

CLINICAL DEVELOPMENT OF THERAPEUTIC MEDICINES: A BIOPHARMACEUTICAL VERSUS PHARMACEUTICAL PRODUCT COMPARISON

JANICE M. REICHERT, PhD

Tufts Center for the Study of Drug Development, Boston, Massachusetts

The clinical development of therapeutic medicines is a time-consuming and resource intensive process. The published literature documents the length of clinical phases, but there are few published reports on the number of clinical studies and the number of human subjects involved in the development of therapeutic medicines. In this Tufts Center for the Study of Drug Development investigation, clinical study data for 12 new biopharmaceutical products approved in 1994 through 2000 were analyzed and compared to the results of published clinical study data for new molecular entities (NMEs) and new active substances (NASs) approved during the same time period. We found that, on average, development of the biopharmaceuticals involved significantly fewer studies per application compared with the studies of NASs (11.8 studies vs. 37 studies) and also fewer subjects per application compared with the studies of either NMEs or NASs (1014 subjects vs. 5697 subjects for NMEs approved in 1998, 4980 subjects for NMEs approved in 1999, or 4478 subjects for NASs). A possible reason for this finding is that many of the biopharmaceuticals included in the analysis were treatments for diseases that affect a potentially small number of subjects, that is, rare, serious, or life-threatening diseases.

Key Words: Clinical development; Biopharmaceutical; Food and Drug Administration; Orphan drug; Priority review

INTRODUCTION

NEW THERAPEUTIC MEDICINES intended for human use must undergo clinical testing to ensure that they are safe and effective before they can be marketed. Most clinical development programs include a series of studies starting with safety studies in either normal volunteers or patients (Phase I), followed by small-scale studies assessing both

safety and efficacy in patients (Phase II), and finally large-scale studies assessing both safety and efficacy in patients (Phase III) (1). The results of the clinical studies are then presented to regulatory agencies for review, which, provided the review is positive, leads to marketing approval.

The clinical development of a therapeutic medicine is, however, a complex, time-consuming, and resource-intensive process. Introduction of various initiatives intended to streamline the process of product development have been made in the United States by the Food and Drug Administration (FDA) and Congress. These initiatives have in-

Reprint address: Janice M. Reichert, PhD, Tufts Center for the Study of Drug Development, 192 South Street, Suite 550, Boston, MA 02111. E-mail: janice.reichert@tufts.edu.

cluded the orphan drug designation, priority review, accelerated approval, and fast-track designation.

Orphan drug designation, available in the United States since 1983 for therapeutic medicines developed for rare diseases (incidence of fewer than 200000 cases per year in the United States), confers substantial benefits to the sponsor during and after the development phase. These benefits include tax credits for clinical research, protocol assistance from the (FDA) Center for Biologics Evaluation and Research (CBER) or Center for Drug Evaluation and Research (CDER), funding for clinical studies, other assistance from FDA's Office of Orphan Products Development, and seven years of marketing exclusivity after product approval (2).

Priority review was instituted at the FDA in 1992; currently FDA's performance goal for review of priority new drug or biologics applications is six months or less. Because priority-review status is a classification based on the estimated therapeutic value of the product (2), the development phase may also be affected. According to the CBER definition, a priority-reviewed product must, if approved, provide a significant improvement in the safety or effectiveness of treatment, diagnosis, or prevention of a serious or life-threatening disease. The CDER definition is less strict; a priority-reviewed product must, if approved, provide a significant improvement in the safety or effectiveness of treatment, diagnosis, or prevention of a disease (3).

Accelerated approval, available from the FDA since 1992 for speeding the approval of new treatments for serious or life-threatening diseases, allows approval to be granted at the earliest phase of development at which safety and efficacy can be reasonably established (2). Finally, fast track provisions were part of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (4). Fast track designation is available for products that are treatments for serious or life-threatening diseases and have the potential to meet an unmet medical need. The designation is intended to expedite both development and review by encouraging frequent communication with the FDA during the

development and approval process. Fast track products may also be eligible for priority review and accelerated approval (eligibility depends on results of each phase of the development program).

Though the length of clinical phases is documented (5,6,7), there are currently few published reports on the number of studies and subjects involved in the development programs of medicinal products (8–11). This information is valuable not only because it provides benchmarks for companies developing or planning to develop drugs and biopharmaceuticals but also because it provides an assessment of the effects of various regulatory initiatives on the process of clinical development. The data on clinical studies presented here provide benchmarks, and also suggest that the orphan drug program and priority-review initiative have had an effect on the clinical development of biopharmaceutical products.

