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Trends in US approvals: new biopharmaceuticals and vaccines

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The efficient development and approval of new therapeutics and vaccines is vital to the health and welfare of patients. Tufts Center for the Study of Drug Development has collected and analyzed data for new protein therapeutics and vaccines approved in the USA during the past decade. Our results suggest trends toward longer clinical and approval phases for the therapeutics, particularly for oncology products. In this Opinion article, we discuss various legislative acts and FDA initiatives that might improve the efficiency of drug development and approval. Furthermore, few new vaccines have been approved in the past 10 years owing, at least in part, to the lack of incentives for the development of the products. We predict that this might change in the future as government and industry respond to the twin threats of the global spread of infectious diseases and potential bioterrorism.

Development and approval trends

The biotechnology industry has grown substantially during the past 30 years and is now an integral part of the US health care system. In the late 1970s, genetic engineering was found to be a reliable and safe method of production for therapeutic proteins that had previously been extracted from natural sources, such as insulin and human growth hormone. Exploitation of this versatile technology has lead to the marketing approval of a plethora of new and innovative products, including designed recombinant protein (rDNA) and monoclonal antibody (mAb) therapeutics.

Development of therapeutics and vaccines is a time-consuming and costly endeavor. We at the Tufts Center for the Study of Drug Development (Tufts CSDD; http://csdd.tufts.edu) have studied the process of clinical development and approval of these products since 1976 and have reported on pharmaceutical and biotechnology industry trends over time. This is the fourth in a series of reports [1–3] on the trends in development and approval times for new protein therapeutics approved in the USA since 1982.

Historically, biopharmaceutical products have tended to be treatments for small populations of patients and serious or life-threatening diseases. Companies developing these products can take advantage of the provisions intended to improve the efficiency of drug development that were included in US orphan-drug legislation and three legislative acts passed since 1992, which have modernized the Food and Drug Administration (FDA). We compared data for 65 new biopharmaceuticals, approved during two periods, 1996–2000 and 2001–2005, to assess variations during time in product type and average clinical and approval phase lengths for various categories (e.g. orphan and priority-reviewed therapeutics). Our results suggest trends toward less development of orphan therapeutics but a continued emphasis on products for serious or life-threatening diseases (Box 1). We also observed trends toward longer clinical and approval phases in all the product categories we examined.

Recent attention to the global threat of infectious agents has heightened interest in novel prophylactic vaccines; therefore, we also examined data for vaccines approved in the USA during the past decade. Only one-quarter of the products were considered innovative – a new product indicated for a previously unmet medical need. The various factors that discourage investment in the development of innovative vaccines and possible solutions to the problems encountered in both new biopharmaceutical therapeutics and vaccines development are now discussed.

Analysis criteria

Tufts CSDD maintains a database currently comprising records for >2000 biopharmaceutical therapeutic and vaccine products that have entered commercially sponsored clinical study. Clinical development and approval data included in the database for products approved by the Food and Drug Administration (FDA) were collected from company surveys and public documents. In this report, the following definitions are used: a new biopharmaceutical therapeutic is defined as a product composed of protein that is unique compared with any therapeutic previously approved for marketing in the USA; vaccine products are composed of new components or new combinations of components; and an innovative product is defined as a new product indicated for a previously unmet medical need. Diagnostics, devices and variants of existing products (e.g. new dosage, formulation or form of delivery) were excluded.

The product clinical phase was defined as the time from the earliest of either the first investigational new drug application filing date or the date that clinical study was first initiated, to the date that the marketing application was submitted to the FDA. The clinical phase therefore includes all clinical development performed outside of the USA before the first investigational new drug application.
Box 1. Trends in new biopharmaceuticals and vaccines approved in the USA during 1996–2005.

