EXHIBIT 3
(Part 2 of 2)

After a new drug has been approved for marketing, the sponsor begins mass production for commercial distribution of the product. The sponsor also begins marketing activities including detailing to physicians[3] by the drug company sales force and direct advertising to health professionals and often to consumers. The manufacturing and distribution must comply with the methods approved as part of the NDA, and drug promotion must also conform with and reflect the information in the FDA-approved labeling for the new drug.

3.4 Post-Approval Safety Surveillance and Risk Management

Because all possible side effects of a drug cannot be anticipated based on preapproval studies involving only several hundred to several thousand patients, FDA maintains a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug approval process.

Knowledge about a product will always be limited to some extent at the time of approval by factors in the product development process. For example, rare side effects and long-term outcomes (both positive and negative) may not be known when a product is approved because of the relatively small size and limited duration of clinical studies. And because of the populations not studied in clinical trials (e.g., pregnant patients, children, people with other diseases) or minimally studied (e.g., geriatric patients), side effects may be discovered if these groups are treated with a product after it goes on the market. Even after a product has been on the market for a long time, uncertainties remain. The Adverse Event Reporting System (AERS) provides FDA's primary source of post-marketing safety data.

New information about a new drug will also emerge from additional clinical trials, such as post-Marketing Commitments (PMCs, also known as Phase 4 studies), and from reports in the literature. FDA uses all available post-marketing safety information to investigate product quality problems, to update drug labeling, and, on more rare occasions, to reevaluate the approval or marketing decision to revise other aspects of risk management plans.

3.5 Estimated FTEs Devoted to Assuring Drug Safety

Recent public attention to the issue of drug safety has included questions about the extent of FDA oversight and the resources devoted to this critical aspect of public health protection. The most readily available numbers are usually budget figures for individual offices within FDA but the work done by those offices represents only a subset of the larger effort required to ensure drug safety.

To provide a more complete and accurate account of the full range of critical drug safety-related activities, FDA recently conducted an internal study, including extensive staff interviewing and analysis of staff time reporting data across CDER. The results of this analysis, based on FY 2004 data, suggest that CDER staff devote 50 percent of their time to drug safety activities. This represents a level of effort totaling about 1,093 full time equivalent (FTE) staff. These figures are based on the agency's FY 2004 staffing.

How does this level of effort compare to the total staffing for work performed in other FDA regulatory work? The table below provides a summary based on FY 2004.

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[3] "Detailing" is a marketing practice conducted by pharmaceutical companies whereby sales representatives visit physicians' offices, explain the features of their company's drug products, and distribute advertising materials and product samples.

FDA Program Area	FY 2004 Actual - Total FTEs
Center for Food and Applied Nutrition	910
Center for Drug Evaluation and Research *Level of Effort devoted to drug safety activities*	2,190 *1,093*
Center for Biologics Evaluation and Research	797
Center for Veterinary Medicine	349
Center for Devices and Radiologic Health	1,061
National Center for Toxicologic Research	207
Field Activities Program (Office of Regulatory Affairs)	3,872
Other Activities (including Office of Commissioner)	755
TOTAL	**10,141**

PDUFA fee revenues enabled FDA to significantly increase the scientific review staffing in almost every CDER office involved in assuring drug safety. For example, since the beginning of PDUFA the additional funds have enabled CDER to more than double its medical staff, growing from 166 medical officers in 1993 to 342 medical officers on staff in 2004. This translates into significantly higher staffing to focus on drug safety issues.

3.5.1 Scope of Activities Included in CDER's Drug Safety Work

In both premarket and postmarket phases, staff across CDER work to assure the highest possible degree of drug safety. In total, NDA review involves chemists, pharmacologists, toxicologists, physicians, statisticians, epidemiologists, pharmacists, biologists, microbiologists, project managers, health and social scientists. The Office of New Drugs (OND) leads and coordinates this review. Postmarket review requires similar varieties of FDA staff expertise found in various CDER Offices.

Safety Work in Specific CDER Offices.

- ***Office of New Drugs.*** About half of OND effort in reviewing truly new drugs is devoted to safety. The primary safety review goals are to: (1) identify side effects and their relationships to critical drug and patient population features; and (2) decide whether the sponsor has conducted sufficient types and numbers of safety studies. In addition, most labeling review focuses on communicating safety. OND also coordinates postmarket evaluation of new information, deciding whether to incorporate into labeling or take other steps when new problems arise.
- ***Office of Pharmacoepidemiology and Statistical Science***. OPaSS experts review the safety of marketed drugs, estimate the public health impact of drug safety signals, evaluate proposed and existing risk management programs, perform epidemiologic research and review, evaluate proposed brand names, labeling and packaging to minimize medication errors, review patient labeling, run the MedWatch adverse event reporting program, and perform other drug safety-related activities. They also provide expert consults on issues of premarket risk management. The CDER Office of Drug Safety [ODS] is included within OPaSS.
- ***Office of Medical Policy.*** OMP confirms the truthfulness of the clinical trial data that support new and generic applications for marketing approval. It also gives sponsors expert consults on product labeling, and monitors and enforces drug company promotional materials and activities to ensure correct communication of risk information.
- ***Office of Clinical Pharmacology and Biopharmaceutics.*** OCPB evaluates the clinical pharmacology and biopharmaceutics pieces of drug applications. Reviewers have a specific safety emphasis on drug-drug interactions and use in special populations (for example, women, children, and people with special health risks).
- ***Office of Pharmaceutical Science.*** OPS ensures that drug manufacturers produce high quality products. It also ensures timely generic drug marketing approval. OPS also conducts research to

develop improved methods to identify and lessen premarket and postmarket risks resulting from poor quality products.

- ***Office of Compliance.*** OC staff inspect domestic and foreign manufacturing sites and assure, among other things, compliance with good manufacturing practice regulations, risk management plans, and adverse event reporting.
- ***Office of CounterTerrorism and Pediatric Drug Development.*** OCTaP provides expertise on pediatric matters, including safety information. It also promotes the development and availability of medical countermeasures against biological, chemical, and nuclear threat agents.
- ***Office of Executive Programs.*** OEP oversees and coordinates CDER activities. It assists scientific and technical staff in developing guidance, responding to congressional inquiries, preparing for high-profile advisory committee meetings, and connecting with relevant communities and the media.

Level of Effort Devoted to Drug Safety in 2004[1]				
Office	Office Percent of Work Time	**Premarket** Estimated FTE	**Postmarket** Estimated FTE	**Total Office** Estimated FTE
OND	51%	275	77	352
OPaSS	60%	32	93	126
[ODS]	[100%]	[9]	[87]	[96]
OMP	44%	6	29	36
OCPB	44%	41	1	42
OPS	51%	179	74	252
OC	38%	13	30	43
OCTaP	73%	22	13	35
OEP	14%	4	4	8
Mgt/Other	--	128[2]	71[2]	199[2]
Total CDER	50%	700	393	1,093

[1] All estimates represent general levels of magnitude and are primarily for comparison purposes.
[2] To get FTE estimates for "Mgt/Other" we applied overall CDER estimates of percent safety activity work time to offices and programs not included in the study.

4.0 Evolution of FDA Performance Commitments Under PDUFA

Since PDUFA enactment in 1992 (PDUFA 1), the law was amended and extended in 1997 (PDUFA 2) and again in 2002 (PDUFA 3) with expiration at the end of Fiscal Year 2007. Each successive 5-year enactment has served to alter the emphasis and scope of the program, to further improve and speed new drug development and regulatory review.