METHODS

This study reports on the clinical studies of 15 new biopharmaceuticals approved by FDA during the time period December 22, 1994 to June 2, 2000 (approval date of abciximab to approval date of tenecteplase). Sources of data included FDA reviews of biologics license applications (BLAs) or new drug applications (NDAs) and other publicly available FDA documents, medical and pharmaceutical industry literature, publicly available company reports, and company press releases.

A new biopharmaceutical was defined as the first unique therapeutic biopharmaceutical product approved for any indication. Identical products approved subsequently were not included, with the exception of the first recombinant version of an approved nonrecombinant protein. Diagnostic monoclonal antibodies, vaccines (excluding recombinant vaccines), and biopharmaceutical products approved for supplemental indications were not included. The categories of biopharmaceutical products included in the present study are recombinant proteins, ther-

apeutic monoclonal antibodies, and purified, naturally-occurring proteins (nonrecombinant). Data for the selected products were stratified in various ways, that is, by product category, by orphan designation, and by review status. Data are not presented here in cases where the stratification resulted in a category containing only one or two products, for example, products approved under the regulations for accelerated approval ($n = 1$) and products with fast track designation ($n = 2$).

Phase I was defined to include studies performed to evaluate pharmacokinetics, bioequivalence, bioavailability, or safety in normal volunteers or patients. Phase II and III were broadly defined to include controlled clinical trials performed to evaluate the effectiveness and safety of a product in comparison with a standard or control intervention or comparing two or more existing treatments. The term 'studies' was used when referring collectively to studies done in Phase I and comparative trials done in Phase II and III of development programs. All studies done during any phase of development for any indication, and all subjects in any treatment arm of each study completed by the date of FDA approval of the product, were included in the analyses. Phase assignment of data was the same as that reported by the sponsoring company. When the phase was not given, data for studies described as pharmacokinetic, bioequivalence, bioavailability, or safety studies were assigned to Phase I. When the phase was reported as Phase I/II, the data were assigned to Phase II. When the phase was reported as Phase II/III or was described as pivotal, the data were assigned to Phase III. Data on the total number of studies and subjects were available for 15 products; data for the number of studies and subjects at each phase of development were available for 12 products. The data set used in the analyses was comprised of data from these 12 products except where noted.

The clinical study data for the biopharmaceuticals were compared with clinical study data for pharmaceuticals classified as either new molecular entities or new active sub-

stances. NME is a term used in the United States to describe the subject of a drug application classified as Chemical Type 1, that is, an active moiety not yet marketed in the United States. NAS is a term used at the International Conference on Harmonization and in the European Union and Japan to describe chemical, biological, or radiopharmaceutical substances not previously authorized as medicinal products.

RESULTS

Data on the total number of studies and subjects involved in development were available for the 15 biopharmaceutical products listed in Table 1. The products were approved in the United States between December 22, 1994 and June 2, 2000; during this period the FDA approved a total of 30 new biopharmaceuticals. The total number of clinical studies and total number of subjects involved in the development of the 15 products are presented in Figure 1. The total number of subjects involved in the development of three of the recombinant protein products was clearly different than that for the other products (the number of subjects was over 20000 for each product), and thus the data for these three were not included in the analyses except where noted. Data on the number of studies and subjects per study for each clinical phase were available for the remaining 12 products.

The majority (67%) of the 12 products included in the analyses were monoclonal antibodies. The remaining products were either recombinant (25%) or nonrecombinant (8%) proteins. Ten products (83%) were reviewed by CBER and two were reviewed by CDER. Seven (58%) received orphan drug designation while five did not. Nine (75%) were granted priority review and three had standard review. Ten of the 12 products (83%) were approved in 1997 (four products) and 1998 (six products).

The mean number of clinical studies performed at each phase of development and the mean total number of studies completed for each BLA or NDA is shown in Table 2.