- A total of 65 new biopharmaceuticals were approved during 1996–2005, with 32 approved during 1996–2000 and 33 approved during 2001–2005.
- Mean clinical development and approval times for new biopharmaceuticals increased during the two five-year periods. Mean clinical development and approval times were 88.0 and 15.9 months, respectively, for the 1996–2000 cohort. Mean clinical development and approval times were 83.0 and 18.5 months, respectively, for the 2001–2005 cohort.
- Increases in mean phase lengths were largest for the oncology therapeutics.
- A total of 15 new vaccines were approved during 1996–2005, comprising fewer than one-quarter of the number of new biopharmaceuticals approved in the same period.
- Only 4 of the 15 vaccines were indicated for a previously unmet medical need. The remaining 11 vaccines were approved for prevention of influenza and childhood illnesses.
- Mean clinical development time for innovative vaccines was similar to that for new biopharmaceuticals approved during 2001–2005.

The FDA approved a total of 16 new protein therapeutics during 2004–2005 (Table 1). Therapeutic rDNA products comprised the majority (62%); the remaining products were mAbs (19%) and non-recombinant proteins (19%). Notably, the FDA determined that most (75%) of the products had the potential to be significant advances in the treatment of disease and were given priority reviews: under current US legislation, the FDA performance goal for a priority review is six months to the first FDA action. If the first action is not approval, the application can be resubmitted for additional review cycles. Of the 12 priority-reviewed products, six were approved in the first review-cycle.

Three new hyaluronidase products of human (recombinant), sheep and cow origin were approved in 2004 and 2005. One additional bovine hyaluronidase product was also approved in 2005, although it was not considered new, according to the inclusion criteria. A bovine hyaluronidase product, Wydase (Wyeth, www.wyeth.com), had previously been on the US market but production was discontinued in 2001. Interestingly, although hyaluronidase is a complex glycoprotein with a molecular weight of ~61kDa, all four products were approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The 505(b)(2) mechanism, suggested as a possible pathway for approval of eligible follow-on biologics [4,5], enables the FDA to rely, in part, on published scientific or medical reports for an approved product as evidence of the safety and effectiveness of an equivalent unapproved product.

Comparison of phase lengths in two periods

Because few protein therapeutics are approved in any given year, we examined approvals in two five-year periods (1996–2000 and 2001–2005) to determine trends in the clinical development and approval phases for these products. The analysis included 32 products approved during 1996–2000 [1,2] and 33 products approved during 2001–2005 [2] (Table 1). The 1996–2000 cohort comprised 19 rDNA, seven mAbs and six non-recombinant proteins, whereas the 2001–2005 cohort was composed of 22 rDNA, nine mAbs and two non-recombinant protein products.

Table 1. New protein therapeutics approved in the USA during 2004–2005

| Trade name | Generic name | Company | Application submission | FDA approval | FDA designations | Approval Phase |
|------------|--------------|---------|------------------------|--------------|-----------------|---------------|
| Apidra     | Insulin glulisine | Aventis Pharmaceutical, Inc. | 18/06/2003 | 16/04/2004 | S | 10.0 |
| Luveris    | Lutropin alfa | Serono, Inc. | 30/04/2001 | 08/10/2004 | S, AA. 0 | 41.3 |
| Kepivance  | Palifermin | Amgen, Inc. | 15/06/2004 | 15/12/2004 | P, FT | 6.0 |
| NAGL AZYME | Galsulfase | BioMarin Pharmaceutical, Inc. | 29/11/2004 | 31/05/2005 | P, FT, O | 6.0 |
| Levemir    | Insulin detamin | Novo Nordisk, Inc. | 05/12/2002 | 16/06/2005 | S | 30.4 |
| FORTAL      | Calcitonin (salmon) | Unigene Laboratories, Inc. | 06/02/2003 | 12/08/2005 | S | 29.2 |
| INCRELEX    | Mecasermin | Tericica, Inc. | 28/02/2005 | 30/08/2005 | P, O | 6.0 |
| HYLENEX (r) | Hyaluronidase (human) | Halozyme Therapeutics, Inc. | 23/03/2005 | 02/12/2005 | P | 8.3 |
| IPLEX      | Mecasermin rinfabate | Insmed, Inc. | 03/01/2005 | 12/12/2005 | P, O | 11.3 |
| ORENCIA    | Abatacept | Bristol-Myers Squibb | 17/11/2004–31/03/2005 | 23/12/2005 | P, FT, R | 8.7 |
| monoclonal antibodies | | | | | | |
| ERLBITUX   | Cetuximab | ImClone Systems, Inc. | 14/08/2003 | 12/02/2004 | P, FT, AA | 6.0 |
| Avastin    | Bevacizumab | Genentech, Inc. | 08/01/2003–26/09/2003 | 26/02/2004 | P, FT, R | 5.0 |
| TYSABRI    | Natalizumab | Biogen Idec, Inc. | 24/05/2004 | 23/11/2004* | P, AA | 6.0 |
| Non-recombinant proteins | | | | | | |
| Vitrase    | Hyaluronidase (ovine) | ISTA Pharmaceuticals, Inc. | 04/08/2003 | 05/05/2004 | P, FT | 9.0 |
| Amphotase  | Hyaluronidase (bovine) | Amphotar Pharmaceuticals, Inc. | 07/07/2003 | 26/10/2004 | P | 15.6 |
| VIGIV      | Vaccinia immune globin intravenous (human) | DynPort Vaccine Company LLC | 21/05/2004 | 18/02/2005 | P, FT, AA, O | 9.0 |

