balance against otherwise economically viable investment programmes for new indications. In this case, patients would be deprived of health benefits from new indications that in many cases are equivalent to or surpass those of the original approved indications[35,37]. Although it might be possible for a firm in this situation to get a new use patent for the new indication, these patents are difficult to impossible to enforce against a generic entrant that manages to get an approved label for a more limited set of indications.

Prior analyses of break-even lifetimes

Data exclusivity provides an investment return period before imitators can enter with an abbreviated application that relies on the innovator's data. It is therefore instructive for the current analysis to examine the minimum time required by a representative portfolio of new therapeutic agents to achieve break-even status from an economic perspective — that is, to cover its R&D costs and earn a risk-adjusted return on capital. To do so, one needs information on R&D costs and other cash outlays and inflows over the full product life cycle. To date, this issue has been investigated in a comprehensive way for new molecular entities introduced in the 1980s and 1990s. The sample of drugs investigated has consisted primarily of NCEs. A few of the initial biological entities that were introduced in the 1980s and early 1990s were also included in the analysis.

The break-even lifetime is illustrated in FIG. 3 for the 1980–1984 portfolio of NCEs[38,39]. The break-even lifetime for the mean drug in this portfolio is just over 16 years. A similar analysis for the 1990–1994 portfolio of NCEs gives a break-even lifetime of 15 years[40]. By contrast, the average market exclusivity periods observed for new molecular entities experiencing initial competition from generic versions in the 1996–2005 period generally fluctuated between 12.5 and 15 years on an annual basis with substantial variation across individual entities (BOX 3, Note 3). There was also a declining trend observed for the molecules with the largest commercial sales that are the principal targets of patent challenges[41]. As noted previously, the distribution of NCEs is highly skewed. A few blockbuster new drug introductions earn several times the mean R&D costs and can achieve a break-even point much faster. But it must be kept in mind that only 30% of the sample of NCEs have cash inflows that exceed the average R&D outflows in present value terms. Hence, the blockbuster products with large commercial sales compensate for the large number of products that never break-even from a net present value standpoint.

With the high degree of risk and uncertainty that exists for R&D in new therapeutics, including biologics, it is difficult to predict in advance which or whether any products in a particular portfolio will be big winners. Many products start with this objective but end up as incremental

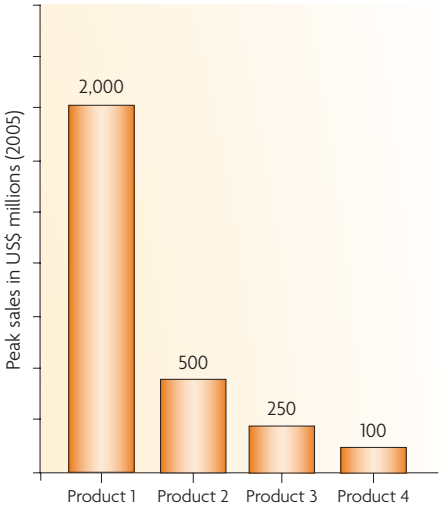

Figure 4 | **Model portfolio based on sales distribution for established biological products.** The peak revenue values are shown for a four-product 'stylized' portfolio. This portfolio reflects the mean values observed for the top four ranked quintiles of the sales distribution of established biotechnology drugs.

advances or fall by the wayside. This is why venture capital firms and biopharmaceutical firms take a portfolio approach. In effect, the few highly successful new pharmaceutical entities have a key role in covering the large fixed costs of R&D and enable the entire portfolio to achieve a positive risk-adjusted rate of return.

Whether this blockbuster model for success in pharmaceuticals can be sustained is uncertain given the trends towards higher R&D costs for new drug introductions, together with shorter product lifetimes for commercially successful drugs and intensifying competition from generics (BOX 3, Note 4). One of the primary strategies used by pharmaceutical firms to deal with these adverse trends is increased acquisitions and partnerships with biotechnology firms[42,43].

Break-even lifetimes for NBEs

Only a few biological entities have been included in prior analyses of R&D returns, given the long time frames that these studies require and the relative youth of the biotechnology industry. However, for current purposes, it is instructive to undertake an analysis that simulates the break-even lifetimes for NBEs launched in the present time frame with different projected sales revenues.

In the break-even lifetime analysis presented here, the annual R&D costs for an NBE from the analysis in REF. 16 for the pre-approval period are used. This is combined with a plausible estimate of post-approval R&D costs for new indications and formulations (BOX 3, Note 5). Using this R&D investment information, the break-even lifetimes for a portfolio of new biotechnology products with peak sales of different values are considered. In particular, this model portfolio is constructed using values on peak sales that approximate the distribution on sales revenues for 30 mature biotechnology products analysed in REFS 22,23.

Sales profiles. In FIG. 4, the peak revenue values are shown for a four-product stylized portfolio. This portfolio reflects the mean values observed for the top four ranked quintiles of the sales distribution of established biotechnology drugs. In particular, biotechnology drugs in the highest ranked 20% cohort had mean sales of approximately $2 billion. The next three quintiles had means of $500 million, $250 million and $100 million, respectively. The bottom quintile, accounting for the lowest ranked 20% of the products in the sales distribution, is excluded because many of these small-selling biologics were approved under the Orphan Drug Act and may not have representative R&D cost profiles. However, excluding all the biologics in the lowest tail of the distribution makes the current analysis conservative and biases break-even lifetimes downward.

We can focus on a stylized portfolio of four products without loss of generality as peak sales are based on historical values for the top four quintiles of the sales distribution. A representative sales life cycle for these four marketed products can be constructed using the annual sales profile realized by the average new drug introduction in the 1990s[40] as a template. Based on this profile, sales are observed to peak in year 9–10 and then decline at a 3.5% annual rate owing to product obsolescence and therapeutic class competition.

FIGURE 5 shows the corresponding life-cycle profile for the mean biotechnology drug in the stylized portfolio. The mean drug in this portfolio has peak sales of $712.5 million, which is the average of peak sales for the four products in FIG. 4. Sales increase at a rapid rate during the early years of the life cycle, reach maturity, and then slowly decline owing to product obsolescence. Competition from generics would cause a much steeper decline in sales than that shown in FIG. 5. However, this is not included in the life-cycle profiles because our basic objective is to understand how many years are typically required for an innovation to break-even before entry of a generic competitor occurs.

