



# Continued Development of Approved Biological Drugs

A Quantitative Study of Additional Indications  
Approved Postlaunch in the United States

White Paper

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Maya Said

Charles-André Brouwers

Peter Tollman

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## A Quantitative Study of Additional Indications Approved Postlaunch in the United States

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### Executive Summary

- ◇ Many biotechnology-derived protein drugs, often referred to as biologics, obtain additional U.S. Food and Drug Administration (FDA)-approved indications after the initial approval; some of these are for use in entirely different therapeutic areas or patient populations and may be found effective at treating conditions for which no effective therapy was previously available.
- ◇ Additional indications are often approved many years after the initial approval. One-third of all additional indications of biotechnology-derived protein drugs investigated in this study were approved by the FDA more than 7 years after the approval of the initial indication. A biologic that has been on the market for 6 years is expected to have on average two additional indications approved over the remainder of its life, while a biologic that has been on the market for 11 years is expected to have on average one additional indication approved over the remainder of its life.
- ◇ Today many potential additional therapeutic indications are in development, with some biologics being explored for more than 20 such additional indications.
- ◇ Many indications lead to additional postmarketing commitments; the average Biologics License Application (BLA) for a biotechnology-derived protein has almost five pending or recently completed postmarketing commitments. These commitments add to the time and investment necessary to bring new indications to market and patients.
- ◇ No comprehensive estimates currently exist for all of the investments in additional indications occurring after initial approval, but considering that the size, complexity, and failure rates of clinical trials required for approval of additional indications are similar to those required for the initial indication, such investments represent a significant part of the overall costs involved in researching and developing new biologics.
- ◇ Moving forward, it is important to have appropriate incentives in place for continued R&D investment in order to ensure that innovation is supported and not slowed down.

As the U.S. Congress considers creating a process that would allow the FDA to approve follow-on biologics (FOBs)—also referred to as biosimilars—on the basis of an abbreviated application by follow-on manufacturers, there has been heightened interest in understanding various aspects of the biologics market. To date, much has been published on the development and overall properties of the biologics market, but one aspect that has not been examined is the research that occurs after biologics have been initially approved.

By the very nature of the science underlying them, biologics typically have a therapeutic potential well beyond their initial therapeutic objective. Many are initially approved for relatively narrow uses or indications. New treatment advances are often realized from biologics that have been on the market for a while but whose pleiotropic effects (effects other than those for which the agent was specifically developed) on the entire human physiology (normal and diseased) were not known until additional research was conducted—often many years after initial FDA approval. This paper sheds some light on the extent of biologics' postlaunch development, by analyzing additional indications approved postlaunch, as well as describing some of the postapproval requirements associated with these indications.



## Analysis Scope and Data Sources

The analysis in this paper is limited to biotechnology-derived protein products approved under the Public Health Service Act (PHSA) and regulated by the FDA's Center for Drug Evaluation and Research (CDER). These correspond to the BLAs of monoclonal antibodies and recombinant DNA products regulated by CDER. Specifically excluded from consideration here are biologics approved under the Food, Drug, and Cosmetic Act (FDCA), such as growth hormones and insulin; BLAs regulated by CDER corresponding to purified protein extracts, such as botulinum toxin; and biologics regulated under the PHSA by the FDA's Center for Biologics Evaluation and Research (CBER), such as vaccines and cell therapies.

Although the first such biologics approved in the United States under the PHSA date back to the mid-1980s, there are only three PHSA-approved biotechnology-derived protein products with more than 20 years of market experience in the United States.<sup>1</sup> Only one-third of all such biologics in the United States today have been on the market for 10 years or more, and half have entered the market since 2000. While the available data are limited—in part due to the fact that half of the biologics reviewed have been on the market for fewer than 7 years—the available data provide valuable insight into the extent and length of postapproval development.

The study data were obtained from the FDA Web site.<sup>2</sup> Specifically, we included in our analyses all BLAs of monoclonal antibodies and recombinant DNA products regulated by CDER and documented on the FDA Web site—a data set that includes 58 BLAs approved between 1986 and 2006. (See Exhibit 1, page 3.) For each BLA, we collected the number and timing of all label changes as they appear on the FDA site. We examined each label change and identified label changes related to additional indications. Many label changes that we do not consider here correspond to formulation and manufacturing changes. These changes are the result of additional development and innovation efforts related to process and manufacturing. They are not, however, within the scope of this study.