4.1 Expansion of Performance Goals as Part of PDUFA Reauthorization

As described in Section 2 of this paper, FDA funding and staffing levels for drug review activities have significantly increased under PDUFA. At the same time, the performance focus of the program has continued to expand, as summarized in the Table 4.1 below.

Table 4.1 Expansion of FDA Performance Commitments Since Enactment of PDUFA

PDUFA 1	PDUFA 2	PDUFA 3
Industry paid a fee • Per submitted NDA/BLA, per establishment, and per product **Goals by FY97** • **Backlog:** Eliminate • **Priority Reviews:** 90% in 6 months • **Standard Reviews:** 90% in 12 months	**Industry paid a fee** • Per submitted NDA/BLA, per establishment, and per product **Goals by FY02** • **Priority reviews:** 90% in 6 months • **Standard reviews:** 90% in 10 months • **Formal Meetings**: schedule 90% within14 days; convene 90% within 30 /60/75 days • **Clinical hold response:** 90% in 30 days • **Special protocol evaluation:** 90% in 45 days • **Electronic Submissions:** Able to receive by end of FY02	**Industry paid a fee** • Per submitted NDA/BLA, per establishment, and per product **Goals by FY07** • **Priority reviews:** 90% in 6 months • **Standard reviews:** 90% in 10 months • **Formal Meetings**: schedule 90% within14 days; convene 90% within 30 /60/75 days • **Clinical hold response:** 90% in 30 days • **Special protocol evaluation:** 90% in 45 days • **Electronic Submissions:** Able to receive by end of FY02 • **Continuous Marketing Application** • **Pre- and Peri- NDA/BLA Risk Management** Plan Activities • **Independent Consultants** for Clinical Trials • **Good Review Management Principles (GRMPs)** for First Cycle Review Performance • **Improved Performance Management** • **Electronic Applications & Submissions**

4.1.1 PDUFA 1: Speeding Up Application Review

During the first few years of PDUFA 1, FDA eliminated backlogs of original applications and supplements that had formed in earlier years when the program had fewer resources. Over the course of PDUFA 1, the Agency committed to review and act on a progressively increasing proportion of original NDAs, BLAs, and efficacy supplements within 12 months and resubmissions and manufacturing supplements within 6 months. The Agency also committed to review and act on 90 percent of priority NDAs, BLAs, and efficacy supplements (i.e., submissions for products providing significant therapeutic gains) submitted in FY 1997 within 6 months. Over the course of PDUFA 1, FDA exceeded all of these performance goals.

4.1.2 PDUFA 2: Speeding Up Drug Development and Maintaining Rapid Review

In 1997, Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA) and reauthorized PDUFA (PDUFA 2) for five more years. Under the PDUFA 2 program, most review times were shortened and the Agency met or exceeded nearly all its review goals. PDUFA 2 also set new goals intended to improve communication between FDA and application sponsors during the drug development process. These goals specified time frames for scheduling formal meetings with industry sponsors during the pre-clinical and clinical development phase, to review and address specific issues relating to their product. The additional goals in PDUFA 2 included commitments to respond to a sponsor's response to a clinical hold, and a commitment to review and assess special study protocols proposed by sponsors.

4.1.3 PDUFA 3: Increasing FDA-Sponsor Interactions During Drug Development and Review and Risk Management After New Drug Approval

In 2002, Congress passed the Bioterrorism Act, which included an extension of PDUFA (PDUFA 3) for five more years, FY 2003 through FY 2007. For the first time, PDUFA 3 also authorized FDA to spend user fee funds on certain aspects of post-market risk management. The review performance and procedural goals associated with PDUFA 3 were similar to those under PDUFA 2 for fiscal year 2002

performance levels, but the PDUFA 3 program addressed drug safety issues and established several new initiatives to improve application submissions and agency-sponsor interactions during drug development and application review.

Under PDUFA 3 FDA created a guidance for review staff and industry on good review management principles and practices (GRMPs) as they apply to the first cycle review of NDAs, BLAs, and efficacy supplements. FDA announced the guidance's availability in the Federal Register of March 31, 2005 (70 FR 16507). FDA also set a goal of testing whether providing early review of selected applications and additional feedback and advice to sponsors during drug development for selected products can shorten drug development and review times.

PDUFA 3 includes two "continuous marketing application" (CMA) pilot programs; CMA Pilot 1 provides for the review of a limited number of pre-submitted portions of NDAs and BLAs. Under CMA Pilot 2, FDA and applicants can enter into agreements to engage in frequent scientific feedback and interactions during the investigational new drug phase of product development. Both the first-cycle and CMA initiatives are currently being evaluated to determine their impact on the effectiveness and efficiency of FDA-sponsor communications, product development, and regulatory review.

In addition, the goals under PDUFA 3 also included new provisions, for example, to develop guidance for industry on good risk assessment, risk management, and pharmacovigilance practices, to fund outside expert consultants to help evaluate and improve review management processes. In PDUFA 3 FDA also agreed to centralize accountability and funding for all PDUFA information technology initiatives and activities. Details of the PDUFA 3 goal commitments can be found at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html.

4.2 Trends in FDA Drug Review Workload

FDA has seen a significant increase in drug review workload both as a result of increases in the volume of sponsor submissions for review, and due to the review performance goals specified under the PDUFA authorizing legislation.

This section summarizes trends in the workload of the PDUFA program. These include FDA review and action on:

- Original NDAs and BLAs
- Efficacy Supplements
- Chemical and Manufacturing Control Supplements
- Sponsor-Requested Meetings
- Sponsor-Requested Special Protocol Assessments

In general, the workload is driven by the technical complexity and staffing requirements of the activities FDA must perform to address the submissions and requests; the intensity of that effort, determined by the deadlines imposed by the PDUFA performance goals; and the volume of sponsor requests and submissions.

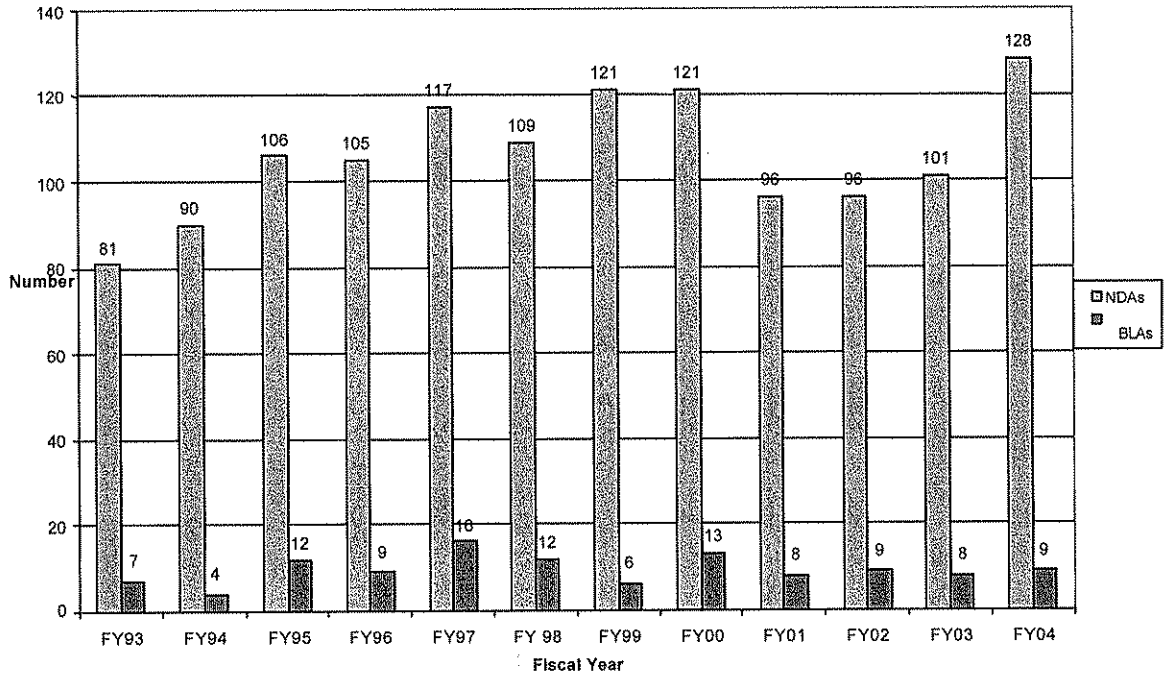
4.2.1 Review of Original New Drug Application (NDA) and Biologics Licensing Application (BLA) Submissions