Given this highly skewed distribution shown in FIG. 4, the mean is heavily influenced by the top decile product. In particular, the mean peak sales value for the four-product portfolio of $712 million is larger than three of the four products in the portfolio. This underscores the importance of a portfolio approach to product development to obtain an occasional significant commercial success. Most venture capital firms that specialize in early stage companies will invest in a large number of firms and investment projects. Most of these candidates will fail, but there is a chance to obtain one or more highly successful products that

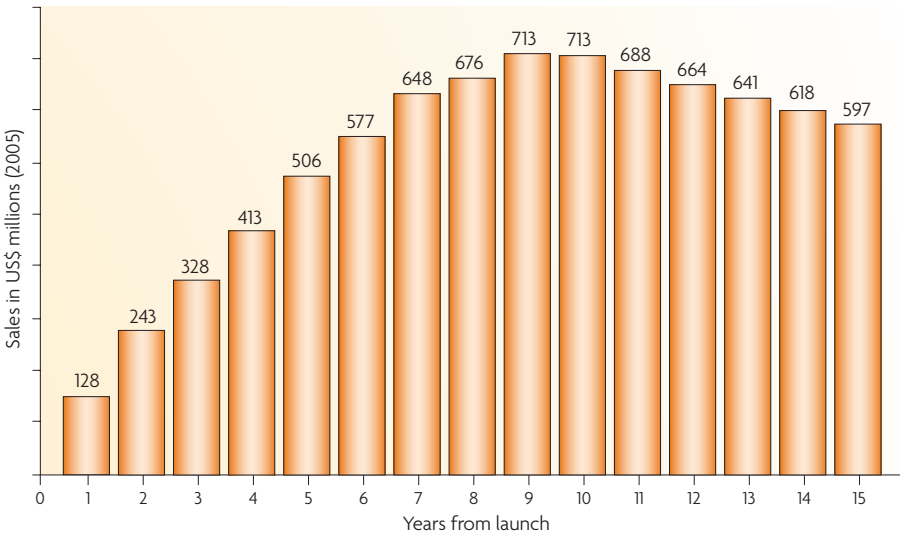

Figure 5 | **Life-cycle profile for the mean product in the model biologic portfolio.** The mean product in the model portfolio has peak sales of US$712.5 million, which is the average of peak sales for the four products in FIG. 4.

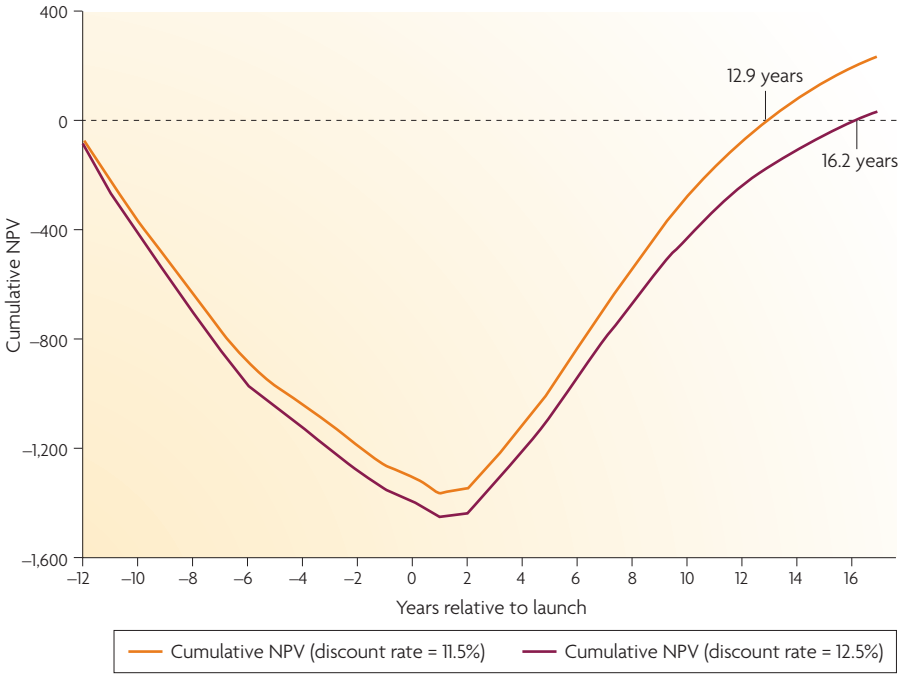

Figure 6 | **Break-even lifetimes for new biological entities.** The figure shows the cash-flow patterns for the mean product in this portfolio analysis from the initiation of research and development (R&D) to payback. When the net present values (NPV) of inflow just equals outflows, this is the break-even point at which a firm recovers its R&D investment and earns a risk-adjusted rate of return. The break-even time is 12.9 years for a discount rate of 11.5%, and 16.2 years for a 12.5% discount rate. The key assumptions are that pre-approval R&D costs are based on REF 16; post-approval out-of-pocket costs equal to 35% of pre-approval costs; post-approval R&D costs are spread evenly over the first 8 years after launch; sales are based on historical distribution of successful biotechnology market introductions; a pre-tax contribution margin of 50%; and all sales are measured in constant 2005 US dollars.

will drive positive overall returns. Similarly, established biotechnology companies will also carry a number of preclinical and clinical projects at different points in the life cycle with a similar strategy in mind.

R&D and capital costs. The recent study of R&D costs by DiMasi and Grabowski[16] found that the typical NBE introduced in recent years had a capitalized cost of $1.24–1.33 billion, measured in 2005 US dollars, and using a discount rate of 11.5% to 12.5%. These cost estimates account for both the R&D costs of success and failures, as all these costs must be recouped from the sales of approved products. However, the analysis involved only pre-approval R&D costs, and did not include the substantial post-approval costs associated with new formulations and indications, or include the often substantial pre-approval investment in constructing manufacturing facilities.