Because the indication information on the FDA Web site prior to 1996 is not comprehensive, we complemented our data set with label information from individual BLAs as well as with additional research using public information posted on companies' Web sites. Our analyses of the number of indications and development patterns postlaunch are likely to lead to an underestimate of the efforts and extent of development involved, because a few indications approved prior to 1996 are likely to be missing from our data set.

For the postmarketing commitments analysis, we used the FDA postmarketing commitment database.<sup>3</sup> It lists all pending commitments (that is, all postmarketing commitments for which the studies necessary to meet the requirement are being planned or are ongoing) as well as commitments completed within the past year for all approved drugs and biologics on the market today.<sup>4</sup> We considered only those commitments corresponding to BLAs of recombinant DNA products and monoclonal antibodies regulated by CDER. In addition, we reviewed individual approval letters for each additional indication for these BLA products in order to identify any additional postmarketing commitments associated with new indications.

1. Intron A, an interferon alfa-2b; Roferon A, an interferon alfa 2a; and Orthoclone OKT3, a monoclonal antibody, were approved by the FDA in 1986. FDA Web site: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>, accessed March 2007.

2. FDA Web site: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>, accessed November 2006.

3. FDA Web site: <http://www.fda.gov/cder/pmc/pmc-download.htm>, accessed November 2006.

4. The database does not include commitments completed more than a year ago.

## Exhibit 1. This Study Includes 58 BLA Products Licensed in the United States Between 1986 and 2006

|    | Proprietary name | Type | BLA approval year |    | Proprietary name | Type | BLA approval year |
|----|------------------|------|-------------------|----|------------------|------|-------------------|
| 1  | Actimmune        | rDNA | 1990              | 30 | Neumega          | rDNA | 1997              |
| 2  | Aldurazyme       | rDNA | 2003              | 31 | Neupogen         | rDNA | 1991              |
| 3  | Amevive          | rDNA | 2003              | 32 | Oncaspar         | rDNA | 1994              |
| 4  | Aranesp          | rDNA | 2001              | 33 | Ontak            | rDNA | 1999              |
| 5  | Avastin          | mAb  | 2004              | 34 | Orencia          | mAb  | 2005              |
| 6  | Avonex           | rDNA | 1996              | 35 | Orthoclone OKT3  | mAb  | 1986              |
| 7  | Betaseron        | rDNA | 1993              | 36 | Pegasy           | rDNA | 2002              |
| 8  | Bexxar           | mAb  | 2003              | 37 | Pegasy Copegus   | rDNA | 2004              |
| 9  | Campath          | mAb  | 2001              | 38 | PegIntron        | rDNA | 2001              |
| 10 | Cathflo Activase | rDNA | 1987              | 39 | Proleukin        | rDNA | 1992              |
| 11 | CEA-Scan         | mAb  | 1996              | 40 | Pulmozyme        | rDNA | 1993              |
| 12 | Elaprase         | rDNA | 2006              | 41 | Raptiva          | mAb  | 2003              |
| 13 | Elitek           | rDNA | 2002              | 42 | Rebif            | rDNA | 2002              |
| 14 | Enbrel           | rDNA | 1998              | 43 | Regranex         | rDNA | 1997              |
| 15 | Epogen/Procrit   | rDNA | 1989              | 44 | Remicade         | mAb  | 1998              |
| 16 | Erbitux          | mAb  | 2004              | 45 | ReoPro           | mAb  | 1994              |
| 17 | Fabrazyme        | rDNA | 2003              | 46 | Retavase         | rDNA | 1996              |
| 18 | Herceptin        | mAb  | 1998              | 47 | Rituxan          | mAb  | 1997              |
| 19 | Humira           | mAb  | 2002              | 48 | Roferon-A        | rDNA | 1986              |
| 20 | Infergen         | rDNA | 1997              | 49 | Simulect         | mAb  | 1998              |
| 21 | Intron A         | rDNA | 1986              | 50 | Synagis          | mAb  | 1998              |
| 22 | Kepivance        | rDNA | 2004              | 51 | TNKase           | rDNA | 2000              |
| 23 | Kineret          | rDNA | 2001              | 52 | Tysabri          | mAb  | 2004              |
| 24 | Leukine          | rDNA | 1991              | 53 | Vectibix         | mAb  | 2006              |
| 25 | Lucentis         | mAb  | 2006              | 54 | Verluma          | mAb  | 1996              |
| 26 | Myoscint         | mAb  | 1996              | 55 | Xigris           | rDNA | 2001              |
| 27 | Myozyme          | rDNA | 2006              | 56 | Xolair           | mAb  | 2003              |
| 28 | Nagalzyme        | rDNA | 2005              | 57 | Zenapax          | mAb  | 1997              |
| 29 | Neulasta         | rDNA | 2002              | 58 | Zevalin          | mAb  | 2002              |

Source: FDA Web site.