Review of NDA and BLA submissions requires an intensive multidisciplinary review, as described in Section 3.3 Under PDUFA, FDA's goal is to review and act on all filed original NDA/BLA submissions within the following time frames: within 6 months for 90 percent of all priority applications; and within 10 months for 90 percent of all standard applications.

In addition, FDA 's goal is to review and act on 90 percent of all NDA/BLA Class 1 resubmissions within 2 months, and 90 percent of all Class 2 resubmissions within 6 months.

The following chart summarizes trends in the number of NDA and BLA submissions during the PDUFA era. While the number of BLA submissions has remained fairly constant during this time period, the number of NDA submissions has increased from 96 filed in FY2002, at the end of PDUFA 2, to 128 in FY 2004. (As noted earlier, about 25 percent of all applications received each year do not pay fees because the applications are for fee-exempt orphan products, or the fees are waived either because it is the first application from a small business or it qualifies for one of the other waiver provisions.)

Figure 4.1 Number of NDAs and BLAs Filed by Fiscal Year

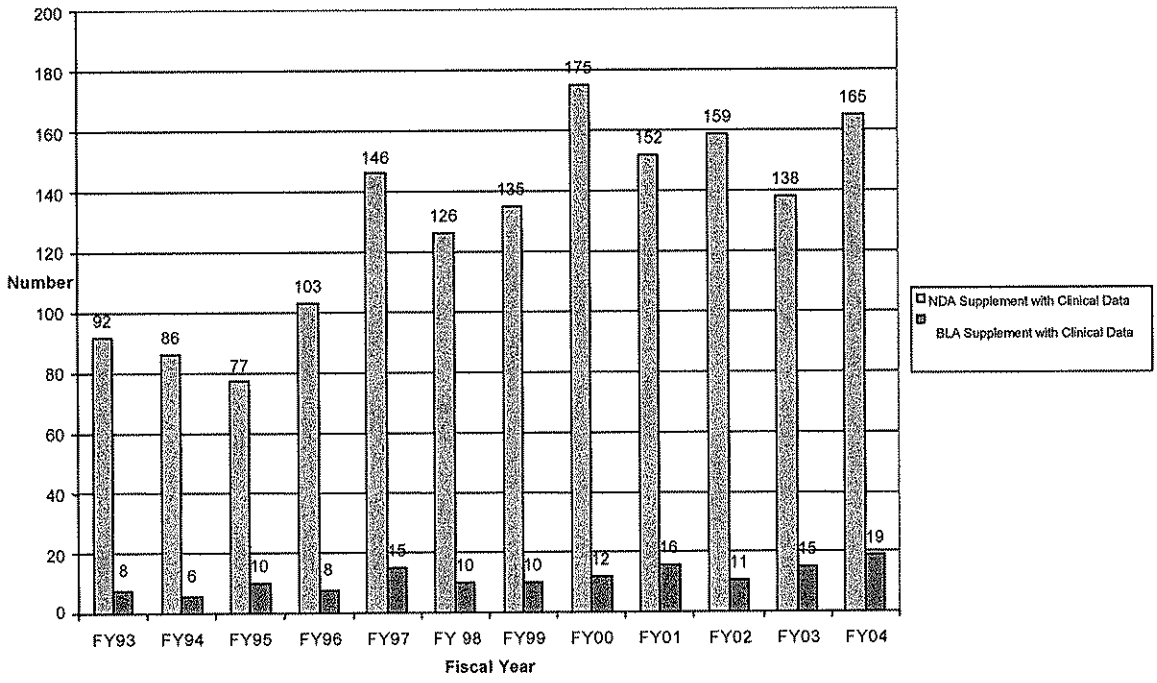


4.2.2 Submissions of NDA and BLA Efficacy Supplements

As described earlier in Section 3.3, following approval of an original NDA or BLA, a sponsor may later submit an application to expand the disease indications included in the drug labeling. This application often includes additional clinical study data to support the proposed change in labeling, and is referred to as an Efficacy Supplement. FDA's review of Efficacy Supplements results in an action letter to the sponsor outlining FDA's decision. Under PDUFA, FDA's goal is to review and act on 90 percent of all filed original Efficacy Supplements: within 6 months for all priority efficacy supplements; and within 10 months for standard efficacy supplements.

Trends in workload for Efficacy Supplements and Manufacturing Supplements for both CDER and CBER are shown in the charts below. The number of filed Efficacy Supplements for FDA review has increased by more than 80 percent, from 100 submissions in FY 1993 to 184 submissions in FY 2004.

