

THE SINGLE CONTROLLED TRIAL: INDUSTRY SURVEY INDICATES THAT IMPLEMENTATION IS STILL A WORK IN PROGRESS

CHRISTOPHER-PAUL MILNE, DVM, MPH, JD

Assistant Director, Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts

The Food and Drug Administration Modernization Act of 1997 amended the standard of approval for effectiveness by providing that under certain circumstances, one adequate and well-controlled clinical investigation and confirmatory evidence would be sufficient. The standard of effectiveness has been a point of contention throughout the modern history of drug development and remains so today. With the imminent need to consider the reauthorization of the Prescription Drug User Fee Act, the implementation of the Food and Drug Administration Modernization Act of 1997 will also be open to discussion. In anticipation of the upcoming Congressional and public debate surrounding these laws, the Tufts Center for the Study of Drug Development conducted a survey of nearly 50 of the leading pharmaceutical and biotechnology firms in order to assess the level and manner of utilization of the single controlled trial at the outset of the Food and Drug Administration Modernization Act of 1997 to serve as a frame of reference for these discussions.

Key Words: Single controlled trial; Effectiveness; Food and Drug Administration Modernization Act of 1997

INTRODUCTION

THE FOOD AND Drug Administration Modernization Act of 1997 (FDAMA) included a provision (section 115) stating that under certain circumstances, data from one adequate and well-controlled clinical investigation and confirmatory evidence may be sufficient to establish effectiveness for FDA approval of drug and biological products. In so doing, Congress and FDA have officially recognized that multiple clinical trials are not

always necessary to claim effectiveness and that advances in the science and practice of drug development may permit an expanded role for the so-called single controlled trial in contemporary clinical development.

The origin of the single controlled trial seems to have links back to both the Center for Biologics Evaluation & Research (CBER) and the Center for Drug Evaluation & Research (CDER) within FDA. This provision essentially codified an FDA policy that had existed for a number of years, but whose application had been limited to some biological products and a few pharmaceuticals for the treatment of cancer, lung disease, heart disease, and especially AIDS (1).

During the implementation of the expedited approval program, FDA demonstrated

Reprint address: Christopher-Paul Milne, DVM, MPH, JD, Assistant Director, Tufts Center for the Study of Drug Development, Tufts University, 192 South Street, Suite 550, Boston, MA 02111. E-mail: christopher.milne@tufts.edu.

its willingness to base approval of drugs for AIDS patients on a single pivotal study (2). In biologics regulation, the standard was safe, pure, and potent. Potent was interpreted to mean effective. The link to the drug standard was indirect. While drugs generally required at least two adequate and well-controlled investigations, biologics sometimes only required one efficacy trial. Up until the time of FDAMA, CBER was viewed as applying the effectiveness standard less rigidly, and one CEO of a biotechnology firm even testified at a 1997 Senate hearing that CBER had stated that one trial was ordinarily enough and that two trials represented the exception (1).

The emergence of the single controlled trial was directly linked to the evolution of the standard of effectiveness. After the 1962 amendments, the existing standard was as follows:

“substantial evidence means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof” (21 U.S.C. 355 (d)).

Over the years there was pressure on FDA to revisit the effectiveness threshold from two different directions: harmonization of CBER and CDER regulations and faster marketing of products (both drugs and biologics) for serious and life-threatening diseases. In 1993, CBER and CDER began talks on harmonization of regulatory requirements. FDA responded to industry concern that the Federal Food, Drug, and Cosmetic Act not be interpreted as requiring multiple clinical trials when one “pivotal” study could suffice. FDA issued a 1995 statement that formally articulated the agency thinking on the use of what later became the single controlled trial by acknowledging the accepted paradigm, but leaving the door open for an updated one. The agency noted that while a second study

is typically necessary to replicate the first one, in some instances it would be possible to replicate results within one large, well-designed, multicenter study (3). By 1996 this agency statement, together with the supplemental indications initiative, took hold and evolved over several years into FDA’s 1997 draft effectiveness guidance.

At this point, FDAMA became the statutory catalyst by which the gradual evolution of the effectiveness standard appeared to undergo a significant change when the following sentence was added to the current regulation: “If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence” (4). The reasons proffered by Congress were that approval based on the single controlled trial would: reduce the number of patients required to undergo clinical trials and the possibility of receiving placebo; reduce the cost of drug development and the ultimate cost of a new drug to the public; reduce the total time needed to obtain FDA approval of a new drug; increase the number of new drugs that can be investigated; and speed the development and availability of important new drugs to help improve public health (5). In turn, FDA’s draft effectiveness guidance was finalized and published in May 1998 by FDA to address the implementation of section 403 of FDAMA (regarding supplements). This document, entitled *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, also provided the basis for current agency thinking on the single controlled trial.