*Company name listed on FDA approval letter; †months; ‡Tysabri voluntarily withdrawn from US market on 28/02/2005. Abbreviations: AA, accelerated approval; FT, fast-track designation; O, US orphan designation; P, priority review; r, recombinant; R, rolling application; S, standard review. Note: product first administration to humans and filing dates are confidential.
Data for analysis was stratified by US orphan designation, FDA review status and therapeutic category.

In all cases, we observed trends toward both longer clinical and approval phases for the protein therapeutics: the mean clinical phase was 83.0 months and the mean approval phase was 18.5 months for all new protein therapeutics approved during 2001–2005 (Figure 1). This was a 22% and 16% increase, respectively, in the clinical and approval phases compared with those for the new protein therapeutics approved during 1996–2000. Orphan-designated and priority-reviewed products, which traditionally have been focal points for the biotechnology industry, showed the most pronounced trends toward longer phases: for both cohorts, the mean clinical phase increased by more than 40% and the mean approval phase increased by more than 30% between the two five-year periods.

Phase length increases between the two periods were evident, although much less dramatic, for non-orphan and standard reviewed products. The mean clinical phase for non-orphan biopharmaceuticals approved during 2001–2005 was 9% longer (79.5 versus 72.8 months) and the approval phase was 12% longer (17.5 versus 15.6 months) compared with non-orphan biopharmaceuticals approved during 1996–2001. For standard-reviewed biopharmaceuticals, the mean clinical phase was 4% longer (72.0 versus 69.4 months) and the approval phase was 15% longer (23.5 versus 20.5 months) for the cohort approved during 2001–2005 compared with that approved during 1996–2000.

The majority of products approved in both periods were treatments for diseases in three therapeutic categories: endocrinology, immunology and oncology. Increases in both the clinical and approval phase lengths were observed in all three categories (Figure 2). Oncology products showed the largest phase length increases between the two periods: 79% in the mean clinical phase and 80% in the mean approval phase. The increase in phase lengths might be explained, in part, by the composition of the 2001–2005 cohort: the oncology biopharmaceuticals approved in this period included first approvals for two radiolabelled murine mAbs (ibrutinomab tiuxetan and $^{131}$I-tositumomab) that had special scientific, technical and regulatory considerations, and two mAbs (alemtuzumab, cetuximab) that were delayed in development owing to business issues.