Figure 4.2 Efficacy Supplements with Clinical Data Filed by Fiscal Year

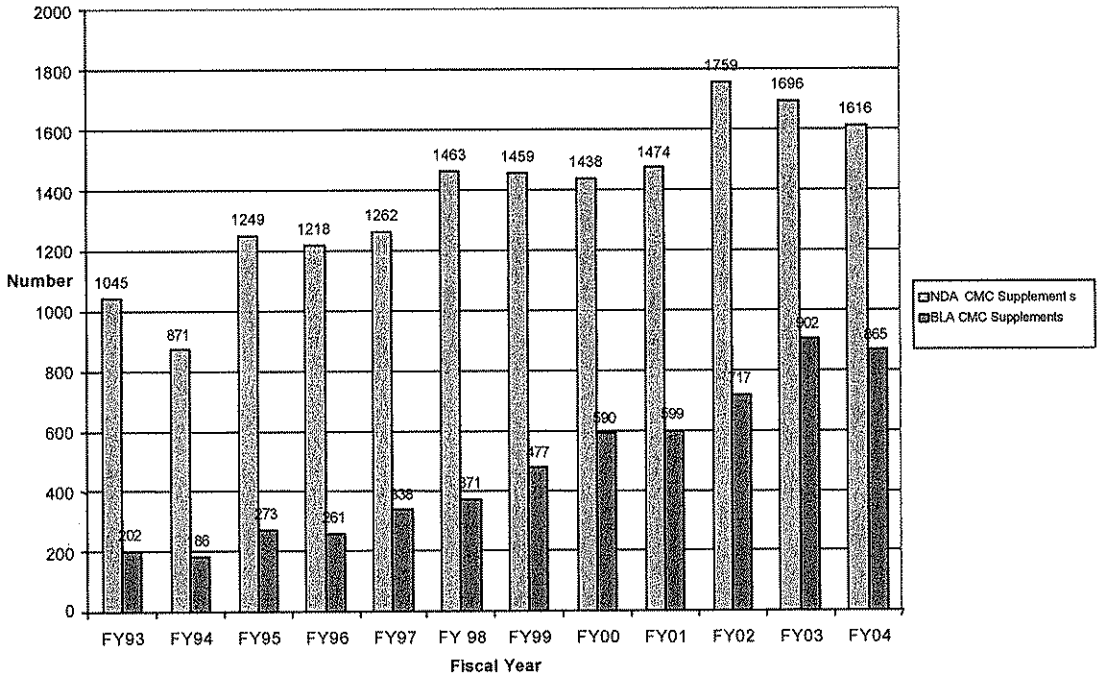


4.2.3 Submissions of Chemical and Manufacturing Control (CMC) Supplements

To obtain marketing approval, a sponsor must show not only that the product is safe and effective, but can be manufactured in large quantities while still retaining all of the qualities of the product that was tested in smaller batches during clinical trials. The details of manufacturing are described in the Chemistry and Manufacturing Controls (CMC) section of the NDA. After product approval, sponsors often continue to refine the manufacturing process. They must submit these changes for FDA review, and await FDA prior approval before implementing more significant changes proposed in CMC supplements.

FDA's goal is to review and act on 90 percent of Changes Being Effective (CBE) CMC supplements within 6 months of receipt, and to review and act on CMC supplements requiring prior approval within 4 months of receipt. Figure 4.3 shows the trend in number of submissions of CMC supplements. Since the start of PDUFA, the number of CMC supplements has approximately doubled, from 1,247 submissions in FY 1993 to 2,481 submissions in FY 2004.

Figure 4.3 Number of CMC Supplements Submitted by Fiscal Year



4.2.4 Sponsor-Requested Meetings with FDA

An industry sponsor can improve the quality of its drug development and related new drug application by early and more frequent consultation with FDA during drug development. For example, the sponsor can ask FDA to review its proposed clinical study designs including the starting doses for clinical trials, the type of patient population that would be enrolled and the clinical outcomes that the sponsor plans to collect during the trials, as a basis for demonstrating safety and effectiveness.

By consulting early with FDA, before investing substantial sums to conduct the clinical trials, sponsors can find out if FDA thinks their proposed design will meet (or exceed) what is necessary to demonstrate safety and effectiveness. By checking early, and revising the protocol before running the trials, sponsors can better serve participating patients and also avoid the delay and expense of conducting trials that FDA later finds are deficient and need to be augmented with additional studies.

With the increasing cost of drug development [4] and thinning pipeline of new drugs [5] more and more companies are seeking this early advice from FDA. When the sponsor requests a meeting they must also submit a background package on the specific product and application issues they wish to discuss in the meeting. Under PDUFA, FDA's goal is to schedule a formal meeting within 14 calendar days of the sponsor's request. In addition, FDA agreed to the following goals for scheduling 90 percent of requested meetings:

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[4] DiMasi, Joseph A., Hansen, Ronald W., and Grabowski, Henry G., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 22(2), March 2003, Pages 151-185.

[5] "Does Lack of Launches Spell End of Expansion?", *Scrip Magazine*, February 2005, pp. 24-25

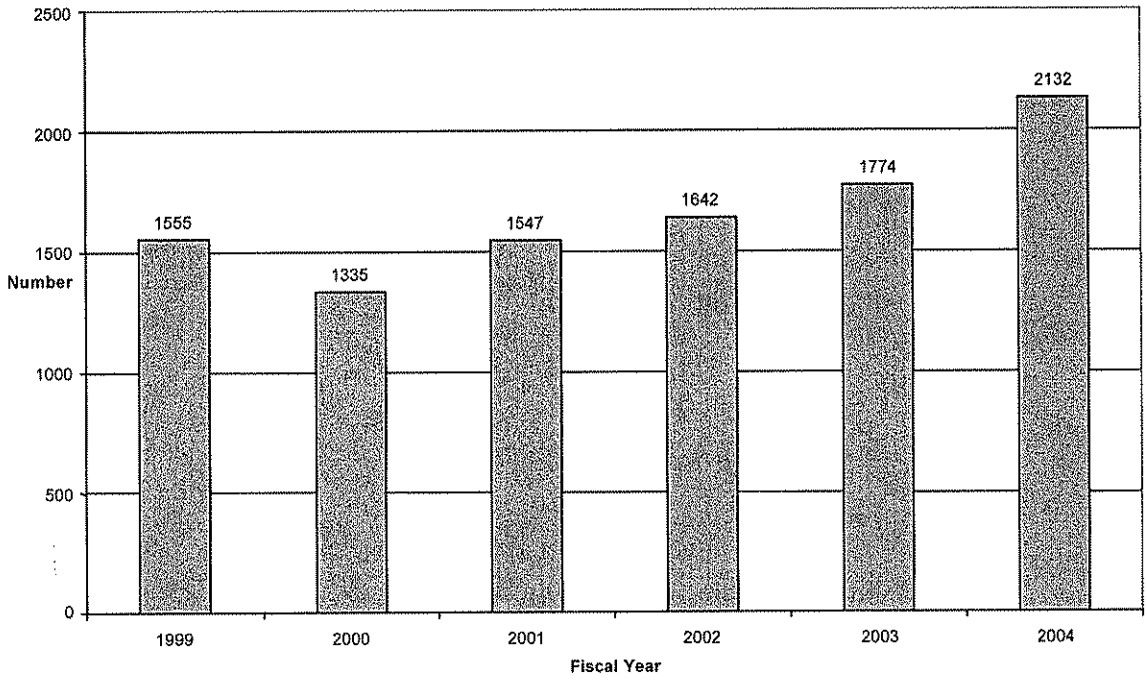
- Type A Meetings—which are necessary for an otherwise stalled drug development program to proceed—within 30 calendar days of FDA receipt of the meeting request;
- Type B Meetings—pre-IND, end of Phase 1, or end of Phase 2/pre-Phase 3, pre-NDA/BLA meeting— within 60 calendar days of FDA receipt of the meeting request; and
- Type C Meetings—any other type—within 75 calendar days of receipt of the meeting request.

These formal meetings with sponsors typically involve the following tasks for FDA:

- In-depth review of the sponsor's package by all appropriate members of the review team and management chain. Identification of scientific and regulatory issues that need to be addressed in addition to those identified by the sponsor. Clarifying with the sponsor the contents of the package. Review of prior submissions relevant to the application, medical literature, relevant guidance documents, etc.
- Compilation of the list of issues for discussion.
- Preparation for and conduct of an FDA-internal pre-meeting. Following up on action items generated in that meeting with review team members and the sponsor.
- Handling of logistics associated with the formal meeting, including scheduling, distributing background materials and agenda preparation.
- Formal meetings with the sponsor.
- Preparation and review of formal meeting minutes.

These meetings with sponsors are important to improving drug quality, but they also impose a significant additional work burden on FDA. Meetings typically require the involvement of 15 FDA staff, and the total level of effort varies from an estimated 120 to 540 staff hours, depending on the number and complexity of issues to be discussed in the meeting. Figure 4.4 shows the trend in the number of industry-requested meetings held each year since the PDUFA performance commitments were established. The number has risen from 1,555 in FY 1999 to 2,132 meetings in FY 2004. The current level of annual meetings translates into an average of 9 industry-requested meetings per business day.