It is instructive to consider the underlying development process for the stylized portfolio shown in FIG. 4, utilizing industry averages for development times and successes. The four-product model portfolio would first require 4–5 years of preclinical R&D to generate several lead candidates. The clinical process would then span an average of about 8 years, and require approximately 3.3 product candidates in clinical trials for every product introduction (that is, a 30% success ratio). However, one can still expect substantial year-to-year variability around these averages even for firms with large diversified portfolios, given the skewed distribution of outputs[24].

With respect to capital expenditure requirements, it is assumed in the analysis here that firms can utilize an established plant for the commercial production of the biological products in this stylized portfolio (BOX 3, Note 6). In particular, rather than undertake a net cash flow analysis associated with the production of a new manufacturing facility, it is assumed that capital costs are captured by depreciation charges that are subsumed in the contribution margin. This approach is conservative, as some new plant construction or retrofitting of an existing plant is normally required in association with significant new product introductions. A correct financial cash-flow analysis would yield lower returns and higher break-even lifetimes, given that cash-flow outlays for new plant facilities precede in time any recovery of cash flows from net income and depreciation charges (BOX 3, Note 7).

Discount rates and contribution margins. The current analysis also assumes risk discount rates in the range of 11.5–12.5%, which is reflective of the equity cost of capital for larger publicly listed biotechnology firms with multiple products on the market in recent periods. However, as discussed above, smaller publicly traded companies and non-listed private biotechnology firms would generally have much higher cost of capital, given the lack of historical track record of profitable marketable products and pipelines that are concentrated in higher and riskier early stage R&D.

In this analysis a steady state contribution margin of 50% is used (BOX 3, Note 8). This value is obtained after a 2-year transition period, during which extra launch costs related to market introduction are concentrated (BOX 3, Note 9). This 50% contribution margin is in line with the contribution margins realized by the eight largest biotechnology firms with multiple products on the market[44]. However, it must be kept in mind that there are few biotechnology companies that are profitable, and the universe of biotechnology firms is populated with development-stage companies whose principal assets are their human capital and intellectual property. They would be expected to realize higher costs to launch a new product than a firm with an established line of approved products.

Results. The results of the model portfolio analysis are shown in FIG. 6, which illustrates the cash-flow patterns for the mean product in this portfolio analysis from the initiation of R&D to payback. Break-even lifetime for the portfolio occurs at 12.9 years in the case of an 11.5% real cost of capital. When a 12.5% real cost of capital is used, the break-even lifetime is increased to 16.2 years. This illustrates the strong sensitivity of break-even lifetimes to the discount rate. This sensitivity reflects the lengthy R&D investment periods associated with pharmaceutical and biopharmaceutical investments.

The analysis of returns here is designed to err on the side of underestimating break-even lifetimes. As discussed, the assumptions on capital expenditures and the cost of capital are conservative. In addition, the lowest quintile of the sales distribution is excluded from the analysis. However, one

factor that is relevant to consider in applying this analysis is how rapidly imitative competition will evolve for NBEs. In the short term, the innovator firms may retain some brand loyalty after the entry of follow-on biologics until prescribers and other participants become more experienced and comfortable with these entities (BOX 3, Note 10). It is generally accepted that follow-on biologics will be evaluated in terms of comparability rather than being treated as identical to the innovator's products based on evidence from at least some clinical-trial data[45]. For the foreseeable future, follow-on biologics also are likely to compete as therapeutic alternatives rather than as interchangeable substitutes as is the case with generic drugs. However, even if this is the case, given the prospective cost savings, there will be strong incentives to position follow-on biologics on preferred tiers through formularies and other practices of managed care organizations. Technological development and global market experience also should operate to ameliorate physician and patient concerns about their usage over time[2].

Conclusions and policy implications

Over the coming decades, biopharmaceutical innovation can provide major improvements with respect to quality and length of life over an expanding set of disease areas. As has been emphasized by Woodcock[45]: "It is important to ensure that facilitating the development of follow-on products through abbreviated pathways does not discourage innovation and the development of new biological products." At the same time, the costs of NBEs can be expected to account for a growing portion of the overall health-care sector budgets for new medicines. It will fall to the United States Congress to balance the objectives of innovation incentives and price competition as was the case when Congress created the Hatch–Waxman Act more than two decades ago.

There are two types of error present in the decision-making process confronting policymakers involving data exclusivity times. If data exclusivity periods are too short, new product candidates with inadequate or uncertain patent protection will be deterred. On the other hand, if data exclusivity periods are too long, price competition could be delayed beyond what is necessary to encourage innovation.

Our analysis indicates that NBEs possess demand and supply side characteristics that support a substantial exclusivity period before imitation from follow-on biologics. On the supply side, early stage research is concentrated in start-up companies that are typically financed by venture capital firms and partnerships with larger entities. The R&D process for NBEs is long, costly and risky. Most candidate molecules never reach the market. The market sales distribution for those molecules that do reach the market is highly skewed, with long payoff periods to profitability. With respect to medical demand and patient care, recent NBEs have resulted in several leading therapeutic advances, with important attendant benefits for human welfare. NBEs have accounted for a disproportionate share of first-in-class and best-in-class therapies in areas with high unmet needs such as oncology and rheumatoid arthritis.

Data exclusivity provides a floor in terms of the time for investors to realize returns before generics firms can enter and rely in whole or part on the innovator's data to gain its approvals. One important consideration for policymakers from basic economic principles is to align data exclusivity periods with the time necessary for the representative NBE to earn a positive risk-adjusted return on the large upfront R&D investment. This paper presents an analysis of break-even times for NBEs to gain insights into this issue. In this regard, a simulation analysis was undertaken of a model portfolio of biotechnology products with sales that are representative of the actual historical distribution. The break-even lifetimes for the mean product were found to be between 12.9 and 16.2 years at alternative discount rates of 11.5% and 12.5%, respectively.

The break-even analysis illustrates the importance of a data exclusivity period to the incentives for innovation in the pharmaceutical industry. Even diversified portfolios that achieve substantial commercial outcomes, including a blockbuster product, require lengthy payback periods. If the patents of the most successful products are subject to legal risk and challenges early in their product life cycle from follow-on competitors utilizing abbreviated regulatory pathways, this would add to the technical and commercial risks inherent in the development of NBEs. This is an especially relevant scenario in the case of NBEs because they are often based on relatively narrow patents that are vulnerable to challenges by follow-on competitors.