Nonetheless, this brief recitation of the history of the standard of proof for effectiveness belies the fact that the issue has long been and remains a contentious one. Historically, it has been cited as the cause of the drug lag (1). It was predicted during the FDAMA debate as likely to become the “single most

contentious issue in new drug development over the next decade" (1). Today it remains a flash point for manufacturers and regulators in the United States as preliminary negotiations for reauthorization of the Prescription Drug User Fee Act (PDUFA)/FDAMA begin. Approval based on single trials (section 115) was one of 11 items on the Pharmaceutical Research and Manufacturers Association's (PhRMA's) Watch List of FDAMA provisions for which PhRMA maintains that additional data are needed to judge whether FDA's implementation has been successful (6). In anticipation of the single controlled trial's pivotal role in the current debate, Tufts Center for the Study of Drug Development surveyed the biotechnology and pharmaceutical industry during the fall of 1999 and winter of 2000 on its use of the single controlled trial based on the criteria set out in FDA's 1998 guidance for industry.

METHODS

As part of the Tufts center's five-year project to track the progress of FDAMA, industry's utilization of the single controlled trial was selected for ascertainment because of its importance to the goals of FDAMA to streamline clinical development and because its effect was considered to be measurable. In order to carry out this project, it was necessary to derive a baseline measure of the industry's utilization of the single controlled trial.

The method of ascertainment was to survey a representative number of pharmaceutical and biotechnology companies that sought New Drug Application (NDA) or Biologic License Application (BLA) approval for any product during a time period from late 1997 to late 1999 (ie, generally applications were filed or approved during federal fiscal years 1998 to 1999). This time period was dictated both by practical and methodological considerations.

For example, although a time period of 1996 to 1997 would have been more certain to constitute a pre-FDAMA baseline, given the launch date of the survey, it would have had the disadvantages of both recall and rec-

ordkeeping bias. In addition, approvals during the selected time period of 1998 to 1999 were not likely to have been directly effected by the statutory language change that occurred officially in late 1997, given the lag period of three years or so from the end-of-Phase II meetings with FDA and a subsequent approval based on a single controlled trial. In a similar vein, the earlier time period would not have reflected the policies acted upon by FDA concerning the use of the single controlled trial that were fairly well-known by the mid-1990s. Sponsors in the latter period would be more likely to have been operating under the guidelines of the FDA policy as articulated in the mid-1990s and formalized as a draft guidance in 1997.

It was hoped that the results would serve as a baseline measure with which to compare survey results later in the FDAMA implementation period. Surveying the entire industry would have been unwieldy, so during late 1999 and early 2000, the Tufts center selected 47 United States-owned and United States subsidiaries of foreign-owned biotechnology and pharmaceutical companies for participation. The sampling frame was constructed by identifying the companies responsible for the top 50% of all drugs in development according to the Tufts center's investigational drugs database through 1998. Biotechnology companies that had sponsored the top 50% of products in development or approved as of the end of 1998 were selected from the center's biopharmaceutical products database.

The survey instrument was a one-page fax-back questionnaire with a brief cover letter explaining the purpose of the survey and assuring the potential respondents that the results would be kept confidential, except for publication of the results in an aggregate form. The initial question ascertained if the survey respondent had sought NDA or BLA approval based on a single, adequate, and well-controlled trial during the selected time period. The following set of questions inquired about basic information related to these products.

Next, the survey respondents were asked

a series of questions based on the agency's thinking on the use of the single controlled trial provided in FDA's May 1998 effectiveness guidance. For example, respondents were queried as to whether their application was based on a single controlled trial with or without supporting information from other adequate and well-controlled studies. If the respondent answered that his company's application was based on the single controlled trial and supporting information from other related studies, he was asked to select any of eight types of related studies spelled out in FDA's May 1998 effectiveness guidance (7). Readers are encouraged to review that section of the guidance document, which is too long to reproduce here (pp. 8–12). Additional choices for answering this question were "pharmacokinetic and/or pharmacodynamic studies" or "other" studies, which respondents were given space to describe. Alternatively, respondents could reply that their single controlled trial was submitted without supporting information from related studies. These respondents were asked to rate the strength of their studies by a five-point scale (5 = very strong; 4 = moderately strong; 3 = somewhat strong; 2 = less strong; and, 1 = not

applicable). Readers are also encouraged to review the section of the guidance document that pertains to these questions as well (pp. 12–16).