TABLE 1
Biopharmaceutical Products Included in the Study

Trade name	Generic name	Company	Approval date	Review center ^a	Rating ^b	Orphan drug ^c
Recombinant proteins						
Retavase	Reteplase	Boehringer Mannheim	10/30/96	CBER	S	N
Neumega	Opreleukin	Genetics Institute	11/25/97	CBER	S	Y
Regranex	Becaplermin	R.W. Johnson	12/16/97	CBER	S	N
Enbrel	Etanercept	Immunex	11/02/98	CBER	P	N
LYMERix	OSP-A	SmithKline Beecham	12/21/98	CBER	S	N
TKNase	Tenecteplase	Genentech	06/02/00	CBER	S	N
Monoclonal antibodies						
Reopro	Abciximab	Centocor	12/22/94	CBER	S	N
Rituxan	Rituximab	IDEC/Genentech	11/26/97	CBER	P	Y
Zenapax	Dacliximab	Hoffmann-LaRoche	12/10/97	CBER	P	Y
Simulect	Basiliximab	Novartis	05/12/98	CBER	P	Y
Synagis	Palivizumab	Medimmune	06/19/98	CBER	P	N
Remicade	Infliximab	Centocor	08/24/98	CBER	P	Y
Herceptin	Trastuzumab	Genentech	09/25/98	CBER	P	N
Mylotarg	Gemtuzumab zogamycin	Wyeth Ayerst	05/17/00	CDER	P	Y
Nonrecombinant proteins						
Sucraid	Sacrosidase	Orphan Medical	04/09/98	CDER	P	Y

a. CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research

b. S = Standard, P = Priority

c. N = No, Y = Yes

For all 12 products the mean number of clinical studies was 5.1, 5.2, and 1.3 for Phase I, II, and III, respectively. The mean total number of studies per BLA or NDA was 11.8. The number of Phase I studies varied depending on the type of product, orphan designation, and review status. Monoclonal antibody products had 34% fewer Phase I studies compared with recombinant protein products, orphan-designated products had 63% fewer Phase I studies compared with nonorphans, and priority-reviewed products had 52% fewer Phase I studies compared with standard-reviewed products. Little variation was observed in the mean number of trials at either Phase II or Phase III. The trends in the data for mean total number of clinical studies per BLA or NDA mirrored the trends in the data for the Phase I studies, that is, monoclonal antibody products had fewer studies compared with recombinant proteins, orphan-designated products had fewer studies compared with nonorphans,

and priority-reviewed products had fewer studies compared with standard-reviewed products.

The mean number of subjects involved per clinical study at each phase of development and the mean total number of subjects included per BLA or NDA are shown in Table 3. For all 12 products the mean number of subjects per study was 21, 59, and 460 for Phase I, II, and III, respectively, and the mean total number of subjects involved per BLA or NDA was 1014. Little difference was observed in the number of subjects involved in Phase I studies when the data were analyzed by product type, orphan designation, or review status. In contrast, large variations were observed in the mean number of subjects involved in Phase II, Phase III, and the total number of subjects per BLA or NDA for these categories. Phase II trials of monoclonal antibody products involved, on average, 49% fewer subjects in Phase II but 135% more subjects in Phase III compared with