Legislation on follow-on biologics should be designed to strike a balance between the incentives for price and innovation competition. In particular, the legislative bills without any provisions for a data exclusivity period, or only very nominal periods of exclusivity, would have adverse effects for new biological innovation activities. Under these legislative scenarios, there would probably be an explosion in patent challenges shortly after a new product is introduced. While the right to undertake patent challenges is an integral part of the US intellectual property system, entry through abbreviated filings should be delayed until the representative NBE has had an opportunity to earn risk-adjusted break-even returns. This important concept for innovation incentives is incorporated in the US legislative proposals that provide for a substantial period of data exclusivity.

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Competing interests statement

The author declares competing financial interests: see web version for details.

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EXHIBIT 11

The Market For Follow-On Biologics: How Will It Evolve?

The market for biologically derived treatments differs in important ways from the market for chemically derived drugs.

by Henry Grabowski, Iain Cockburn, and Genia Long

ABSTRACT: With spending on biologics rising and patent expiry approaching for several blockbuster biologics, Congress and the Food and Drug Administration are considering creating a clear pathway for so-called follow-on biologics. Differences between drugs and biologics will affect market outcomes in various ways. Conservative budget impacts are appropriate in the short run because fewer competitors will enter, and average prices will drop less than was the case following the Hatch-Waxman Act. Over the long term, intellectual property provisions will be important considerations for policymakers designing a pathway for follow-on biologics that balances price competition and innovation incentives. [*Health Affairs* 25, no. 5 (2006): 1291–1301; 10.1377/hlthaff.25.5.1291]

Biologics represent a sizable segment of the U.S. drug industry, with sales expected to exceed $60 billion by 2010.[1] Because these products are growing at twice the rate of prescription drugs (2004), health plans, employers, and government insurers have concerns about their potential financial impact, while patients are concerned about continued access to potentially beneficial therapies. With patents for a number of blockbuster biologics (medical treatments derived from living organisms) expiring in the next several years, Congress and the Food and Drug Administration (FDA) are under pressure to enable the expedited approval of so-called follow-on biologics (also referred to as biogenerics or biosimilars), thus paving the way for the development of a robust U.S. follow-on biologics industry, following the lead of the Hatch-Waxman Act for generic drugs.

Proponents of an approach similar to that embodied in Hatch-Waxman make several assumptions about its economic impact: First, there will be many entrants, and competition will be based primarily on price; second, prices will drop substantially, and consumers will have better access to biologics; and third, incentives for innovation will not weaken. However, the market for follow-on biologics might develop differently from that for generic drugs for a number of reasons.

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We examine important differences between biologics and drugs that could affect market outcomes. We then consider how the market is likely to evolve, conditional on the regulatory environment, technological and marketing barriers to entry, and market acceptance. We also point out some important open policy questions and identify priority areas for further empirical investigation.

The Hatch-Waxman Act And Biologics

The Drug Price Competition and Patent Term Restoration Act of 1984 (often referred to as the Hatch-Waxman Act) established the Abbreviated New Drug Application (ANDA) process for generic drug approval. In reviewing ANDAs, the FDA relies on a prior finding of safety and efficacy for a referenced pioneer drug, with a generic applicant having only to demonstrate bioequivalence between its product and the referenced drug.[2] Prior to 1984, generic drugs were subject to the same approval requirements as innovator drugs.

Although the Hatch-Waxman Act provides a clear path for generic drug market entry, it generally does not apply to biologics. Drugs are regulated by the federal Food, Drug, and Cosmetic Act (FD&C Act), and biologics are generally regulated under the Public Health Service Act (PHS Act), which has no equivalent provision to the ANDA allowing the expedited approval of generic versions of approved, on-market products. Some early biologics, such as human growth hormone (hGH), insulin, and conjugated estrogens, were approved as drugs under the FD&C Act. ANDAs could be approved for these products, subject to FDA resolution of the scientific and other issues involved.[3] However, congressional action will be required before follow-on versions of biologic products regulated under the PHS Act can be approved by the FDA. Congress and the FDA are considering various scientific and legal issues surrounding follow-on biologics, to define a regulatory process for them.

Biologics are typically more complex molecules than chemical drugs; they are not manufactured through chemical synthesis but instead are produced through biological processes involving manipulation of genetic material and large-scale cultures of living mammalian, microbial, or yeast cells. Biologics made in different cell lines or manufacturing plants might behave differently as medicines and exhibit unexpected adverse events in vivo. These basic differences in turn lead to important differences in the economics of discovery, development, manufacturing, and distribution for drugs and biologics. Consequently, this could lead to different economic outcomes in terms of average prices, number of competitors, returns on spending for research and development (R&D), and other market measures.

Economic Analyses Of Pharmaceuticals And Biologics

■ **Innovators' R&D costs.** A number of studies have investigated the average cost to discover and develop a new drug. Joseph DiMasi and colleagues estimate R&D costs at $403 million per new drug in an oft-cited study.[4] When capitalized to

the point of marketing approval at a real discount rate of 11 percent, the total preapproval cost is $802 million (in 2000 dollars).[5] Although the sample of biologics in this study was small, the limited data suggested that development costs were similar for biologics and drugs.

A recent analysis by DiMasi and Henry Grabowski examined the R&D costs for a data set of recombinant proteins and monoclonal antibodies.[6] The authors assembled drug-specific data on R&D costs by phase of development for a sample of seventeen biologic products drawn from these two categories. These data were integrated with a larger database on transition probabilities and development times for new biologics. The authors found that the R&D costs for new biologics are comparable in magnitude to DiMasi and colleagues' previous estimates for drugs (after adjustments were made for the different time periods covered by the two studies).[7] However, they also found that the underlying R&D cost components differed substantially between new biological entities and drugs. Specifically, biologics realized higher probabilities of clinical success (30 percent compared with 21.5 percent for new drugs) but also experienced longer mean clinical development times (ninety-eight versus ninety months). These findings are consistent with earlier analyses of these parameters.[8]

The DiMasi-Grabowski study also suggests that the development of biologics entails higher manufacturing process costs than is true for drugs. This reflects the need to resolve novel manufacturing challenges at the R&D stage for products developed through fermentation or fragile mammalian cell cultures. By contrast, manufacturing process issues in R&D are more straightforward for new chemical drugs. Process specifications and know-how will be important for the FDA to consider from both a regulatory and an intellectual property (IP) perspective in developing guidelines for follow-on biologics.