Next, respondents were asked separate questions as to whether the single controlled trial was related to a fast track request, orphan drug designation, and/or pediatric indication. Also, the respondents were asked to which review division or office the application was sent and whether the FDA encouraged the submission of the single controlled trial. Next, the respondents who had answered that they had not submitted an application based on a single controlled trial were asked if they plan to do so (no specific time frame was provided), and if they did not plan to do so, why not. Lastly, respondents were asked to identify the department in which they worked.

RESULTS

In total, 36 of 47 companies completed surveys, for an overall response rate of 77%. The survey results indicate that the response rates were essentially the same for the two major segments of the industry. Fifteen out

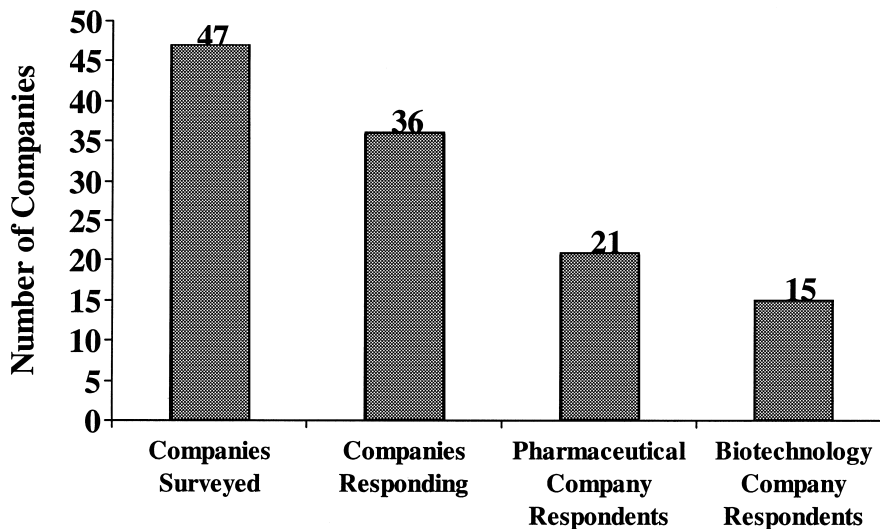


FIGURE 1. 2000 Tufts Center for the Study of Drug Development Single Controlled Trial Survey: Profile of industry response. Source: Tufts Center for the Study of Drug Development 2001.

of 20 biotechnology companies (75%) and 21 out of 27 pharmaceutical companies (78%) responded to the survey (Figure 1).

Overall, 12 companies used the single controlled trial during the reporting period (one company used the single controlled trial for 2 products and another company reported using the single controlled trial for a named product but provided no other information). Another 12 companies reported that although they had not used the single controlled trial for products submitted during the reporting period, they planned to use the single controlled trial. Another 12 companies had not used the single controlled trial, nor did they plan to (nonresponses to this question only, for otherwise completed surveys, were considered negative responses; 4 [3 biotechnology and 1 pharmaceutical] out of 12 respondents fell into this category). One company responded that although it had used the single controlled trial it did not plan to do so again.

Only 3 of 15 (20%) biotechnology companies responding to the survey used the single controlled trial during this period and only 4 of 15 (27%) were planning to use it for a marketing application (Figure 2). In contrast, 9 of 21 (43%) pharmaceutical companies responding to the survey used the single controlled trial during this period, and another 8 of 21 (38%) were planning to use it.

The types of applications for which companies used the single controlled trial were diverse and involved both full and supplemental NDAs and BLAs, and NDAs for new molecular entities (NMEs). While 66% (8 of 12) of the NDAs/BLAs using the single controlled trial were seeking approval for indications for which single controlled trials were generally expected to be acceptable to FDA, such as supplemental, pediatric, and orphan indications, 33% (4 of 12) were for NDAs not identified as pertaining to any special regulatory programs and two of these NDAs were, in fact, for NMEs. While the Gastrointestinal & Coagulation Products Review Division was, overall, the most frequently identified site for review within FDA for applications using the single controlled trial, all three of the NME applications went to other CDER review divisions (Table 1).