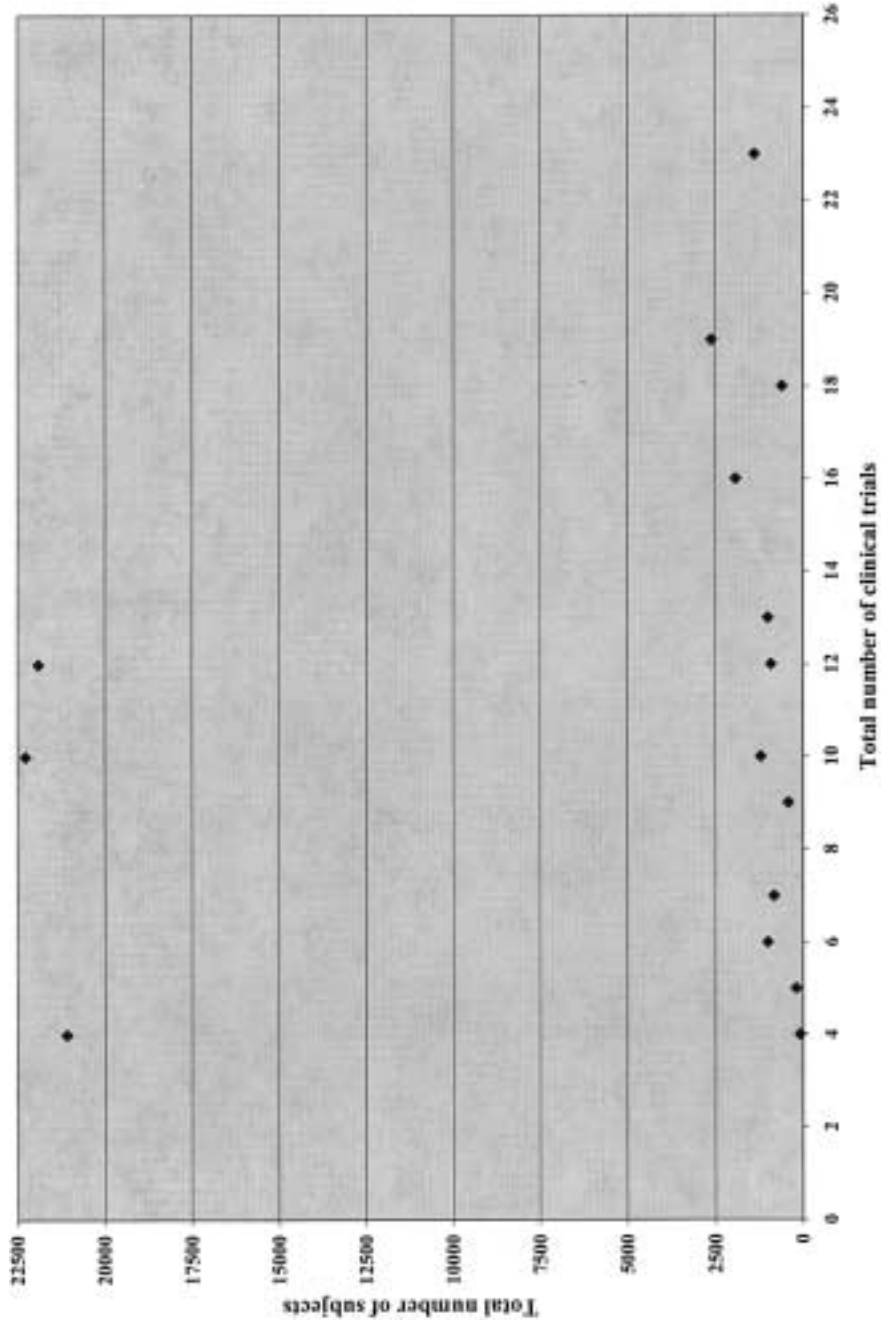


FIGURE 1. Total number of clinical studies and total number of subjects involved in the development of 15 biopharmaceutical products approved during 1994 to 2000.

TABLE 2
Mean Number of Clinical Studies at Each Phase of Development
and Total Number of Studies Completed per BLA or NDA for
12 Biopharmaceuticals Approved During 1994 to 2000

	Number of Phase I studies	Number of Phase II trials	Number of Phase III trials	Total number of studies per BLA or NDA
All (n = 12)	5.1	5.2	1.3	11.8
Mabs (n = 8)	4.8	5.1	1.5	11.4
rDNA (n = 3)	7.3	6.0	1.3	15.7
Orphan (n = 7)	3.0	5.4	1.3	9.7
Nonorphan (n = 5)	8.0	4.8	1.4	14.8
Priority (n = 9)	4.0	5.2	1.4	11.0
Standard (n = 3)	8.3	5.0	1.0	14.3

trials of recombinant proteins, with the net result being that, per BLA or NDA, monoclonal antibody products involved 14% more subjects compared with recombinant proteins. Clinical studies of biopharmaceuticals with orphan designation involved, on average, 51% fewer subjects in Phase II, 63% fewer subjects in Phase III, and 65% fewer subjects per BLA or NDA compared with products without an orphan designation. The priority-reviewed products, most of which were indicated for treatment of serious or life-threatening diseases, involved 43% fewer subjects in Phase II trials, 60% fewer subjects in Phase III trials, and 37% fewer subjects per BLA or NDA compared with standard-reviewed products.

The mean and median number of studies and number of subjects involved per BLA or

NDA for all 15 biopharmaceuticals listed in Table 1 were calculated. When all products were included the mean number of studies per BLA or NDA was 11.2 (median 10.0) and, as shown in Table 4, the mean number of subjects involved per BLA or NDA was 5160 (median 1007).