■ **Imitators' R&D costs.** It remains to be seen what the regulatory requirements will be for follow-on biologics. Given that biologics made with different cell lines or manufacturing facilities might exhibit different efficacy and safety characteristics, it is likely that some clinical trial data will be required before a follow-on biologic is approved. New follow-on entrants might not have to repeat all of the original sponsor's clinical steps or incur the costs associated with large Phase III clinical trials. However, even relatively small trials of biologics in a few hundred patients are likely to cost tens of millions of dollars and take several years to complete. In the case of European approvals, some generic companies' estimates suggest that a plausible range could be $10–$40 million.[9] The exact amount is likely to depend on how well-characterized the molecule is and on other scientific and technological factors. This contrasts with the $1–$2 million cost and approximately two years necessary to demonstrate bioequivalence for generic drugs.[10]

While Congress and the FDA consider the legal and scientific framework for follow-on biologics, branded competition for biopharmaceuticals such as hGH and recombinant insulin has emerged using the New Drug Application (NDA)

regulatory pathway. In the case of hGH, six manufacturers are approved for marketing in the United States.[11] These manufacturers received FDA approval under separate NDAs by conducting their own comprehensive Phase III studies to demonstrate efficacy and safety. The products are not rated as bioequivalent by the FDA and cannot be substituted for each other, although managed care plans might view them as undifferentiated. Competition in hGH is also multidimensional: Products are marketed under separate brand names and compete on price, promotion, and product differentiation (for example, with different delivery systems such as pen dispensers). Follow-on biologics might retain some elements of this competition, as discussed further below.

■ **Manufacturing cost and risk.** The required capital investment in property, plant, and equipment and the costs of manufacturing are also likely to be higher for follow-on biologics than for generic drugs. Cell culture facilities require sizable capital and labor investment, taking, on average, three to five years to construct and costing $250–$450 million. Investment in manufacturing plants must often be made before drugs enter clinical testing. Cost of materials is also high; in 2002 these materials cost twenty to one hundred times more than those used for drugs.[12]

■ **Market size.** As in the market for drugs, the sales distribution of biologics is highly skewed, with relatively few compounds accounting for a disproportionate share of sales and profits. Of thirty new biologics introduced from 1982 to 1994, one-fifth accounted for roughly 70 percent of total 2002 sales.[13] Biologics in the top quintile or decile of sales will attract the most interest from follow-on manufacturers. Several studies have established that the number of entrants for generic drugs is strongly related to the size of the brand-name product's sales prior to entry.[14]

It is also relevant that many biologics have been "niche drugs" targeting rare conditions and small numbers of patients. As a result, during 1983–2001, biotech firms accounted for two-thirds of the research on orphan drugs—whose estimated maximum U.S. markets were no more than 200,000 patients—although they represented fewer than half of FDA approvals.[15] Among these products, only those with sizable revenues would be expected to attract generic competition.

■ **Product margins.** Average net income as a percentage of gross revenue and gross margin percentage for mature biotech companies approximate those of major pharmaceutical manufacturers, although the distribution of expenses differs somewhat, with a higher percentage of gross revenues to R&D and lower percentage to sales, marketing, and administrative costs.[16] However, there are few such companies. The universe of biotech firms is populated with development-stage companies. Most are not profitable, and the variance of such financial statistics is greater than for the pharmaceutical industry. The market structures of the two industries are therefore very different.

■ **Distribution structure and supply-chain incentives.** Markets for biologics and drugs also differ in the structures of their distribution systems and in the economic incentives for participants in the value chain. Most drugs are oral agents dis-

"Changes in regulation could lead to hard-to-predict long-term effects on capital investment in the biotech industry."

tributed through retail and mail-order pharmacies. Strong financial incentives and systems favor rapid generic penetration. Managed care plans adjudicate and budget for these claims as pharmacy benefits. They have implemented strong formulary management systems, including preferred formulary status and lower copayments for or mandatory use of generics. Financial incentives for drug retailers also favor rapid generic drug substitution, because they often earn higher gross profit margins on generic drugs than on brand-name drugs.[17] Medicare Part D drug plans will extend these incentives for generic drug penetration with formulary designs that are at least as aggressive as those in their current commercial lines of business.

In contrast, biologics include both injected or transfused agents delivered in a physician's office, clinic, or hospital and self-injectible products dispensed through pharmacies. Medicare reimbursement for infusions delivered in clinics and physicians' offices historically has been maintained at artificially low levels, resulting in the need for cross-subsidies between these rates and the spread between average wholesale price (AWP) and actual acquisition cost. This has been addressed somewhat by increasing procedure reimbursement, decreasing infused-agent reimbursement with the shift in January 2005 from AWP- to average sales price (ASP)–based reimbursement, and the recent implementation of the voluntary competitive acquisition program (CAP). The long-term impact on incentives for the substitution of lower-cost products is unknown.[18]

Because many biologic therapies are designed to treat cancer and other life-threatening diseases and might not have close substitutes, managed care organizations in the past have been reluctant to restrict access or to pursue aggressive cost or utilization control processes. Biologics often have been managed within plans as medical benefits, which have been less subject to centralized formulary controls than pharmacy benefits have. This is changing, particularly in indications where there is a choice between multiple brand-name biologics, and tiered formularies reflect considerations of net cost after manufacturer rebates.[19] Increasingly, a fourth tier, which includes expensive biologic therapies and coinsurance rather than copayment, is emerging. These institutional practices will likely accelerate with the introduction of follow-on biologics, but the speed of change will depend on how rapidly concerns about safety can be satisfactorily addressed.