The regulatory status and FDA review time of the products were ascertained by survey data, supplemented by public source data available from FDA and the Pharmaprojects online database. FDA approval times for one standard and two priority NDAs for NMEs using the single controlled trial were 10, 4.5, and 6.5 months, respectively. As a frame of reference, these review times were half that of the average FDA review times for all standard and priority NMEs approved from 1996

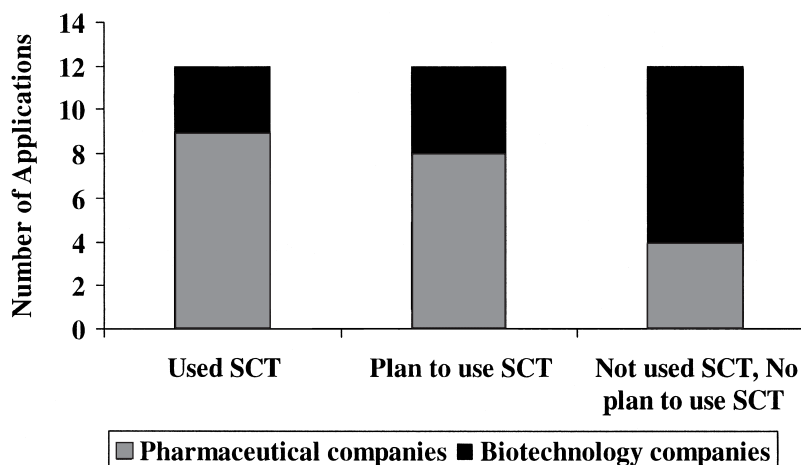


FIGURE 2. Use of the single controlled trial by responding companies. Source: Tufts Center for the Study of Drug Development 2001.

TABLE 1
Profile of 12 NDAs/BLAs in which a Single Controlled Trial was Used

Application Type	Special Program Designation	CDER Review Division or CBER Office	Status of NDA/BLA	FDA Review Time
NDA		Gastrointestinal & Coagulation Products	Approved (4P)	11 months
SNDA	Orphan	Gastrointestinal & Coagulation Products	Approved (3P)	16 months
SNDA		Gastrointestinal & Coagulation Products	Not Approvable	
SNDA		Gastrointestinal & Coagulation Products	Approved (S)	12.5 months
NDA (NME)	Orphan	Oncology	Approved (1S)	10 months
NDA	Accelerated Approval	Oncology	Approved (1P)	6.5 months
BLA	Orphan	Office of Therapeutics Research & Review	Approved (P)	7 months
SBLA	Orphan, Pediatric	Office of Therapeutics Research & Review	Approved	7 months
SNDA	Pediatric	Neuropharmacology	Unknown	
NDA (NME)		Anti-inflammatory, Analgesic, & Ophthalmic	Approved (1P)	4.5 months
NDA		Anesthetic, Critical Care, & Addiction	Unknown	
NDA (NME)	Rolling NDA	Cardio-renal	Approved (1P)	6.5 months

Source: Tufts Center for the Study of Drug Development 2001

to 1998 (19 and 12 months, respectively) (8).

FDA's 1998 guidance addresses two approaches to using the single controlled trial as evidence of effectiveness for product approval:

1. The single controlled trial results are submitted *with* supporting information from other related adequate and well-controlled studies, and
2. The single controlled trial results are submitted *without* supporting information.

Of three applications using the single controlled trial *without* supporting information, two went to CDER's Oncology Products review division, while one went to the Gastrointestinal & Coagulation Products review division. All three applications were NDAs and all three were approved (Figure 3).

Of nine applications *with* supporting in-

formation, three went to CDER's Gastrointestinal & Coagulation Products review division. All three of these were supplemental NDAs. However, applications were submitted to four other CDER review divisions (Figure 3). Only one was a supplemental application, while the other three were full NDAs, two of which were for NMEs. Both of the NMEs were approved.