Mean and Median Number of Studies and Subjects Involved per NDA for Pharmaceuticals

A limited amount of data on the mean and median number of studies and number of subjects involved per application has been published for pharmaceuticals approved between 1994 and 1999. The Center for Drug Development Science (8) reported data for 12 of 51 NMEs approved by the FDA in 1994

TABLE 3
Mean Number of Subjects per Clinical Study at Each Phase of
Development and Total Number of Subjects included per BLA or NDA
for 12 Biopharmaceuticals Approved During 1994 to 2000

	Number of subjects per study in Phase I	Number of subjects per trial in Phase II	Number of subjects per trial in Phase III	Total number of subjects per BLA or NDA
All (n = 12)	21	59	460	1014
Mabs (n = 8)	19	49	538	1137
rDNA (n = 3)	25	96	229	995
Orphan (n = 7)	16	42	263	576
Nonorphan (n = 5)	23	85	714	1627
Priority (n = 9)	21	52	360	883
Standard (n = 3)	20	92	897	1406

TABLE 4
Mean and Median Total Number of Subjects per Application for
Biopharmaceuticals, NMEs, and NASs

	Mean total number of subjects per application	Median total number of subjects per application
Biopharmaceuticals 1994–2000 (n = 12)	1014	960
Biopharmaceuticals 1994–2000 (n = 15)	5160	1007
NMEs ⁹ 1998 (n = 17)	5697	4325
NMEs ¹⁰ 1999 (n = 19)	4980	5435
NASSs ¹¹ 1995–1999 (n = 23)	4478	NA

NMEs = new molecular entities; NASs = new active substances; NA = not available.

and 1995. Though means and medians were not given, approximate ranges were included (23 to greater than 150 studies per NDA; about 1000 to over 13000 subjects involved per NDA). Parexel reported survey data for 17 of 30 NMEs approved by the FDA in 1998 (Table 4) (9). The mean and median total number of subjects per application were 5697 and 4325, respectively. Of these 17 NMEs, none were for treatment of orphan diseases, and 47% were priority-reviewed. Parexel also reported survey data for 19 of 35 NMEs approved by the FDA in 1999 (Table 4) (10). The mean and median total number of subjects per application were 4980 and 5435, respectively. Of these 19 NMEs, 11% were for treatment of orphan diseases, and 56% were priority-reviewed.

The most comprehensive published report on the number and size of clinical studies was done by Centre for Medicines Research (CMR) International (11). The data were from a survey of 46 companies; 23 provided information about a dossier for an NAS submitted to regulatory agencies in Europe, Japan, or the United States between February 1995 and April 1999 (Tables 4, 5, and 6). None of the dossiers were for biologics; data on the orphan designation and review status of the applications were not available. CMR International reported the mean number of studies was 37 (Table 5; median number of studies was 40 in 1995 to 1996, 39 in 1997, and 21 in 1998 to 1999) and the mean number of subjects involved per dossier was 4478 (Table 4; median number of subjects was

3864 in 1995 to 1996, 5582 in 1997 and 3750 in 1998 to 1999). In addition, the mean number of studies (Table 5) and number of subjects per dossier for each phase of development were reported. A mean of 21 studies were done at Phase I, and a mean of 6 trials were done at Phase II. At Phase III the mean number of trials was 10. The mean number of subjects per dossier was reported as 434 for Phase I, 696 for Phase II, and 3348 for Phase III. Calculation of the mean number of subjects per study at each phase from these data provided the results for NASs shown in Table 6 (21 subjects per study for Phase I, 116 subjects per trial for Phase II, and 335 subjects per trial for Phase III).

DISCUSSION

The results presented here indicate that the clinical development of biopharmaceuticals entails fewer studies and a smaller number of subjects compared with the development of NMEs and NASs. However, the limitations of the data used for the analysis must also be considered. The data presented here are from biopharmaceuticals that were predominantly monoclonal antibody (67%), orphan-designated (58%), or priority-reviewed (75%) products. Six (50%) of the products were both orphan-designated and priority-reviewed; five of these were monoclonal antibodies. Monoclonal antibody products are designed to target specific cells. These products might be expected to have fewer safety issues and side effects, which could poten-

TABLE 5
Mean (Median) Number of Clinical Studies at Each Phase of Development and Total Number of Studies Completed per Application for Biopharmaceuticals and NASs