Intellectual Property Considerations

IP provisions in the Hatch-Waxman Act have led to evolving levels of strategic behavior on the part of both generic and brand-name pharmaceutical firms. These provisions also have been the source of much litigation. Specifically, Hatch-Waxman provided an inducement to patent challenges by rewarding the first suc-

cessful generic challengers with 180-day exclusivity. As a consequence, generic firms now follow "prospecting" business models involving patent suits, and virtually all profitable pharmaceuticals face patent challenges after their first five years of market life.[20] Generic entry based on an ANDA can occur after the five-year data exclusivity period expires, but subject to a thirty-month stay on entry while courts adjudicate patent validity and infringement. Brand-name firms also have used various IP provisions to forestall entry, such as multiple stays on entry. Congress addressed this behavior in the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003.[21]

IP is a critical intangible asset for biotech and pharmaceutical firms.[22] Given the entrepreneurial nature of the biotech industry, a higher probability of a successful challenge to a company's patent portfolio could lead to adverse consequences and insolvency for many development-stage biotech companies. This means that changes in regulation could lead to hard-to-predict long-term effects on the complex network of capital investment in the biotech industry. These IP issues are open policy questions that will need to be resolved for follow-on biologics. We discuss some of the trade-offs regarding them later.

How Will The Market Evolve?

Regulatory environment, technology and manufacturing barriers, and market acceptance and competition will determine market outcomes for follow-on biologics. In our opinion, limited competition of either the nonbranded or the branded variety is most likely in the short run because of regulatory conservatism, relatively high barriers to entry, and initial caution on follow-on product acceptance. For the typical drug, generic prices begin to approach their long-run marginal cost when there are at least ten competitors in the market.[23] For commercially successful drug products, there has been sufficient entry to drive prices close to marginal costs within a relatively short period after patent expiration, generally less than a year and, more recently, just a few months. The time required likely will be much longer in the follow-on biologic market than in the generic drug market. The basis for this view is explained below, along with a discussion of some changes that could reduce likely regulatory and institutional barriers.[24]

■ **Regulatory environment.** Until Congress changes the PHS Act to create a process for competition in follow-on biologics, prospective entrants will have to do extensive clinical trials under separate Biological Licensing Applications (BLAs). As discussed above, some biologics approved under the FD&C Act, such as hGH and recombinant insulin, already have multiple competitors based on NDAs, but entry costs are high, and price competition to date could be limited. Sandoz's suit to direct the FDA to act on its 2003 application for the hGH Omnitrope reflects an alternative third route, through Section 505(b)(2) of the FD&C Act, which allows the FDA to rely on the published scientific literature or its previous findings for similar products. In June 2006, the FDA approved Sandoz's application but narrowly circum-

"The recent wave of biologic approvals suggests that there might be limited idle manufacturing capacity in the near future."

scribed its approval to protein products approved under the FD&C Act with a single active ingredient, with a well-understood mechanism of action, and that also could be well characterized with existing technology. Furthermore, Omnitrope is not rated as therapeutically equivalent, or substitutable for, other approved human growth hormone products.[25]

Given the rapid growth in spending on biopharmaceuticals and the extensive number of new products likely to be introduced in the coming years, we expect that Congress will act to create some form of an abbreviated process for follow-on biologics. At the same time, given the uncertainty surrounding safety risks, one would expect that Congress will give considerable discretion to the FDA to determine the extent of any clinical testing that will be required for these approvals. In particular, we expect that the scientific criteria for what constitutes a biosimilar product will be left to the discretion of the FDA.

The FDA has been cautious when a new technology poses potential safety hazards. European regulators are ahead of the United States in developing regulations for follow-on biologics, and the European Agency for the Evaluation of Medicinal Products (EMEA) has indicated a case-by-case approach, with some data on clinical efficacy and safety necessary for market approval. To date, two hGH follow-on products to somatropin, Sandoz's Omnitrope and Biopartners' Valtropin, have been approved in Europe.[26] The FDA could adopt a more restrictive approach than Europe's when incorporating technical guidelines that are applicable to multiple classes of biologics. The recent market withdrawal of two cyclooxygenase-2 (COX-2) inhibitors and the appointment of the special Institute of Medicine Committee to study the impact of FDA procedures on product safety will amplify cautious institutional tendencies on this score.[27]

■ **Technology and manufacturing barriers.** There are also important open issues concerning technology and manufacturing barriers to entry and how rapidly manufacturing costs will decline over time as a result of process innovation.

The recent wave of biologic approvals and expanded pipelines suggests that there might be limited idle manufacturing capacity in the near future. If so, we expect that potential producers of follow-on products would need sizable investments in their own facilities to compete. This would be a major financial hurdle for all but the largest entrants or established generic product manufacturers. The generic product manufacturing industry is undergoing consolidation, but only a few established companies appear capable of undertaking the costs and risks.

Over longer time frames, expansion in manufacturing capacity and technological advances in process engineering could greatly decrease the fixed and variable costs for follow-on biologics. In particular, a new group of follow-on manufactur-

ing "specialists" might emerge, which might be biotech product firms, manufacturing technology platform firms, or established generic manufacturers (either stand-alone manufacturers or generic arms of diversified large pharmaceutical firms). Expanded roles for outsourced manufacturing specialists could emerge, just as Contract Research Organizations (CROs) have "hollowed out" some aspects of clinical development, if they are able to lower manufacturing costs for biologics.

Competition in process technology could drive down costs, ease market access for new products, raise expected returns to upstream firms, and stimulate entry and innovation. However, these gains might or might not be ultimately passed on to patients. Manufacturers or "integrators" who control IP and market access might capture rents, as suggested by the experience of new entrants, which typically share a larger fraction of profits with manufacturing/marketing partners to bring products to market.

■ **Market acceptance and competition.** Market acceptance and competition uncertainties include the substitution rates for existing brand-name biologics and what incentives, reimbursement systems, and marketing expenditures will be needed to encourage rapid substitution.

We expect that users will be cautious with respect to follow-on products in the short term, until clinical experience has accumulated. Some clinical trials will likely be needed to demonstrate that a follow-on product is therapeutically equivalent to the original product. The perspectives of specialist physicians and organized patient groups in therapeutic areas with high usage of biologics will be important in driving or limiting demand for follow-on products.