FDA's 1998 guidance discussed eight examples of "related studies" that can provide independent substantiation for NDAs/BLAs basing proof of effectiveness on single controlled trial results *with* supporting information:

1. Different doses, regimens, or dosage forms,
2. Studies in other phases of the disease,
3. Studies in other populations,
4. Studies in combination or as monotherapy,
5. Studies in a closely related disease,

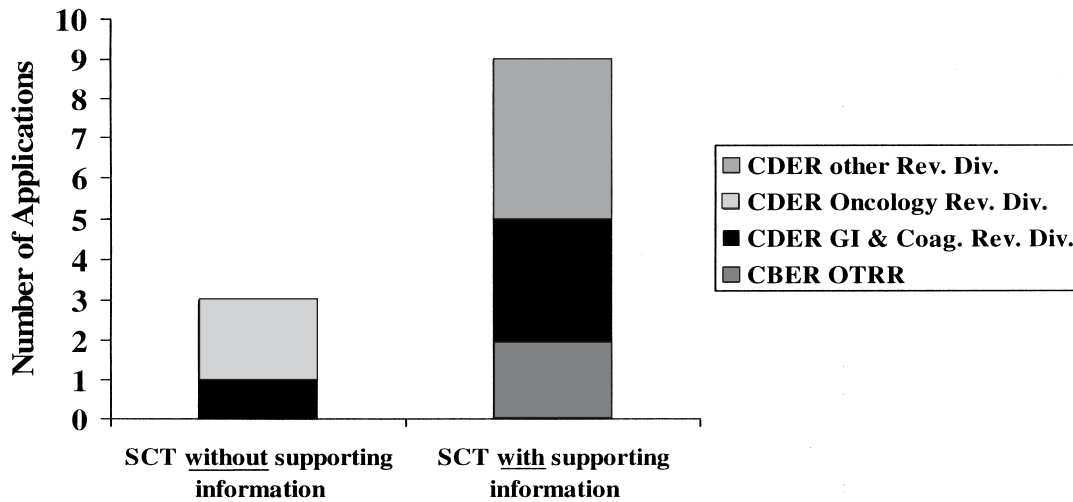


FIGURE 3. Number of NDAs/BLAs using one of two single controlled trial approaches for proving effectiveness, by CDER/CBER review division. Source: Tufts Center for the Study of Drug Development 2001.

6. Studies in less closely related disease, but where the general purpose of therapy is similar,
7. Studies of different clinical endpoints, and
8. Pharmacologic/pathophysiologic endpoints (7) (Figure 4).

Our survey questionnaire added two more choices to this list—pharmacokinetic and/or pharmacodynamic studies and “other” studies—and then asked respondents which ones they had used to support their single controlled trials (Figure 4).

Of nine NDAs/BLAs in which this approach was taken, the most frequently utilized type of related study was one of “different doses, regimens, or dosage forms,” which was employed in five of nine applications (55%). The least utilized types of related studies were those based on a “closely related disease,” with only one application using that approach, and related studies based on a “less closely related disease, but where the general purpose of therapy is similar,” with no applications using that approach. Applicants can, of course, use more than one type of related study to support their single controlled trial. While 33% of applications used only one

type of related study, 55% of applications used two or three types of related studies, and 11% of applications used as many as five types of related studies.

FDA’s 1998 guidance also identifies five characteristics that may allow a single controlled trial *without* supporting information to serve as proof of effectiveness. These have been summarized by Dr. Robert Temple, CDER’s associate director of medical policy, as follows:

1. A large, multicenter study,
2. Consistency across subsets,
3. Multiple studies within a study,
4. Multiple endpoints, different events, and,
5. A statistically very persuasive study.

Study participants who sought to support their effectiveness claim based on a single controlled trial without supporting information were asked to self-rate the strength of their single controlled trials relative to these characteristics.

Of the three NDAs in which this approach was taken, all three applicants self-rated their single controlled trials as being very strong studies in regard to two characteristics: A