Note: mAb = monoclonal antibody; rDNA = recombinant DNA product.

### Postlaunch Research Leads to Additional Indications Long After Initial FDA Approval

Analysis of BLAs finds new indications being approved long after initial approval:

- ◇ To date, 47 percent of BLAs for recombinant DNA products and monoclonal antibodies regulated by CDER have at least one additional FDA-approved indication after the initial approval.<sup>5</sup>
- ◇ One-third of the new indications for BLAs were approved within three years of the initial indication, while another third of the new indications were approved more than seven years after the approval of the initial indication.

5. The average is likely understated as the sample includes many biologics that had been on the market for only a few years at the time this paper was written.

- ◇ On average, a biologic that has been on the market for 6 years is expected to have two additional indications approved over the remainder of its lifetime. A biologic that has been on the market for 11 years is expected to have on average one additional indication approved over the remainder of its lifetime.

As mentioned earlier, given the limitations of the data we used, these figures are likely to underestimate the full extent of postlaunch development.

It is also worth noting the number and range of additional indications approved after the initial launch of some products. Remicade, for instance, is currently approved for 14 indications. It was launched in 1998 as an acute treatment for luminal and fistulizing Crohn's disease, and within a few years, it was approved as a maintenance medication for both nonfistulizing and fistulizing forms of the disease. Remicade was also approved to reduce the signs and symptoms of rheumatoid arthritis (RA) in 1999, and subsequently, it was approved for three other uses in RA patients. In the past three years, additional new indications have been approved, including ankylosing spondylitis, ulcerative colitis, pediatric Crohn's disease, and plaque psoriasis in 2006. A number of new indications are being explored.<sup>6</sup> These include potential use in the treatment of ulcerative colitis in both adult and pediatric patients.<sup>7</sup> Another notable example is Rituxan, which was initially approved in 1997. Ten years later, it is undergoing clinical trials for 10 new indications.<sup>8</sup>

Biologics launched more recently have followed a similar pattern. Avastin, for example, was approved only three years ago for the treatment of metastatic carcinoma of the colon and rectum. Avastin was later approved for the treatment of metastatic colorectal cancer and metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel. Today there are 23 potential additional indications under development related to Avastin, including exploration of its potential for use in the treatment of breast and ovarian cancer.<sup>9</sup>

These biologics constitute striking illustrations of the level of R&D investment that can occur postapproval and of the considerable time that is needed to gain additional knowledge of the pleiotropic effects on the entire human physiology and their full therapeutic potential. It is remarkable that such products take between one and two decades to reach initial approval and that many continue to be developed for new therapeutic uses more than a decade later.

Furthermore, no significant differences in the number of new indications were found by biologic type (that is, monoclonal antibodies versus recombinant DNA products) or with initial approval status—notably, whether the indication was designated as orphan. In particular, 49 percent of recombinant DNA products, which represent 60 percent of all investigated BLAs, have at least one additional FDA approved indication after the initial approval, compared with 44 percent of monoclonal antibodies.

An examination of BLAs initially approved for orphan indications, which represent 35 percent of investigated BLAs, finds 50 percent of those BLAs with at least one additional FDA approved indication after the initial approval, compared with 45 percent of BLAs whose initial indication was not orphan. The analysis also found that 30 percent of all additional indications are orphan or pediatric indications.

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6. There is no guarantee that indications under development will be approved. The ongoing development referenced in this paper is current as of July 2007, but in the time since, that development could have been terminated.

7. Johnson & Johnson Web site: <http://www.investor.jnj.com/pharma-pipeline.cfm?textOnly=false>, accessed July 2007.

8. Genentech Web site: <http://www.gene.com/gene/pipeline/status/index.jsp>, accessed July 2007.

9. Ibid.

Investment into bringing new indications to market and patients is not limited to additional expenditures of time and resources into R&D. Additional resources are dedicated to postmarketing commitments for each new indication.