Figure 4.4 Number of Meetings Scheduled with Industry Sponsors By Fiscal Year



4.2.5 Sponsor-Requested Special Protocol Assessments

Special protocol assessments provide sponsors with another valuable opportunity for early FDA feedback and advice, to improve drug development, and increase the likelihood that the submitted new drug application will include sufficient evidence of safety and effectiveness to be approved on the first 'cycle' of review. Beginning with PDUFA 2, FDA committed to evaluate certain protocols and specific issues submitted by sponsors, to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

In requesting FDA's evaluation, the sponsor must submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which they seek agreement. For example, the sponsor may submit questions about whether the dose range in the carcinogenicity study is adequate, considering the intended clinical dosage; or whether the proposed clinical endpoints are adequate to support a specific efficacy claim.

Within 45 days of receiving the protocol and specific questions, FDA will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If FDA does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

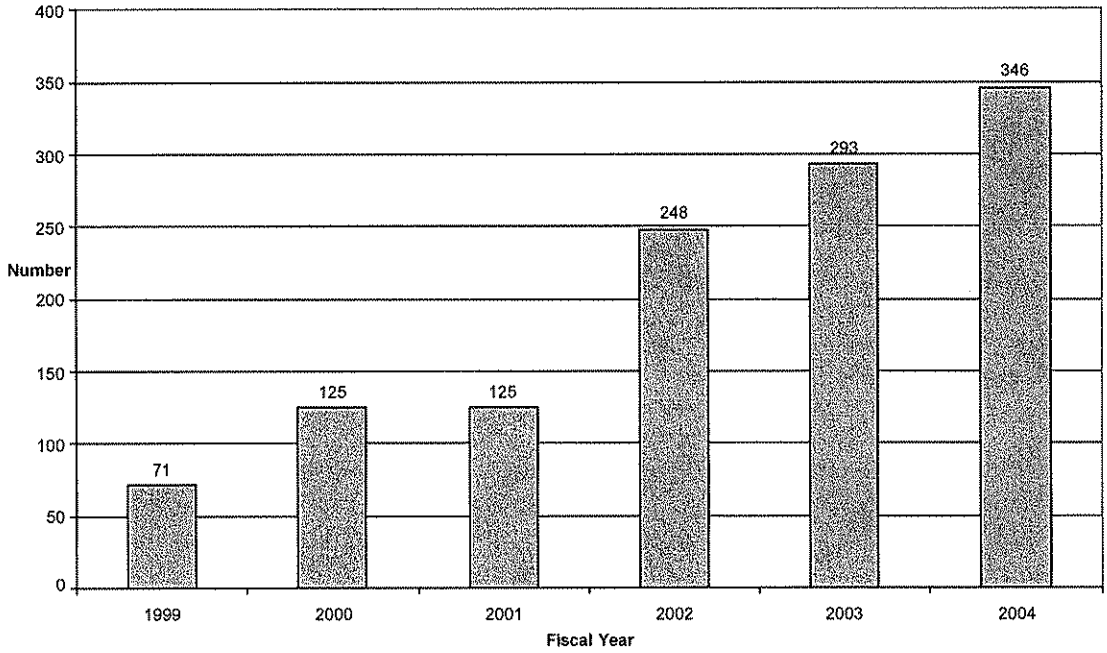
Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim. In order for Phase 3 protocols to qualify for this comprehensive protocol assessment, the sponsor must have had an end of Phase 2/pre-Phase 3 meeting with the relevant FDA review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.

If a protocol is reviewed under this process and agreement with FDA is reached on design, execution, and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, FDA agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental point here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, FDA will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

Written special protocol evaluations provides extremely valuable information for sponsors, significantly reducing regulatory uncertainty and business risks in the subsequent drug development. However, the high complexity and short deadlines associated with special protocol assessment impose a significant work burden on FDA, comparable to or greater than the level of effort required to conduct sponsor-requested meetings.

Figure 4.5 shows the trend in the number of sponsor-requested special protocol assessments. It shows the total number (CDER and CBER) of Special Protocol Assessment Receipts for each fiscal year 1999 through 2004. The number has increased by nearly 400 percent, from 71 to 346 per fiscal year during this period.

Figure 4.5 Special Protocol Assessment Submissions by Fiscal Year

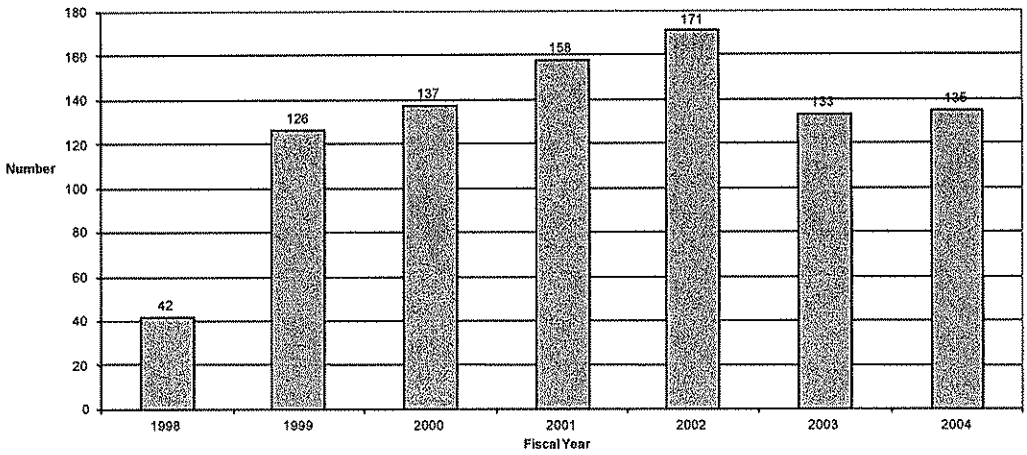


4.2.6 Complete Response to Commercial IND Clinical Holds Received

Under PDUFA, FDA's goal is to reply to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the sponsor's response, and do this for at least 90 percent of such submissions. As noted in earlier discussion, rapid resolution of safety issues that led to clinical hold helps ensure patient safety while enabling access to the experimental treatment. Figure 4.6 shows the total number (CDER and CBER) of Complete Response to Commercial IND Clinical Holds Received (Clinical Holds)

for each fiscal year 1999 through 2004. The number of Clinical Holds increased by over 200 percent (from 42 to 135 per fiscal year) over this period.

Figure 4.6 FDA Response to Sponsor's Complete Response to IND Clinical Hold



5.0 Current Challenges for PDUFA and New Drug Review

This section describes some key resource challenges for FDA's capacity for new drug review and also for surveillance to ensure safety and effectiveness in the use of new drugs. PDUFA has been successful in making the drug review process better-staffed, more rigorous and more predictable and FDA's overall review times have been cut in half. FDA's review workload has grown very significantly, particularly during the years of PDUFA 2 and 3, with the addition of goals for sponsor-requested meetings and special protocol assessments. Starting in PDUFA 3, industry paid substantially higher fees that helped cover the costs associated with these significantly increased but highly-valued FDA activities. However, the workload levels have continued to grow, outpacing the workload adjustment of fees.