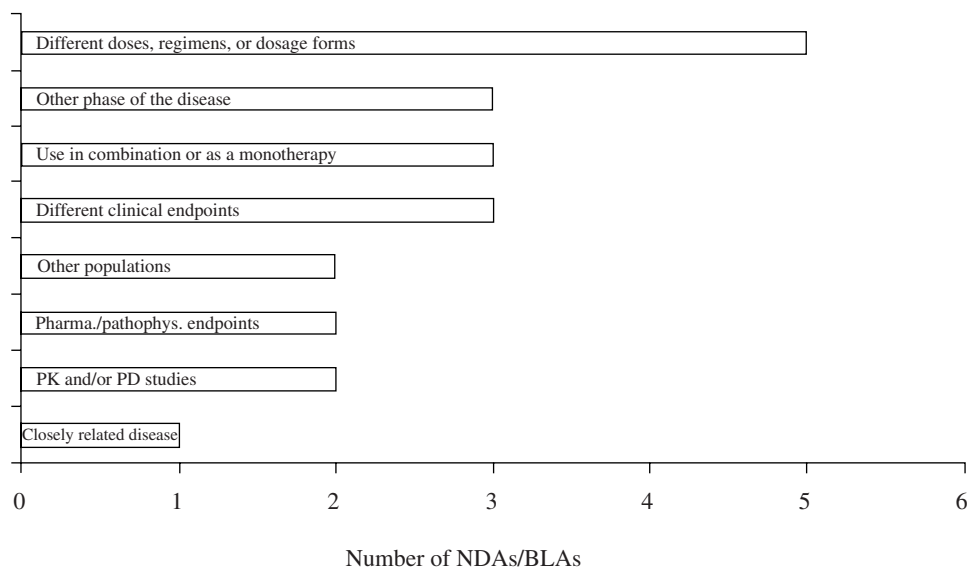


FIGURE 4. Types of “related studies” for NDAs/BLAs using a single controlled trial *with* supporting information, by number of survey applications using each type. Source: Tufts Center for the Study of Drug Development 2001.

large, multicenter study with no single site disproportionately responsible for the positive effect, and consistency of important covariates across study subsets (Table 2). For two of the three NDAs, the applicants self-

rated their studies as less convincing in regard to the other three study characteristics or considered these study characteristics not to be applicable to their studies.

Finally, the survey also explored why

TABLE 2
Strength of Study Self-Rated by Three Applicants using a Single Controlled Trial *Without* Supporting Information

Rating by			Study Characteristics
Applicant 1	Applicant 2	Applicant 3	
5	5	5	No single site provided unusually large percentage of patients or was responsible for positive effect
5	5	5	Consistency across study subsets of important covariates
5	1	1	Multiple studies within single controlled trial demonstrating effectiveness separately but not independently
5	3	1	Multiple endpoints with statistically persuasive evidence of effect on more than one endpoint
5	2	1	Statistically very persuasive finding with a very low p-value

Source: Tufts Center for the Study of Drug Development 2001
(5 = very strong; 4 = moderately strong; 3 = somewhat strong; 2 = less strong; and 1 = not applicable)

some product sponsors choose not to pursue the single controlled trial approach. Several possible reasons were offered by respondents:

- Inability to achieve a level of statistical significance that can convince FDA of effectiveness,
- Generalized doubt that one efficacy trial will suffice for approval (According to FDA, the term efficacy refers to findings in an adequate and well-controlled trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data),
- FDA and advisory committees will not be supportive of one trial if other drugs in the class are approved based on multiple efficacy studies,
- They cannot fully characterize the safety profile without multiple trials involving large numbers of patients,
- Running more than one efficacy trial can increase the odds of having a positive study at the end of the development program, and
- The feasibility of basing approval on a single efficacy study depends on the drug and where in the market it would be.

DISCUSSION

Of the 36 companies responding to the survey, 15 were in the top 25 based on the number of products in development according to the 1998 Scrips League Tables. This is indirect confirmation that the sample frame selected for the survey was at least representative of single controlled trial utilization in the most active companies with regard to research and development. This is obviously more the case with big pharma than with biotech, as only one of the Scrips top 25 in 1998 could be described as a biotechnology company. Nonetheless, the responding biotech companies comprise the sponsors of close to 200 products. That being the case, the result that more than 80% of pharmaceutical companies, but less than 50% of biotechnology companies, are using or planning to use the

single controlled trial may also be somewhat surprising. The single controlled trial approach is generally considered to have originated in the biologics area. While it represents a departure from the usual FDA paradigm for drug product approval, it has been stated that CBER ordinarily considered one trial to be sufficient and two trials to represent the exception (1).

Several simple explanations could shed some light on this apparent unexpected result. One is that big pharma simply has many more products in development at one time, and therefore, the percent of companies using the single controlled trial at any period of time will be fairly high, even if the total number is fairly low. This is a better explanation for the high percent of big pharma companies using the single controlled trial than it is for the lower than expected use of single controlled trials by the biotechnology companies. Another explanation is that the results are only a snapshot of time, even if it was essentially a two-year period, and not reflective of a trend. There are, however, two possible explanations that portend changes for the biotech industry. One is that the biotech companies sampled are among the largest of biotech and they are simply becoming more like big pharma in the way they approach product development. Another related explanation that accounts for both sets of results is that the single controlled trial is viewed by FDA as a mechanism within its new standard of effectiveness that may expand its use for drug applications while narrowing its utility for biological products (1).