To secure FDA approval, these additional indications require extensive development programs. In addition to the clinical studies needed to show the safety and effectiveness of the biologic in new patient populations and to support the application for a new indication, companies often commit to conducting additional studies after approval. These are referred to as *postmarketing commitments*.

Currently, about 80 percent of BLAs for recombinant DNA products and monoclonal antibodies have at least one pending postmarketing commitment, and several have upwards of 15 commitments. The average number of these commitments for investigated BLAs is 4.7. For monoclonal antibodies, the average is 5, and for recombinant DNA products, the average is 4.5.

## **The Extended Postlaunch Development of Biologics Helps Ensure That They Reach Their Full Therapeutic Potential**

As the various examples discussed illustrate, many biologics are initially developed for a single indication, but they are subject to further R&D leading to treatments for additional indications. Sometimes, these new uses are in an entirely different therapeutic area and treat conditions for which no effective therapy was previously available. As a result, biologics are often found over time to address multiple unique patient populations by proving to be suitable for several indications. However, these discoveries take time because, in part, each new approval requires a distinct development program and a separate regulatory process, which together can take three to six years.<sup>10</sup>

Given the evolving science underlying biologics, as well as the cost and risk of failure of any clinical development program, companies often have to develop their products gradually. It is therefore likely to take many years for a given biologic to be developed and to gain approval for the patient populations corresponding to the different therapies.

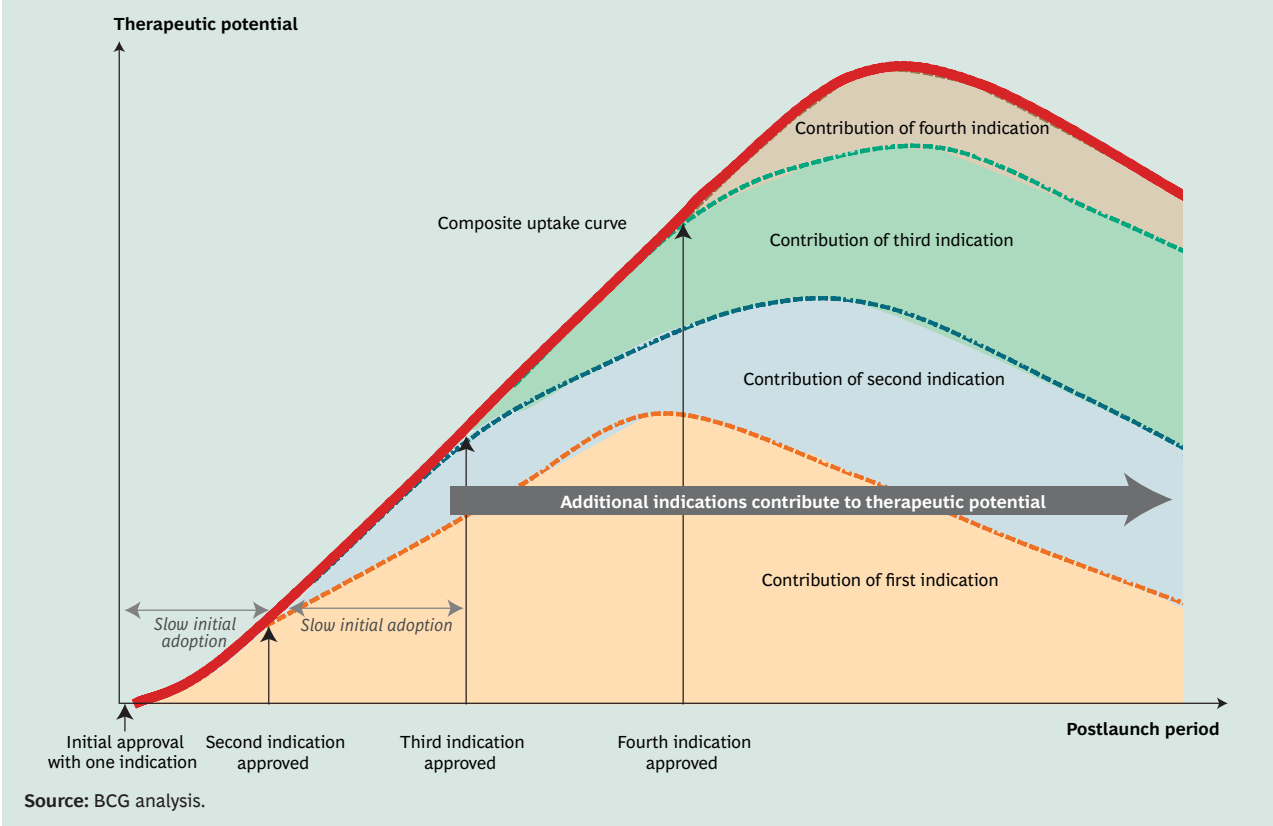
In addition, biologics often represent a departure from previous treatment approaches and are based on a novel therapeutic target and pathway as well as a distinctive delivery system. Examples of novel therapeutic targets include beta-interferon therapy for multiple sclerosis (MS), T-cell blockers for psoriasis, tumor necrosis factor inhibitors for RA and psoriasis, and monoclonal antibodies targeting various cell-surface receptors to treat different kinds of cancers. Examples of new delivery systems include infusion associated with some of the MS and RA biologics.