At the same time, FDA PDUFA payroll costs have far outpaced the increase in the PDUFA appropriations trigger amount and overall appropriations for drug review have been less than envisioned when PDUFA 3 was enacted. Appropriations for drug and biologics programs have actually declined since 2003, while FDA's payroll costs, the largest cost for the programs, goes up each year by 4 to 5 percent. If this trend continues FDA is uncertain about its continued ability to satisfy the PDUFA Appropriations trigger, a pre-condition for FDA's authority to collect user fees.

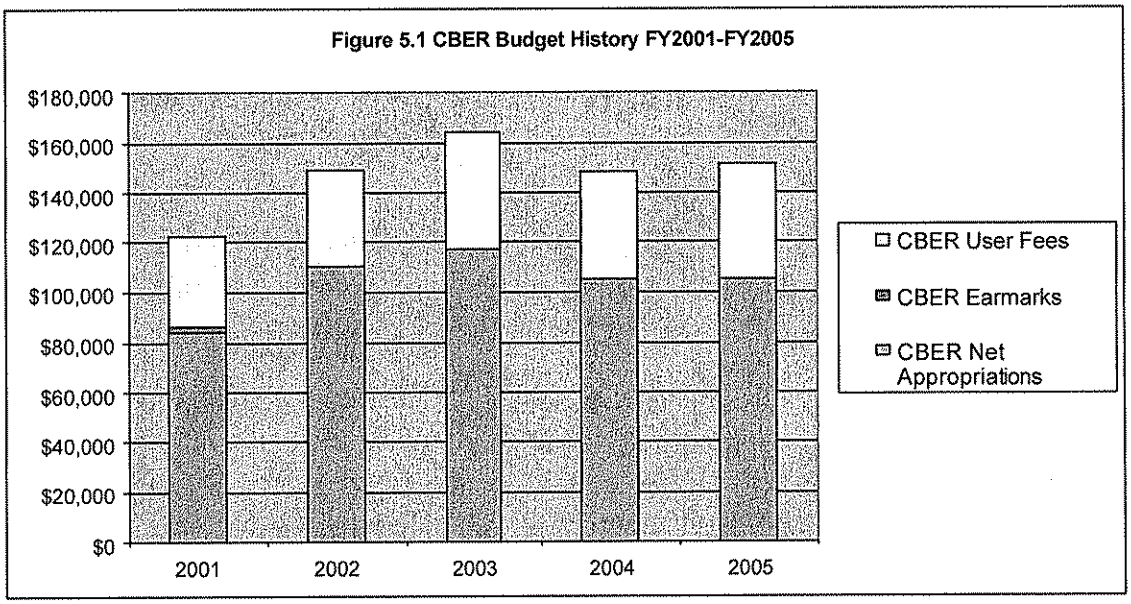
5.1 Challenges Related to Rising Costs

Over the past several years, the decline in appropriated dollars to cover the increased cost of on-board drug review "process" staff and to cover the cost of required non-payroll expenses (e.g., facilities and rent) has required that more user fee dollars be used to cover those costs. As a consequence, fewer fee dollars have been available to hire the additional staff envisioned when PDUFA 3 was enacted.

Figures 5.1 and 5.2 show overall budget trends for CBER and CDER, in nominal dollars (not adjusted for inflation) for fiscal years 2001 through 2005. Appropriated funds available to cover PDUFA costs have declined because total CDER and CBER budget authority has remained relatively flat or gone down, while payroll costs increase at 5 to 8 percent each year (as table 5.1 shows) and non-PDUFA program

mandates and budget earmarks have increased. For example, CBER has received earmarks for blood safety and influenza vaccine-related activities, in addition to mandates for work in counterterrorism, tissue safety and gene therapy tracking.

Figure 5.1 CBER Budget History FY2001-FY2005



During fiscal years 2001 through 2005, CDER has receiving increased earmarks for FDA generic drug activities growing from $150,000 for generic drug education in FY 2001 to an earmark of $56 million for generic drug review in FY 2005, and mandates to increase the availability of medical countermeasures, pediatric drug labeling and address other important public health issues. The lack of growth in appropriated dollars for PDUFA has meant that appropriated dollars have not kept up with increasing payroll and non-payroll costs of the program, due to mandatory federal pay increases and the additional cost of recruiting and retaining physician disease specialists, pharmacologists, and other highly marketable senior scientific and health care professionals needed to perform regulatory review.

Figure 5.2 CDER Budget History FY2001-FY2005

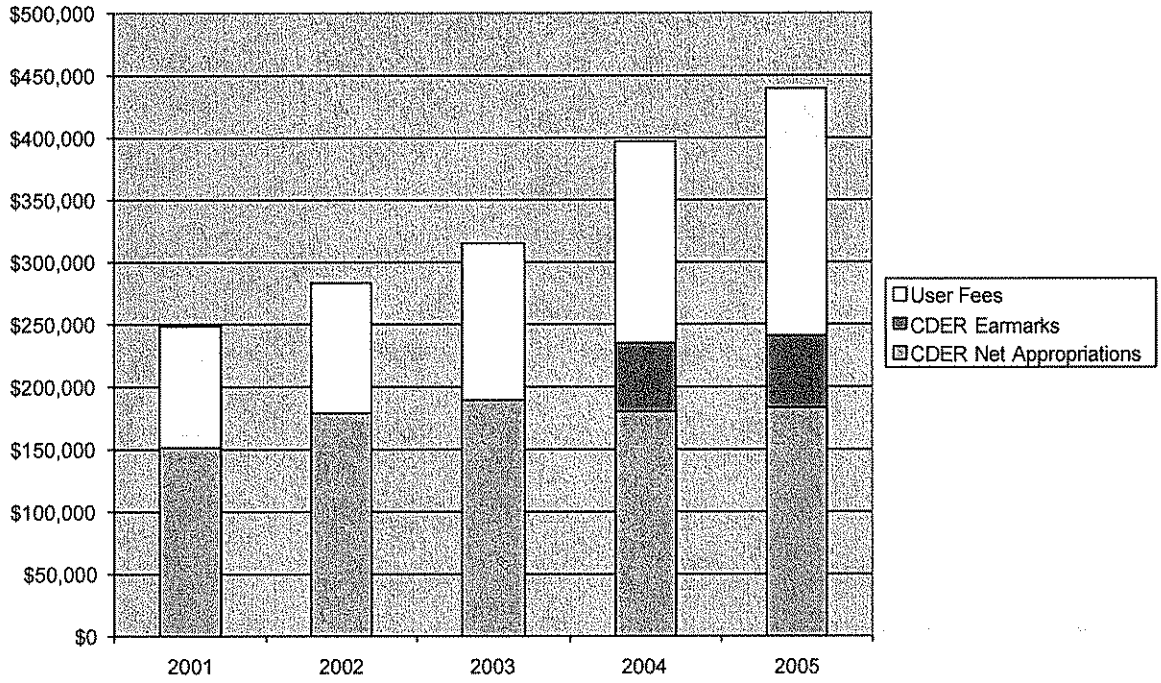


Table 5.1 below illustrates the trend in cost growth, showing payroll cost growth for CDER, the FDA product center responsible for performing approximately 90 percent of the PDUFA review work. Since 1992, the total number of center staff has grown by about 55 percent, and the average salary has more than doubled.