To overcome barriers to acceptance among physicians and patients, follow-on biologic entrants might find it necessary to establish "reputation bonds" with brand-name products to capture and maintain market share. In this environment, market access is facilitated through specialist education and detailing, as well as through contracts with major health plans and coordination with centralized formulary policies. Relative to generic drugs, companies might have to incur the added costs of professional detailing forces, perhaps comparable to those of specialty drugs and biotech companies (estimated elsewhere at forty people).[28]

The Case Of Combination Hormonal Contraceptives

In considering how market structure in follow-on biologics could evolve, the case of combination hormonal contraceptives might be instructive. The investment costs and technical complexity of establishing bioequivalence are somewhat higher than for other drugs, and entry has been concentrated in a handful of specialty generic firms. Generic contraceptives are certified by the FDA as bioequivalent to the referenced brand, but they are marketed under separate brand names (that is, as branded generics). There are no more than three generic competitors for even the very largest-selling contraceptive drugs.[29] As a consequence, generic

price competition is more limited, relative to other drug classes with comparable market sales.

The barriers to entry can be expected to be greater initially for follow-on biologics than for these hormonal contraceptive products. Hence, we can expect some of the differences observed in this market to be present for follow-on biologics. It is also important to remember that the current rapid pace of generic entry and penetration that now characterizes most drugs with substantial sales when patents expire took many years to evolve. We expect that this also will be true for follow-on biologics.

Discussion And Concluding Comments

In sum, we expect that regulatory conservatism, high manufacturing barriers to entry, and limited acceptance of follow-on products will constrain the number of market entrants, the key driver of lower generic drug prices. A robust follow-on industry is likely to emerge as regulatory standards evolve and demand develops, but this will probably take time, even for some well-characterized biologics.

Consequently, we believe that conservative assumptions are appropriate in "scoring" the budgetary savings from legislation that creates a regulatory framework for follow-on biologics, even assuming that scientific, public health, and safety issues are resolved. Technological advances and institutional changes eventually will facilitate entry by multiple follow-on manufacturers, but this will take time. In the meantime, prices might drop only moderately, but substantial gains could occur for a small number of entrants with the required skills and assets.

When creating a legal framework for follow-on biologics, however, legislators and regulators should adopt a long-term perspective. Over the coming decades, biopharmaceutical innovation can provide major improvements with respect to the quality and length of human life but could also exacerbate cost pressures and access disparities in health care. It will fall to Congress and the FDA to balance the objectives of innovation incentives and price competition, as was the case when Congress created the Hatch-Waxman program more than two decades ago.

The optimal design of a legal framework for follow-on biologics is beyond the scope of this paper. But given the entrepreneurial character of the biotech industry, we think that it is especially important that Congress carefully consider the intellectual property provisions that will govern competition between innovators and imitators. In particular, Congress will have to consider whether to award market exclusivity to the first follow-on biologic to challenge a patent successfully. If it enacts such a provision, it will also need to determine the data exclusivity period for innovators, because this determines the earliest point in time that follow-on biologics can enter based on an abbreviated process that relies in whole or part on innovators' safety and efficacy data.

Intellectual property has been an important factor for biotech start-ups in securing venture funding and partnerships with larger firms. Product life cycles for

new medicines span decades, and R&D decisions are made with long time horizons on future returns. Legislators might view the encouragement of patent challenges and attendant litigation as a good short-term mechanism for exposing more biologics to follow-on price competition. But increased uncertainty and IP litigation in biotech also would have major negative-incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines. Most of these firms have few if any profitable products.

The European Union (EU) recently instituted a ten-year data-exclusivity period for pharmaceutical innovators.[30] This prevents patent challengers from filing applications relying on innovators' safety and efficacy data until at least ten years have elapsed. The comparable period in the United States is five years. Given the high costs and long time required to develop a new medicine, five years is generally not sufficient to cover R&D costs and earn a risk-adjusted return.[31] A longer data-exclusivity period for biologics could be useful for policymakers to consider in their efforts to balance innovation incentives and price competition.

Further investigation and quantitative analysis and simulation would be valuable to policymakers, including the following: modeling the number of market entrants and resulting prices by therapeutic area after follow-on entry; estimating fixed costs of market entry and variable costs of manufacturing, with comparison to generic drugs; identifying likely marketing investments by therapeutic area and their impact on market organization; and estimating long-term effects on R&D investment and innovation and investment risk in the biotechnology sector.

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NOTES

1. Gordon Johnson, vice president for regulatory affairs, Generic Pharmaceutical Association, Remarks at FDA/DIA Scientific Workshop on Follow-on Protein Pharmaceuticals, Arlington, Virginia, 16 February 2005.
2. G.J. Mossinghoff, "Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process," *Food and Drug Law Journal* 54, no. 2 (1999): 187–194.
3. A third alternative discussed subsequently lies with section 505(b)(2) of the FD&C Act, which allows the FDA to rely on the published scientific literature or its previous findings for similar products.
4. J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–185.
5. DiMasi and colleagues' estimates rise to $897 million if postapproval costs such as additional clinical testing and the development of new indications are included.
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EXHIBIT 12

United States Patent [19]

Lin

[11] **Patent Number: 4,703,008**

[45] **Date of Patent: Oct. 27, 1987**

[54] **DNA SEQUENCES ENCODING ERYTHROPOIETIN**

[75] Inventor: **Fu-Kuen Lin**, Thousand Oaks, Calif.

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[21] Appl. No.: **675,298**

[22] Filed: **Nov. 30, 1984**

Related U.S. Application Data

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[51] **Int. Cl.**[4] **C12N 5/00**; C12N 15/00; C12N 1/20; C12N 1/00; C12Q 1/68; C07H 15/12

[52] **U.S. Cl.** **435/240.2**; 435/172.3; 435/253; 435/6; 435/317; 435/320; 536/27; 935/9; 935/10; 935/13; 935/79; 935/80

[58] **Field of Search** 435/68, 317, 172.3, 435/253, 240; 935/6, 10, 11, 27, 69, 73, 13

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[57] **ABSTRACT**

Disclosed are novel polypeptides possessing part or all of the primary structural conformation and one or more of the biological properties of mammalian erythropoietin ("EPO") which are characterized in preferred forms by being the product of procaryotic or eucaryotic host expression of an exogenous DNA sequence. Illustratively, genomic DNA, cDNA and manufactured DNA sequences coding for part or all of the sequence of amino acid residues of EPO or for analogs thereof are incorporated into autonomously replicating plasmid or viral vectors employed to transform or transfect suitable procaryotic or eucaryotic host cells such as bacteria, yeast or vertebrate cells in culture. Upon isolation from culture media or cellular lysates or fragments, products of expression of the DNA sequences display, e.g., the immunological properties and in vitro and in vivo biological activities of EPO of human or monkey species origins. Disclosed also are chemically synthesized polypeptides sharing the biochemical and immunological properties of EPO. Also disclosed are improved methods for the detection of specific single stranded polynucleotides in a heterologus cellular or viral sample prepared from, e.g., DNA present in a plasmid or viral-borne cDNA or genomic DNA "library".