**Efficiency improvements needed**

The importance of providing patients with new and innovative therapeutics is unquestionable. To facilitate access, the FDA, in conjunction with the pharmaceutical and biotechnology industries, has developed various strategies to increase the efficiency of the clinical development and review process. For example, they have implemented key provisions of *Prescription Drug User Fee Act (PDUFA) II* of 1997 [6] and *PDUFA III* of 2002 [7], the second and third of a series of five-year legislative acts that have modernized the FDA. These provisions address the need to improve the quality of applications through effective communication between the FDA and product sponsors, increase predictability of various FDA actions and develop standardized information technology to streamline activities throughout the process.

| Category     | Clinical Phase | Approval Phase |
|--------------|----------------|----------------|
| Orphan, 96–00 (n=16) | 63.3           | 15.6           |
| Orphan, 01–05 (n=12) | 89.7           | 20.3           |
| Priority, 96–00 (n=15) | 66.5           | 10.1           |
| Priority, 01–05 (n=16) | 95.5           | 13.3           |
| All, 96–00 (n=32)      | 68.0           | 15.9           |
| All, 01–05 (n=33)      | 83.0           | 18.5           |

**Figure 1.** Mean clinical and approval phases for categories of new biopharmaceuticals approved in the US during 1996–2000 and 2001–2005.
Although the efforts are welcome, our results show that, as implemented to date, the improvements have not provided either a consistent or sustained effect. In addition to the increases in mean phase lengths for new biopharmaceuticals documented here, we have also observed increased clinical and approval phases for recently approved new chemical entities (NCEs) compared with those approved during 1996–1998 [8]. Specifically, the mean clinical and approval phases for 58 NCEs approved during 2002–2004 were 84.0 and 18 months, respectively. By comparison, the mean clinical phase for the 110 NCEs approved during 1996–1999 was 70.3 months and the mean approval phase for the cohort was 16.8 months. The FDA has recently examined issues associated with the recent slowdown in product approvals [9] and has identified targeted research [10] that might improve the efficiency of the development process for all therapeutics in the future.

**Vaccines approved during 1996–2005**

The vaccine market is currently dominated by five pharmaceutical firms: Chiron (www.chiron.com), Glaxo-SmithKline (www.gsk.com), Merck (www.merck.com), Sanofi Pasteur (www.sanofipasteur.com) and Wyeth (www.wyeth.com). These firms focus on the production of influenza vaccines and vaccines for childhood illnesses; these comprised the majority of the vaccines approved during the past decade (Table 2). By contrast to the therapeutic products area, there are few incentives to develop either new or innovative vaccines and this situation has resulted in a paucity of products for the US market. Of the 15 vaccines approved since 1996, we considered only four products (rotavirus, Lyme disease, pneumococcal and meningococcal vaccines) to be innovative, and two of these are no longer on the market. The remaining 11 ‘follow-on’ vaccines represent incremental improvements in previously existing products, such as combination products that reduce the number of injections given to children or intranasal delivery for influenza vaccine, and increase the choice of vaccine products available for prevention of a specific infection.

The mean clinical and approval phases were 80.0 and 13.9 months, respectively, for the four innovative vaccines. The clinical phases for the follow-on vaccines tended to be shorter than the average for the innovative vaccines, which is not surprising considering the well-known nature of the infectious agents and of the desired outcome of the studies (e.g. immune response to the vaccine). However, the approval phases for the follow-on vaccines were remarkably variable, ranging from 3.2–97.4 months (Table 2). Not surprisingly, priority-reviewed products had the shortest approval phases. The vaccines with lengthy approval phases (>2 years) were follow-on products – presumably, there was no pressing medical need for approval of the products.

**Vaccine development issues**

Our results suggest that innovative vaccines can be developed in similar time frames, compared with therapeutics. However, several major issues discourage
The development of innovative vaccines: product benefit-to-risk profile, liability and return on investment. Prophylactic vaccines are given to healthy people of all ages to prevent disease. The safety of the product is thus paramount, but the risk of adverse events in all people given any pharmaceutical product will never be zero. In recognition of this problem, the US National Childhood Vaccine Injury Act of 1986 (P.L. 99–660) established the Vaccine Injury Compensation Program (VICP), which became operational in 1988. The VICP acts as an efficient alternative to the judicial system for those seeking recourse, who allegedly were injured by a select group of vaccine products, including childhood hepatitis A and trivalent influenza vaccines. Innovative vaccines are currently excluded from coverage under VICP.