This novelty aspect is likely to result in a slow initial uptake for each indication, owing to the time needed for the medical profession to gain familiarity with the product. This slow initial uptake applies to each new indication and is therefore a constantly repeated feature. Exhibit 2, on page 6, illustrates qualitatively the potential staggering of new indications leading to achievement of full therapeutic potential, which is defined as the time needed to identify all the different therapeutic applications and to reach all the patient populations corresponding to the different therapies that might result from this progressive development strategy.

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10. This estimate is based on the time it currently takes to conduct phase II and phase III clinical development and regulatory review for biologics, as well as the average time it takes from starting phase II clinical trials on new indications to securing approval for the new indication. See Tufts Center for the Study of Drug Development Impact Report, “The cost to develop new biotech products is estimated to average \$1.2 billion,” Vol.8, No. 6, November/December 2006, for an estimate of the average clinical development time for biologics.

## Exhibit 2. A Progressive Development Strategy and Innovative Therapies Extend the Time Needed for Biologics to Reach Their Full Therapeutic Potential



### Conclusions

It is important to note that the progression to full therapeutic use is intrinsic to biologics innovation, and it is made possible by both product and process patents, which provide innovators with the opportunity and the potential to secure a return on their investments—assuming that the product gains regulatory approval and market acceptance. The investments required to bring a product to its full potential are very large. In addition to the \$1.2 billion in capitalized investment currently needed to reach a first approval, a company needs to support the postlaunch development of additional indications and the fulfillment of any postmarketing commitments.<sup>11</sup> No comprehensive estimates currently exist that capture the full extent of investment occurring after the initial approval, but considering that the size and the complexity of the clinical trials for each new indication are similar to the size and the complexity of those conducted prelaunch and that the failure rates remain high, such costs are likely high and represent an important part of the overall R&D investment involved in researching and developing new therapeutic biologics.

As Congress considers legislation to develop an abbreviated pathway for approval of follow-on biologics, it is important that any legislation include strong incentives for continued R&D investment to ensure that innovation is

11. H. Grabowski, “Data Exclusivity for New Biological Entities,” June 2007. Accessible at <http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf>. Also see Tufts Center for the Study of Drug Development Impact Report, “The cost to develop new biotech products is estimated to average \$1.2 billion,” Vol.8, No. 6, November/December 2006.



supported and not slowed down. While it is critical to provide appropriate incentives to encourage R&D that leads to new biologics, it is equally important to provide appropriate incentives that allow the innovator sufficient time to explore the full therapeutic potential of each biologic for patients. It is also crucial to provide the innovator with an opportunity to break even or achieve a reasonable rate of return for the companies taking the risks and making the R&D investments that lead to new biologics and each new indication.





## About the Authors

**Maya Said** is a project leader in the Boston and Paris offices of The Boston Consulting Group. **Charles-André Brouwers** is a partner and managing director in the firm's New Jersey office. **Peter Tollman** is a senior partner and managing director in BCG's Boston office.

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## For Further Contact

The authors welcome your questions and comments. For inquiries about this study please contact the authors by e-mail at:

[said.maya@bcg.com](mailto:said.maya@bcg.com)

[brouwers.charles-andre@bcg.com](mailto:brouwers.charles-andre@bcg.com)

[tollman.peter@bcg.com](mailto:tollman.peter@bcg.com)

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