This concern has been expressed before. According to a theory promulgated in a legislative analysis by the law firm of Hogan & Hartson, which specializes in food and drug law, FDA expressly includes biological products within the scope of its 1998 effectiveness guidance, with the intent to broaden the application of the two-trial standard to include most biological products and narrowing those situations under which biological products may be licensed pursuant to the Public Health Service Act with the support of a single trial (1). More recently, this assertion

received support in an educational session at the 1999 Meeting of the American Society of Clinical Oncology, when it was noted that although there are numerous characteristics of biologics that warrant different considerations by regulatory agencies (eg, risk of transmitting infection, appropriate preclinical and early clinical studies, enrollment requirements for study entrants—immunocompetence vs. classic measurable disease, etc.) the two types of products have the same intended actions—diagnosis, cure, or mitigation of disease—and there is no need for different efficacy standards (10).

Another way to consider the relative direction of the use of the single controlled trial by the pharmaceutical and biotechnology sectors is to construct a rough frame of reference based upon the number of companies using the single controlled trial, which received approvals during FDA fiscal years 1998 and 1999. In order to do this, two assumptions must be made:

1. That the representativeness of a sample of companies based on number of products in research and development would be a surrogate for similar representativeness for number of approvals, and
2. That the number of approvals by sampled companies is proportional to the number of approvals of all companies.

That being so, of applications approved during 1998 and 1999, those using the single controlled trial comprised an estimated 12% of 173 NDAs and 17% of 15 BLAs. Again, while the percent of BLAs is greater than that of NDAs, it is lower than one might expect.

Another finding emerges from this calculation: 12% of 65 NMEs approved during 1998 and 1999 used the single controlled trial approach. In contrast to what may be happening with biological products, this number of NMEs approved on the basis of the single controlled trial is higher than expected. Perhaps this is an indicator that the single controlled trial is poised to enter the mainstream of drug development.

However, the survey findings also support the possibility that the single controlled trial may be destined to be confined to a few special development programs uses. Pediatric indications of adult drugs, orphan drugs, and accelerated approval, in addition to supplemental approvals, together account for 8 of 12 products reported in the survey. The nexus of the single controlled trial to studies based on surrogate endpoints appears to be evident in the literature. For example, a review of the 20 drugs that had received accelerated approval as of mid-1997 indicated that a number of them had been approved on the basis of a single Phase III trial for efficacy (11). This acceptability for pediatric indications of adult drugs is also historical. In its 1994 labeling regulation, the FDA has stated that if additional controlled data are needed to support a drug's effectiveness in a pediatric population, a single controlled trial generally should suffice (2). Orphan drug development as well has been associated with the use of the single controlled trial (12).

The ambivalence of industry and FDA as to the type of application that the single controlled trial might be most useful for was also mirrored by the way in which sponsors approached supporting information for their single controlled trials. While the majority of respondents (9) submitted their single controlled trials with supporting information from related studies, an approach that seems to evoke a higher comfort level among FDA, a significant minority of respondents (3) let the single controlled trial stand on its own merits. This is unexpected as FDA's Dr. Temple has questioned whether FDAMA even permits this (even though the FDA 1998 guidance document discusses it) and believes that at best it would be limited to "... situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation . . . and a second trial would be practically or ethically impossible" (9).

With regard to sponsors that submitted product applications with supporting information from related studies, some of their

preferences for study types differed from those favored by FDA. In particular, related study types one to five are considered fairly straightforward by the FDA's Dr. Temple (discussed previously, also see Figure 4). However, related study types six and seven are termed by Temple as "more difficult cases" (9). Finally, type eight is considered the "most difficult case," but is also acknowledged by Temple to have broad applicability (9). According to the survey results, sponsors that took this approach generally used study types one to five most frequently. However, while the more difficult type six was not used by any respondent, type seven was used by three respondents, and the most difficult type eight study was used by two respondents. Apparently, there is some experimentation taking place with the single controlled trial.

The somewhat anomalous results from our survey perhaps indicate the unsettled state of the use of the single controlled trial. Critics say that there has been no official measure to implement the single controlled trial, other than the 1998 guidance document, which really represents no change from the pre-FDAMA policy and was really intended to address the FDAMA provision on supplements. FDA supports the view that the amendment of the effectiveness standard is codification of existing policy and thus, no specific implementation measures are called for.