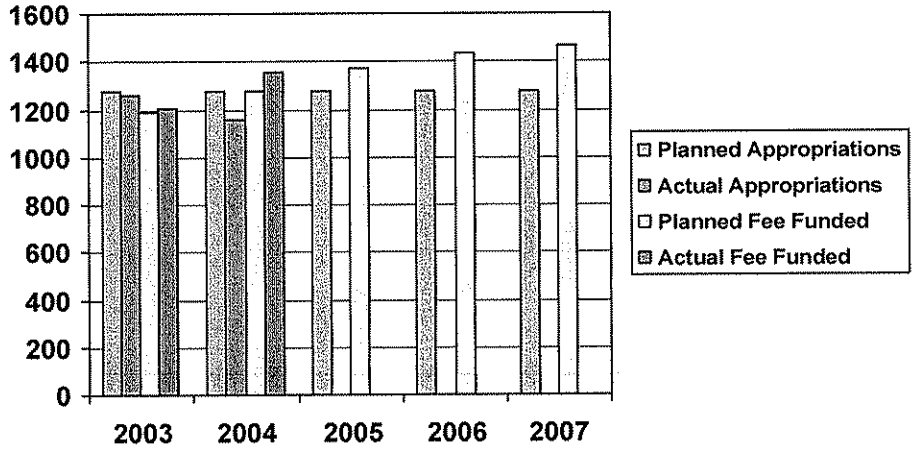
Table 5.1 CDER Past and Projected Average Salary and Benefits Cost and FTE

Fiscal Year	Average Salary and Benefits	FTE Supported
FY1992	$61,813	1407
FY1993	$65,287	1399
FY1994	$68,788	1473
FY1995	$71,412	1547
FY1996	$75,333	1609
FY1997	$78,371	1676
FY1998	$82,924	1647
FY1999	$87,208	1691
FY2000	$92,238	1781
FY2001	$97,710	1792
FY2002	$105,171	1788
FY2003	$111,462	1912
FY2004	$120,765	2124
FY2005	$126,700 *	2170*
FY2006	$133,000 *	2200*
FY2007	$139,700 *	2210*

* *Figures are estimates; FY05-07 final data not yet available*

At the beginning of PDUFA 3, FDA projected a constant share of appropriated funds, assuming these funds would grow at a rate that would continue to support 1277 of the FTE devoted to the review of human drug applications. But appropriations available for drug review have gone down while pay costs have gone up. Given the limited availability of appropriated funds, fee revenues have had to be used to offset cost increases at current staffing levels. The result is that FDA has been able to hire fewer additional scientific review staff to address the increasing review workload than anticipated. Figure 5.3 depicts the trend in planned versus actual FTE paid from appropriated funds versus fee collections.

Figure 5.3 PDUFA FTE Paid for by Planned vs. Actual Appropriations and Fee Funds

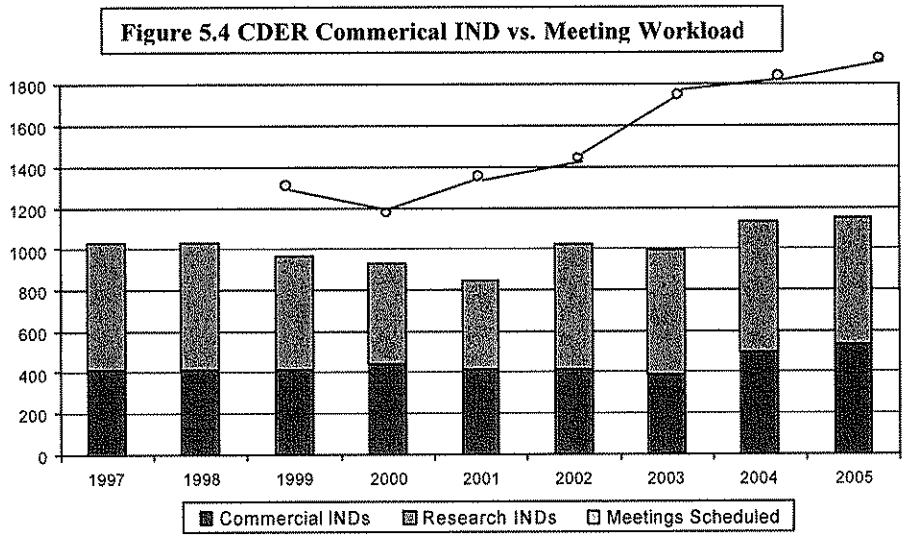


Because additional fee dollars have been applied toward the increased cost of current FTEs, fewer fee dollars have been available to hire the number of additional review staff planned under PDUFA 3, to address the underfunded workload increases of PDUFA 2, particularly related to industry-requested meetings and protocol assessments. In both of these areas workload grew further during PDUFA 3.

Although the current law provides for fee adjustments based on increases in review workload, the workload adjuster, as currently specified, fails to capture the most labor-intensive and fastest growing component of work. The current workload adjuster is based on the weighted average of the change in the total number of:

- Human drug applications (NDA/BLAs)
- Efficacy supplments (ES)
- Manufacturing supplements (CMC) and
- Commercial investigational new drug (IND) applications.

Figures 4.1 through 4.3 in Section 4 show steady but moderate growth in the 3 submission types that translate directly into PDUFA goal-driven work. By contrast, growth in the number of industry-requested meetings and special protocol assessments, which occur during the IND phase, are not correlated with, nor captured by the volume of commercial IND submissions. Figure 5.4 shows the trend in commercial INDs submittted to CDER versus the number of industry-requested meetings conducted by CDER. This graph illustrates FDA's finding that the number of submitted commercial INDs is a poor proxy for PDUFA IND-phase workload.

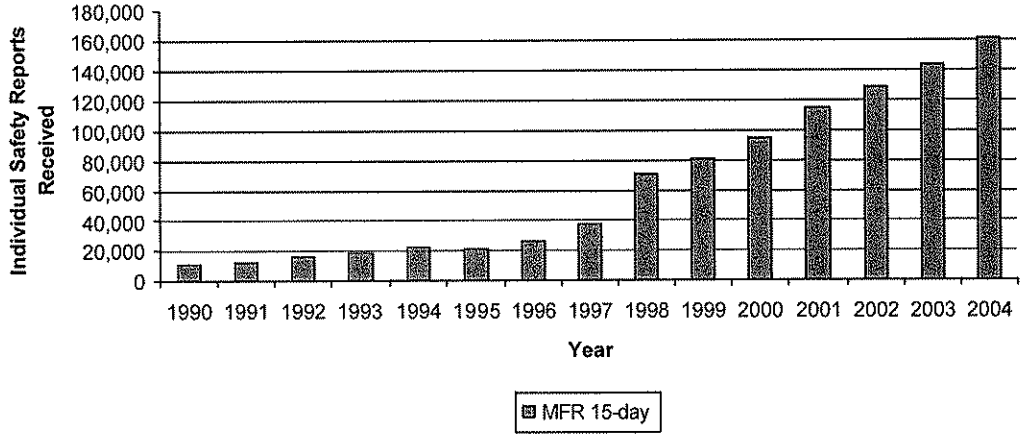


5.2 Challenges Related to Post-Market Surveillance

PDUFA 3 gave FDA new authority to allocate user fee funds to support post-marketing safety-related activities. For drugs and biologics approved on or after October 1, 2002, PDUFA 3 allows FDA to spend user fees to monitor the safety of products during their first two years on the market, three years for potentially dangerous medications.

