

Is There Any Commitment in Commitment Studies?

By Norman M. Goldfarb

FDA approval of a new drug for marketing usually requires that the pharmaceutical (or biotech) company provide strong evidence that the drug prevents, cures or ameliorates a disease. However, there are now three circumstances in which a new drug can be approved, provided the pharmaceutical company agrees to conduct additional clinical trials to verify safety or efficacy:

Accelerated Approval

In 1992, 21 CFR 314.510 established the rules for FDA approval of drugs for serious and life-threatening diseases based on surrogate endpoints (e.g., blood chemistry vs. cure):

FDA may "grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."

Under this regulation, FDA may require or request that pharmaceutical companies conduct postmarketing Phase IV studies to catch problems that were not found during Phases I to III:

"Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence."

Animal Efficacy Rule

In 2002, 21 CFR 314.610 added a similar exemption for drugs that have been tested on animals but cannot be tested on humans because, for example, they prevent or ameliorate "serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances." Postmarketing study requirements apply if circumstances permit, e.g., during a bioterror attack.

Pediatric Testing

In 2003, the Pediatric Research Equity Act authorized FDA to require post-approval pediatric studies of drugs that have been approved for adults or are ready for approval in adults.

Other

FDA may require a pharmaceutical company to conduct post-approval studies on drugs whenever it believes such studies are warranted to protect public health.

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Reporting Requirements

The Food and Drug Administration Modernization Act of 1997 (Section 506B) requires that pharmaceutical companies report annually to FDA on the status of their postmarketing study commitments. Beginning with fiscal year 2001, FDA has published an annual report in the Federal Register summarizing the status of these commitments. In part to call public attention to delinquent commitments, FDA's website also includes a searchable database of postmarketing studies commitments.¹ In February 2006, FDA published a guidance document with greater detail about the content, format and timing of postmarketing study reports.¹

Trends in Postmarketing Study Commitments

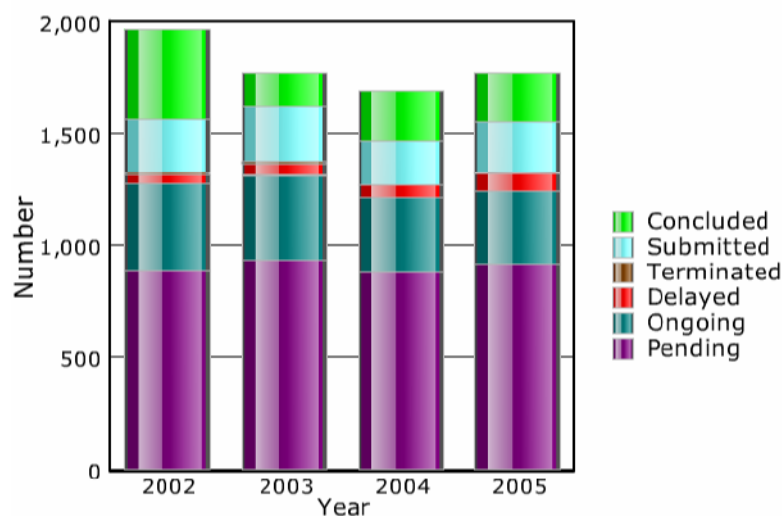
Even the largest Phase III clinical trials are too small to detect rare serious adverse events that can enrage the public, incite the media, attract industrious politicians, and trigger the release of adrenaline in the plaintiff's bar. Postmarketing studies have thus taken on increasing importance in recent years. In theory, the resulting attention to these commitments should cause pharmaceutical companies to complete the studies more quickly. One might therefore make the following hypothesis:

"Publishing postmarketing study commitments online has caused pharmaceutical companies to become more aggressive in clearing their commitment backlogs."

To test this hypothesis, Figure 1 charts the statistics in six categories from FDA's annual reports. The numbers behind the chart are in Table 1. Table 2 presents the definitions of the categories.

Figure 1 demonstrates that the hypothesis appears to be true for FY 2002, but false for the years thereafter. The combined number of studies concluded and submitted for conclusion in FY 2002 was relatively high. However, the numbers for the following three years are significantly and consistently lower – 39%, 34% and 31%, respectively – perhaps because the low-hanging fruit had been harvested in 2002, the fear had subsided, or pressure on profits had increased. The number of delayed studies actually increased by 93% over the four-year period. Over the three-year period from FY 2003 to FY 2005, the number of open

Figure 1. FDA Postmarketing Study Commitments
(NDA, ANDA & BLA, Fiscal Years Ending in September)



commitments dropped by one, from 1765 to 1764 (0.06%). The lack of progress was not caused by an increase in the number of new commitments required by FDA; the new commitments almost exactly matched the number of concluded commitments.

Table 1. Commitment Numbers

Status	2002	2003	2004	2005
Pending	887	934	881	915
Ongoing	387	376	333	325
Delayed	42	53	52	81
Terminated	10	10	3	3
Submitted	236	244	200	228
Concluded	401	148	219	212

The oldest commitment, dating to 1977, is for a study to ascertain whether the Novartis drug baclofen may induce ovarian cysts. Baclofen is used as a muscle relaxant and to relieve the muscle spasms, pain, and muscular rigidity associated with multiple sclerosis. Novartis has been filing annual reports on this commitment for the past 28 years.

FDA has the authority – never used – to withdraw marketing approval for a drug if postmarketing study commitments are not met. Now that transparency and moral suasion have proven incapable of accomplishing public policy objectives, the door may open to more forceful measures by FDA, in Congress or in the courtroom.

Table 2. Status Category Definitions

<p>Concluded. (a) Fulfilled. The applicant has submitted the final study report for the commitment and upon review of the final study report FDA is satisfied that the applicant has met the terms of the commitment. (b) Released. FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.</p>	<p>Delayed. The study is proceeding, but it is behind the original or final study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to FDA. While the original schedule — not a revised schedule — serves as the basis for defining a study as delayed, each phase of the study is considered in its own right. If the applicant has one delayed phase, but makes up for it in the next phase and gets back on schedule, the delayed status will no longer apply.</p>
<p>Submitted. The applicant has completed or terminated the study and has submitted a final study report to FDA but the Agency has not yet advised the applicant whether the study commitment has been fulfilled.</p>	<p>Ongoing. The study is proceeding according to, or is ahead of, the original schedule. A study is considered ongoing until a final study report is submitted to FDA, as long as the activities are proceeding according to the original schedule.</p>
<p>Terminated. The applicant ended the study before completion or does not intend to complete the study as it was originally designed and the applicant has not yet submitted a final study report to FDA.</p>	<p>Pending. The study has not begun (i.e., no subjects have been enrolled), but the projected date for patient accrual (enrollment) has not passed. If patient accrual has started, but is not complete, and the projected date for completion has passed, the study is categorized as delayed.</p>

References

1. "Postmarketing Study Commitments: Introduction", FDA, last accessed 5/12/06 at <http://www.fda.gov/cder/pmc/default.htm>

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