Low return on investment also adversely affects innovative vaccine development. Vaccine research, development and manufacturing requirements are similar to those of therapeutics, but vaccines generally are cheaper and are administered in smaller and fewer doses compared with most therapeutics, particularly those for chronic conditions. Therefore, investment in vaccine product development is less attractive than that for therapeutics. Within the vaccine category, more risk is associated with the development of innovative vaccines compared with incremental improvements made to previously approved products. The emphasis on childhood vaccines during the past decade has occurred, in part, because the market for childhood vaccines, most of which are government-recommended and required for entry into schools, is well established and understood. Markets for innovative vaccines are usually less clear. The innovative pneumococcal conjugate vaccine Prevnar has proven to be an exception – sales topped $1 billion in 2004 – but the product is recommended for children and is covered under VICP.

Overcoming barriers

The complex and varied nature of the issues that arise during the clinical development and review of therapeutics and vaccines confound the identification of easy answers. Although provisions in the three PDUFA legislative acts passed to date have addressed some of the more obvious problem areas in the process, numerous, and perhaps more intractable, issues remain. However, these are being systemically considered and addressed. For example, the FDA has recently introduced additional flexibility at the first phase of clinical development by permitting micro-dose studies, also known as phase 0 studies, in humans. This change should enable companies to validate a hypotheses based on preclinical study results and might increase success rates by enabling early identification of the most promising clinical candidates.

The Critical Path initiative, published by the FDA [9,10], is intended to encourage the efficient development of new therapeutics. The initiative acknowledges the need for better information technology, more informative preclinical safety tests and improved understanding of biomarkers and manufacturing issues. The FDA has identified specific opportunities for improvement of the development process [11] and has recently initiated several collaborative projects on these topics with other government agencies and with industry. In addition, initiatives might be included in future legislation, including PDUFA IV, the passage of which is required to reauthorize user fees and continue the performance goals for the FDA in 2007.

Although inefficiencies in the development of therapeutics have been slowly addressed during the past decade, it is the recent attention given to pathogens that pose a national security risk that has altered the vaccine development landscape in the USA. Both intentional
release of pathogens as an act of bioterrorism and unintentional spread through travel and tourism potentially might result in high casualties and economic loss. As a defensive public health measure, prophylactic vaccines for priority pathogens, such as West Nile and corona virus, should be available. Funding for such vaccines, in addition to anti-infective therapeutics, has been made available through various US government sources, including Project BioShield legislation, National Institutes of Health Challenge Grants, and Department of Defense programs. To date, a few vaccines for priority pathogens have progressed into early clinical studies.

However, more needs to be done to foster the research and the efficient development of innovative vaccine products. For example, expansion of VICP to include innovative vaccines intended for any age group and incentives for vaccine development intended for small US markets might encourage additional investment in prophylactic vaccine products. On a positive note, pharmaceutical and biotechnology firms with focused vaccine development programs currently have some promising new products. A novel rotavirus vaccine, RotaTeq (Merck), was approved by the FDA on 3 February 2006, and vaccines for human papilloma virus infection have either completed phase III or are already in FDA review.

The on-going need for constructive, interactive and iterative discussions between the FDA and sponsors that are focused on the scientific and technical requirements for product marketing approvals has been acknowledged [12]. This cooperative environment, coupled with the expected improvements in the process that result from the current initiatives, might help to increase approval rates, decrease phase lengths and improve the safety and effectiveness of products. Improved efficiency in the development of therapeutics and vaccines should ultimately result in innovative products that help patients in need or stave off infectious disease.

**Additional information**
A table of the median values of the product categories in Figures 1 and 2 is available from the author, upon request.

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