There also seems to be a difference in perspective with the European authorities, who believe that the purpose of Phase III is to confirm the findings obtained so far in preclinical studies, tolerance studies, dose-finding studies, and other Phase II studies. The fundamental requirement of the Phase III documentation is that it consists of adequate and well-controlled data of good quality from a sufficient number of patients; the extent of confirmatory Phase III data needed will depend upon what is established for the product in earlier phases, and what is known about related products. The minimum requirement is generally one controlled study with statistically compelling and clinically relevant results (13).

The FDA interpretation of its controlling authority is that it preserves the presumption that, as a general rule, two adequate and well-controlled studies are needed to prove the products' safety and effectiveness (14). The distance in regulatory language seems like a pond, but in concept it might as well be an ocean. The European Medicines Evaluation Agency states, in essence, that the starting point, albeit a minimal one, is the single trial. The FDA starting point is that two trials are required. Only under certain circumstances is a single trial acceptable, at the discretion of FDA.

Will the single controlled trial ever become the regulatory floor in the United States as it is in Europe? The statutory language and regulatory policy seem to make that possibility unlikely as things stand. However, even as a former senior FDA official once noted that the current level of single controlled trial acceptance happened by slow accretion of examples (12), FDA's current director of medical policy admits that decisions evolve over a long period of time with complex influences (9). While CBER recognizes the role of outreach by the agency and expert advice from advisory committees (15), CDER points to FDA-sponsor conferences at critical junctures in drug development, advisory committees, new guidelines, and new data as the factors that will help shape the future of the single controlled trial (9).

Acknowledgment—The author would like to thank Carl Peck, Julie Nelson, Charles Grudzinskas, and James Cross for reviewing and suggesting improvements to the survey questionnaire.

REFERENCES

1. Kulynych J. Will FDA relinquish the "gold standard" for new drug approval? Redefining "substantial evidence" in the FDA Modernization Act of 1997. *Food Drug Law J.* 1999;54(1):127–149.
2. Mathieu M. *New Drug Development: A Regulatory Overview*. Revised 5th edition. Waltham, MA: Parrexel;2000.
3. US Food and Drug Administration. Statement Regarding the Demonstration of Effectiveness of Human Drug Products and Devices. Rockville, MD: US Food and Drug Administration; August 1, 1995.

4. Food and Drug Administration Modernization Act of 1997. Pub Law 105-115 (1997 Nov 21); 21 USC 355a; 111 Stat. 2296.
5. House Report 105-310, to accompany H.R. 1411. Prescription Drug Modernization Act of 1997. October 7, 1997. 105th Congress, 1st Session.
6. PDUFA III could move through Congress in 2001, Rep. Burr suggests. *Pink Sheet*. 2001 May 7;63(19): 3-4.
7. US Food and Drug Administration. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. Rockville, MD: US Food and Drug Administration; May 1998.
8. Clinical development times for new drugs drop 18%, reversing 12-yr trend. *Impact Report*. Boston, MA: Tufts Center for the Study of Drug Development; July 1999.
9. Temple R. Experiences with single trials leading to Section 115 of FDAMA and May 1998 evidence document. Presented at "The Use of the Single, Adequate and Well-controlled Efficacy Trial (SCT) to Support Approval," Washington DC, January 22-23, 2001.
10. New paradigms for clinical development of biologic products. *Biotechnology Law Report*. August 1999; 328(4):18.
11. Cocchetto DM, Jones DR. Faster access to drugs for serious or life-threatening illnesses through the use of the accelerated approval regulation in the United States. *Drug Inf J*. 1998;32(1):27-35.
12. Botstein P. One controlled clinical trial for a new use, route, formulation, or population. Presented at "The Use of the Single, Adequate and Well-controlled Efficacy Trial (SCT) to Support Approval," Washington DC, January 22-23, 2001.
13. European Medicines Evaluation Agency. *Points to consider on application with 1. Meta-analyses; 2. One pivotal study (draft)*. Committee for Proprietary Medicinal Products (CPMP), European Agency for the Evaluation of Medicinal Products. London: European Medicines Evaluation Agency, May 31, 2001.
14. FDA Backgrounder: The FDA Modernization Act of 1997. Nov. 21, 1997. <http://www.fda.gov/opacom/backgrounders/modact.htm>.
15. Weiss KD. DIA conference on the use of the SCT to support approval. Presented at "The Use of the Single, Adequate and Well-controlled Efficacy Trial (SCT) to Support Approval," Washington DC, January 22-23, 2001.