Knowledge about a product will always be limited to some extent at the time of approval by factors in the product development process. And because of the populations not studied in clinical trials or minimally studied, side effects may be discovered if these groups are treated with a product after it goes on the market. The Adverse Event Reporting System (AERS) provides FDA's primary source of post-marketing safety data.

Figure 5.5



Manufacturers are required to report serious drug adverse effects to FDA within 15 days of their receipt of that report, typically from a health care provider. Figure 5.5 below shows the trend in those reports. Manufacturer 15-day reports have grown almost 9-fold from 1992 to 2004. Increases in reports may in

part be the result of the increasing use of drugs, increasing patient opportunities for benefits and also increasing the exposure to risks. The number of prescriptions dispensed to US patients has grown from 1.9 billion in 1992 to 3.5 billion in calendar year 2004.[6]

FDA currently has a limited capacity to receive timely information on adverse events, and to analyze that data. For example, over 100 thousand manufacturers' 15-day reports are currently received on paper forms that must be hand-entered into FDA's electronic database. FDA needs a stronger capacity to receive timely, complete and high-quality information about patients' adverse experiences with new products, a stronger ability to quickly and accurately analyze new safety findings, and effective methods of communicating new information to patients and health care providers. These improvements require additional resources.

The budget pressures and reduced ability to spend new fees for additive capabilities, as described above, have also limited FDA's ability to significantly increase the resources available for post-market surveillance, analysis and risk management. The restriction of PDUFA funding support to products approved on or after October 2002 has also meant that fee funds could not be used to support further investigation of safety issues related to products approved within the past five to ten years, such as COX-2 and SSRI drugs that have received more recent public attention. The limited availability of fee funds and limited ability to apply them to post-market surveillance work has limited FDA's ability to address the surveillance capacity issues via PDUFA.

5.3 Direct-to-Consumer Advertising (DTCA) of Prescription Drugs

Industry sponsors are not required to submit Direct-to-Consumer Advertising (DTCA) materials for FDA review prior to using the materials in their promotion and this review is not part of the PDUFA "process for the review of human drugs". It is linked, however, to fundamental aspects of new drug review and it also presents the prospect of a mushrooming review workload.

A fundamental part of NDA review is the review of information that the sponsor wishes to include in the drug label, which includes the disease indication, patient population for which the drug would be approved and key safety information. FDA only approves labeling supported by scientific evidence of safety and effectiveness presented in the NDA, and any subsequent market promotion, including any direct-to-consumer advertising, must be consistent with the FDA-approved drug label and FDA regulations.

DTCA has been found beneficial to some consumers. Researchers found that of those consumers prompted by DTCA to have a physician visit to discuss treatment or seek medical advice, about 25 percent had a new diagnosis, and 43 percent of those new diagnoses were for "high priority" conditions based on federal government criteria. Some of the new diagnoses that were discovered as a result of these visits were often under diagnosed and under treated. The most common new diagnoses were allergies, high cholesterol, arthritis, hypertension, diabetes and depression[7]. Many surveyed physicians think DTCA encourages patients to seek treatments they don't need, but many also think DTCA helps educate and inform patients about disease conditions and treatments available to them[8].

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[6] *Prescription Drug Trends: A Chartbook*, Kaiser Family Foundation, 2000 and www.imshealth.com

[7] J.S. Weissman, D. Blumenthal, A.J. Silk, K. Zapert, M. Newman, and R. Leitman, "Consumers' Reports on the Health Effects of Direct-to-Consumer Drug Advertising", *Health Affairs Web Exclusive*, February 26, 2003

[8] J.S. Weissman, D. Blumenthal, A.J. Silk, M. Newman, K. Zapert, R. Leitman and S. Feibelmann, "Physicians Report on Patient Encounters Involving Direct-to-Consumer Advertising", *Health Affairs Web Exclusive*, April 28, 2004

Industry believes that DTCA benefits public health, and the Pharmaceutical Research and Manufacturing Association (PhRMA) has stated that DTCA "fosters an informed conversation about health, disease, and treatments between patients and their health practitioners." However, responding to some public concerns about DTCA and its potential impact on increased drug use, on August 2, 2005, PhRMA announced its Guiding Principles for Direct to Consumer Advertisements About Prescription Medicines. Principle number 8 states: "Companies should submit all new DTC television advertisements to the FDA before releasing these advertisements for broadcast."

Figure 5.6 Number of Broadcast Drug Ads Proposed (Submitted for FDA Review) vs. Disseminated (Not Reviewed by FDA)

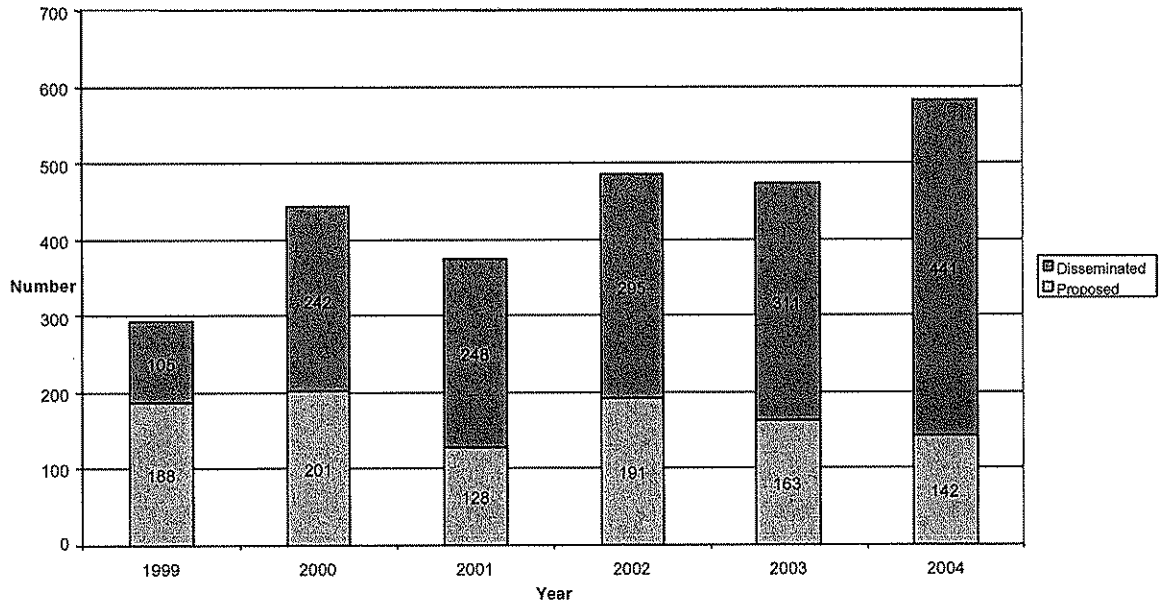

Figure 5.6 shows recent trends in the numbers of broadcast drug advertisements disseminated without FDA review, versus the number proposed and submitted to FDA for review prior to dissemination. In 2004, DDMAC reviewed 142 proposed broadcast ads, with the 4 full-time staff available to perform these reviews. Although FDA review of all materials would ensure alignment with the approved labeling and a fair balance of information on benefits and risks, current FDA resourcing for this work would probably result in delayed reviews if all companies were to submit their ads. Such delays would likely affect companies' ability to meet their marketing timelines, and discourage them from submitting the materials for prior FDA review.