	Number of Phase I studies	Number of Phase II trials	Number of Phase III trials	Total number of studies per application
Biopharmaceuticals 1994–2000 (n = 12)	5.1 (2.5)	5.2 (5.0)	1.3 (1.0)	11.8 (11.0)
NASs (11) 1995–1999 (n = 23)	21 (NA)	6 (NA)	10 (NA)	37 (NA)

NASs = new active substances.

tially reduce the number of studies performed. Orphan designation is given to products intended for treatment of diseases affecting less than 200000 people in the United States. Enrolling large numbers of appropriate subjects with “orphan” diseases in clinical studies might not be feasible, thus studies of these products would tend to be few and small. The majority of the priority-reviewed biopharmaceuticals included here are for the treatment of serious or life-threatening diseases such as cancer (trastuzumab, gemtuzumab zogamycin, rituximab) and organ transplant rejection (basiliximab, dacliximab). The same difficulty in enrolling subjects might have affected the studies of these products. For example, gemtuzumab zogamycin, which was orphan-designated and received both a priority review and accelerated approval, was approved for the treatment of acute myeloid leukemia on the basis of Phase I and Phase II studies only; no Phase III trials were done because the rarity of the disease significantly limited the number of patients eligible for a trial.

For the group of biopharmaceuticals considered here, orphan-designated products were studied in the smallest number of subjects (576 per BLA or NDA). Priority-reviewed products were studied in only slightly more subjects (883 per BLA or NDA), which was still below the average for all products. Compared to the NMEs included in the two Parexel data sets (1998 and 1999 data combined), the biopharmaceuticals were more likely to have orphan-designation (58% vs. 5%) and were more likely to be priority-reviewed (75% vs. 53%). It is not surprising then that, on average, fewer subjects were involved in the clinical studies for the biopharmaceuticals (mean of 1014 subjects) compared with the NMEs (mean of 5319 subjects for 1998 and 1999 data combined). When the data for all 15 biopharmaceuticals were included, the mean total number of subjects per application was 5160, close to the value for the NMEs. The median, however, was 1007, which indicates that the mean value was skewed by the data for the three products that were “outliers” (those studied in greater than 20000 subjects

TABLE 6
Mean Number of Subjects per Study at Each Phase of Development for Biopharmaceuticals and NASs

	Number of subjects per study in Phase I	Number of subjects per trial in Phase II	Number of subjects per trial in Phase III
Biopharmaceuticals 1994–2000 (n = 12)	21	59	460
NASs ^a (11) 1995–1999 (n = 23)	21	116	335

NASs = new active substances; a = results derived from data provided in reference 11.

each). In contrast, the mean and median values for the total number of subjects per application for the NMEs were similar, which suggests that there was less skew in the data.

Differences at each phase of development were apparent when the mean number of studies and subjects per study for the biopharmaceuticals included here were compared with similar data for NASs reported by CMR International. The Phase I development of biopharmaceuticals involved fewer studies compared with NASs (mean of 5.1 vs. 21 studies) but the same number of subjects per study (mean of 21 subjects). At Phase II biopharmaceuticals were studied in similar numbers of trials (mean of 5.2 vs. 6 trials) but the trials involved about half the number of subjects (mean of 59 vs. 116 subjects) compared with the NASs. The greatest difference was at Phase III, where biopharmaceuticals were studied in 13% of the number of trials compared with the NASs (mean of 1.3 vs. 10 trials), though Phase III trials involved a greater mean number of subjects per trial (mean of 460 vs. 335 subjects). The mean total number of studies per application was much lower for the biopharmaceuticals regardless of whether the data for the three products that were "outliers" were excluded (means of 11.8 and 11.2 for the 12 and 15 biopharmaceutical products, respectively, vs. 37 for the NASs). As was noted in the comparison of the mean total number of subjects per application of the biopharmaceuticals with the NMEs, development of the biopharmaceuticals involved significantly fewer subjects compared with NASs.

CMR International's report indicated that 9 of the 23 dossiers included in its study sought marketing authorization for multiple indications, with a maximum number of eight indications. In contrast, none of the 15 biopharmaceutical BLAs or NDAs included here sought approval for more than one indication. Four products were studied in more than one indication during Phase II or III, with a maximum of four indications, but alternate indications for these four products were studied in only one or two trials each. The termination of the trials for the alternate indications might

have been due to negative results from the trials, or the company might not have had the resources to pursue development for multiple indications. Either reason would prevent the sponsoring company from developing the product for the treatment of more than one patient population, thus limiting the number of trials performed.