31 Claims, 21 Drawing Figures

Translation of Monkey EPO cDNA

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Sau3A
GATCCCGCGCCCCCTGGACAGCCGCCCTCTCCTCCAGGCCCGTGGGGCTGCCCCTGCCC

CGCTGAACTTCCCGGGATGAGGACTCCCGGTGTGGTCACCGCGCCCCTAGGTCGCTGAG

                                  -27                 -20
                              Met Gly Val His Glu Cys Pro Ala Trp
GGACCCCGCCCAGGCGCGGAGATG GGG GTG CAC GAA TGT CCT GCC TGG

                                        -10
Leu Trp Leu Leu Leu Ser Leu Val Ser Leu Pro Leu Gly Leu Pro
CTG TGG CTT CTC CTG TCT CTC GTG TCG CTC CCT CTG GGC CTC CCA

          -1  +1                                    10
Val Pro Gly Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
GTC CCG GGC GCC CCA CCA CGC CTC ATC TGT GAC AGC CGA GTC CTG

                                20                  *
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Val Thr Met
GAG AGG TAC CTC TTG GAG GCC AAG GAG GCC GAG AAT GTC ACG ATG

          30                                    *     40
Gly Cys Ser Glu Ser Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
GGC TGT TCC GAA AGC TGC AGC TTG AAT GAG AAT ATC ACC GTC CCA
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in the context of mammalian cell expression of DNA inserted in a hybrid vector of bacterial plasmid and viral genomic origins, a wide variety of expression systems are within the contemplation of the invention. Conspicuously comprehended are expression systems involving vectors of homogeneous origins applied to a variety of bacterial, yeast and mammalian cells in culture as well as to expression systems not involving vectors (such as calcium phosphate transfection of cells). In this regard, it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of "exogenous" DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host. Expression systems of the invention further contemplate these practices resulting in cytoplasmic formation of EPO products and accumulation of glycosylated and non-glycosylated EPO products in host cell cytoplasm or membrances (e.g., accumulation in bacterial periplasmic spaces) or in culture medium supernatants as above illustrated, or in rather uncommon systems such as *P. aeruginosa* expression systems (described in Gray, et al., *Biotechnology*, 2, pp. 161–165 (1984).

Improved hybridization methodologies of the invention, while illustratively applied above to DNA/DNA hybridization screenings are equally applicable to RNA/RNA and RNA/DNA screening. Mixed probe techniques as herein illustrated generally constitute a number of improvements in hybridization processes allowing for more rapid and reliable polynucleotide isolations. These many individual processing improvements include: improved colony transfer and maintenance procedures; use of nylon-based filters such as GeneScreen and GeneScreen Plus to allow reprobing with same filters and repeated use of the filter, application of novel protease treatments. [compared, e.g., to Taub, et al. *Anal. Biochem.*, 126, pp. 222–230 (1982)]; use of very low individual concentrations (on the order of 0.025 picomole) of a large number of mixed probes (e.g., numbers in excess of 32); and, performing hybridization and post-hybridization steps under stringent temperatures closely approaching (i.e., within 4° C. and preferably within 2° C. away from) the lowest calculated dissociation temperature of any of the mixed probes employed. These improvements combine to provide results which could not be expected to attend their use. This is amply illustrated by the fact that mixed probe procedures involving 4 times the number of probes ever before reported to have been successfully used in even cDNA screens on messenger RNA species of relatively low abundancy were successfully applied to the isolation of a unique sequence gene in a genomic library screening of 1,500,000 phage plaques. This feat was accomplished essentially concurrently with the publication of the considered opinion of Anderson, et al., supra, that mixed probe screening methods were "... impractical for isolation of mammalian protein genes when corresponding RNA's are unavailable.

What is claimed is:

1. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:

(a) the DNA sequences set out in FIGS. 5 and 6 or their complementary strands; and

(b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).

2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

3. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding monkey erythropoietin.

4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

5. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 1, 2, or 3.

6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

8. A cDNA sequence according to claim 7.

9. A monkey species erythropoietin coding DNA sequence according to claim 8.

10. A DNA sequence according to claim 9 and including the protein coding region set forth in FIG. 5.

11. A genomic DNA sequence according to claim 7.

12. A human species erythropoietin coding DNA sequence according to claim 11.

13. A DNA sequence according to claim 12 and including the protein coding region set forth in FIG. 6.

14. A DNA sequence according to claim 7 and including one or more codons preferred for expression in *E.coli* cells.

15. A DNA sequence according to claim 14, coding for expression of human species erythropoietin.

16. A DNA sequence according to claim 15 including the protein coding region set forth in FIG. 7.

17. A DNA sequence according to claim 7 and including one or more codons preferred for expression in yeast cells.

18. A DNA sequence according to claim 17, coding for expression of human species erythropoietin.

19. A DNA sequence according to claim 18 including the protein coding region set forth in FIG. 8.

20. A DNA sequence according to claim 7 covalently associated with a detectable label substance.

21. A DNA sequence according to claim 20 wherein the detectable label is a radiolabel.

22. A single-strand DNA sequence according to claim 20.

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

26. A transformed or transfected COS cell according to claim 25.

27. A transformed or transfected CHO cell according to claim 25.

28. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 7.

29. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

30. A DNA sequence according to claim 7 coding for [Phe^{15}]hEPO, [Phe^{49}]hEPO, [Phe^{145}]hEPO, [His^{7}-]hEPO, [Asn^{2}des-Pro^{2} through Ile^{6}]hEPO, [des-Thr^{163} through Arg^{166}hEPO, or [Δ27-55]hEPO.

31. A purified and isolated DNA sequence as set out in FIGS. 5 or 6 or the complementary strand of such a sequence.

* * * * *