Compared with the published data for pharmaceuticals, the marketing approvals for the majority of the biopharmaceutical products included here were based on fewer clinical studies and a smaller number of subjects. The data suggest that this result was due to the fact that biopharmaceuticals were more likely to be treatments for diseases affecting small numbers of patients and/or treatments for serious or life-threatening diseases, and that the biopharmaceutical products were developed for only one indication. The possibility that the numbers of studies and subjects involved in the development of orphan-designated, priority-reviewed pharmaceuticals intended for treatment of a single indication are similar to the results reported here for biopharmaceuticals has not been excluded. The data to make this comparison are not currently available.

The results presented here suggest that the FDA initiatives that provide orphan drug designation and/or priority-review status to eligible biopharmaceutical products have an effect on the development programs of those products. The development of therapeutic medicines will continue to change over time as additional initiatives designed to streamline and speed the process are introduced both in the United States and abroad. For example, a number of provisions in FDAMA are intended to simplify and increase the efficiency of the development process (fast track initiative, and the use of a single, well-controlled trial to prove efficacy). Also, the European Union has recently adopted orphan drug regulations. The European Union orphan drug designation, which allows for up to 10 years of market exclusivity, is for products that diagnose or treat conditions with a prevalence of five per 10000 in the general population.

Finally, standardization of the development process will occur in the European Union, Japan, and the United States as a result of the International Conference on Harmonization (ICH) of technical requirements for the registration of pharmaceuticals for human use. Objectives of the harmonization effort are the reduction in development times and resource use and easier simultaneous launch of medicinal products in multiple countries. A number of important ICH guidelines (General Considerations for Clinical Trials, Ethnic Factors in the Acceptability of Foreign Clinical Trials, The Extent of Population Exposure to Assess Clinical Safety; <http://www.ifpma.org/ich5.html>) have already been implemented in all three regions. In addition, a draft version of the common technical document to be used in the three regions for the registration of pharmaceuticals for human use is now available.

The effects of the FDAMA initiatives, the European Union orphan drug regulations, and the ICH guidelines on the clinical development of therapeutic medicines cannot currently be determined in any meaningful way. Tufts CSDD will continue to track and report on these effects in future studies.

Acknowledgements—The author gratefully acknowledges colleagues at Tufts CSDD for their comments and suggestions on the manuscript.

REFERENCES

1. Mathieu M. *New drug development: a regulatory overview*. 4th edition. Waltham MA: Parexel, 1997: 10–13.
2. Travis L. How to work with the FDA approval system to accelerate drug development. *Regul Aff Focus*. 2000; Feb;5(2):17–22.
3. *Priority review policy, Center for Drug Evaluation and Research Manual of Policies and Procedures*. Food and Drug Administration [<http://www.fda.gov/cder/mapp/6020-3.pdf>].
4. Food and Drug Administration Modernization Act of 1997. US Public Law 105–115 (Nov 21, 1997); 21 USC 355a; 111 Stat 2296.
5. Reichert JM. New biopharmaceuticals in the US: trends in development and marketing approvals 1995–1999. *Trends Biotechnol*. 2000 Sep;18(9): 364–369.
6. Kaitin KI, Healy EM. The new drug approvals of 1996, 1997, and 1998: drug development trends in the user fee era. *Drug Inf J*. 2000;34(1):1–14.
7. Reichert JM, Chee J, Kotzampaliris C. The effect of PDUFA and FDAMA on the development and approval of therapeutic medicines. *Drug Inf J*. 2001; 35(1).
8. Peck CC. Drug development: improving the process. *Food Drug Law J*. 1997;52(2):163–167.
9. Emerging clinical trial enrollment benchmarks: trial size statistics for new drugs approved in 1998. In: *Parexel's Pharmaceutical R&D Statistical Sourcebook 2000*. Waltham MA: Parexel, 2000:76.
10. Emerging clinical trial enrollment benchmarks: trial size statistics for new drugs approved in 1999. In: *Parexel's Pharmaceutical R&D Statistical Sourcebook 2000*. Waltham MA: Parexel, 2000:75.
11. Describing dossiers: characterising clinical dossiers for global registration. *CMR International R&D Briefing* [<http://www.cmr.org/25.pdf>].