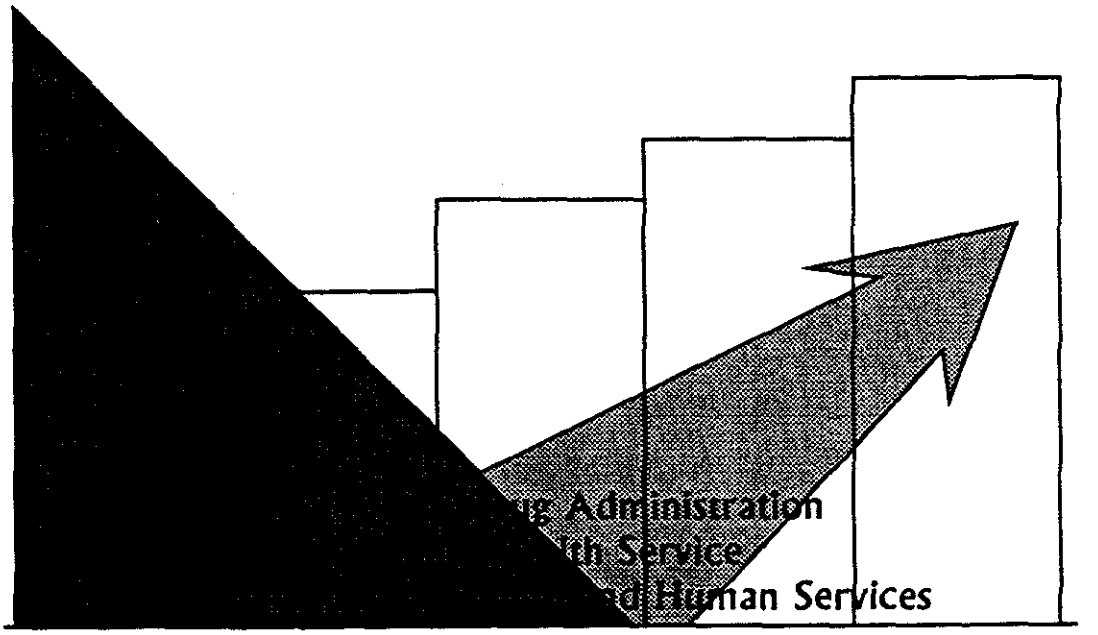
FINAL FINANCIAL REPORT

Prescription Drug User Fee Act of 1992

Fiscal Year 1997 Report to Congress

February 1, 1998



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BACKGROUND

The Prescription Drug User Fee Act of 1992 ("PDUFA", "User Fee Act", or "Act") authorizes the Food and Drug Administration ("FDA" or "Agency") to collect fees from the pharmaceutical industry to augment FDA's base resources. These additional resources are to be used to expedite the review of human drug applications, so that drug products can reach the marketplace more quickly. Total fee revenues that FDA is to collect in each fiscal year (FY) are set in the Act. These amounts are to be adjusted for FYs 1994 through 1997 to reflect the greater of increases in the Consumer Price Index or the rate of pay increases to federal employees in the Washington, D.C., area. Application, establishment, and product fees set out in a schedule in the Act are to be adjusted on an annual basis to achieve the adjusted revenue targets set forth in the Act.

Section 104 of the Act requires FDA to submit two reports to Congress each year. They are a performance report and a financial report due within 60 and 120 days of the end of the FY, respectively. The performance report, which discusses FDA's progress in meeting the goals referred to in the Act, was released December 1997. The financial report addresses FDA's implementation of the authority for the collection and use of user fees during a fiscal year.

This final financial report presents the user fee revenues and related obligations for FYs 1993, 1994, 1995, 1996, and 1997 and the costs applicable to the process for the review of human drug applications at the FDA for the same period. FY 1992 costs for the process for the review of human drug applications have been included and adjusted as specified in the Act, because this amount is a baseline for future year calculations. Arthur Andersen & Company independently reviewed FDA's procedures for calculating these costs in 1995, and found the methodology to be reasonable.

Additionally, in FY 1995, in compliance with the Chief Financial Officers Act requirements, FDA's Office of Financial Management prepared a financial statement that reported the condition and results of the PDUFA account as of and for the year ended September 30, 1994. The Office of the Inspector General (OIG) audited this financial statement and issued its audit report on September 25, 1995. The OIG rendered an unqualified opinion on the PDUFA account's statement of operations and changes in net position.

COMMISSIONER'S REPORT

This Final Annual Report to Congress on the financial aspects of FDA's implementation of the Prescription Drug User Fee Act of 1992 (PDUFA) covers FY 1997, from October 1, 1996, through September 30, 1997. The PDUFA established certain conditions that must be satisfied each year in order for FDA both to collect the user fees established in the Act and to spend those revenues to enhance FDA's process for the review of human drug and biological product applications. This report documents how those statutory conditions were met in FY 1997. Since the conditions were met, FDA both collected and spent PDUFA user fees in FY 1997.

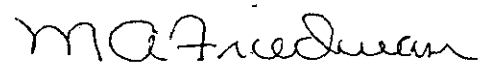
The PDUFA established FY 1992 costs as a baseline. These costs are then adjusted for the lessor of inflation since 1992 or changes in overall government domestic discretionary spending since 1992, as required by the Act, and presented in financial reports each year for comparison. The statements and tables included in this report provide information on the user fees FDA collected and spent in FY 1997, and also provide comparative data for FYs 1996, 1995, 1994, 1993, and baseline cost data for 1992. Over the past five years, FDA has collected over $328 million in user fees of which $292 million has been obligated and spent.

In FY 1997, FDA collected $93,234,125 in user fees and had gross receivables of $10,639,550 at year end. In addition, at year end, the Agency had a substantial number of reviews in process for applications received in FY 1997 (and a few received in 1996), for which the second half of the application fee will not be billed until FDA issues an action letter on the application. Most of these action letters will be issued, and fees collected, in FY 1998; some may not be issued until FY 1999 or beyond.

In FY 1997, FDA obligated and spent $84,289,046 of fees collected this year or carried over from previous years, of which over 95 percent were for direct review actions. Of the $84,289,046 that FDA spent in FY 1997, $62,039,000 was for staff and payroll costs. Throughout FY 1997, the Agency financed with user fees about 696 more FTE for included activities than were utilized in 1992. This large infusion of human resources into the process is one of the most important factors that enabled FDA to continue to meet the performance goals in the Act.

The balance of the fee revenue spent in FY 1997 represents investments in the Agency's infrastructure and other activities supporting the process for the review of human drug applications. These include vital investments in the continued development of information technologies.

We are pleased with our progress in enhancing the review of human drug applications in FY 1997 that has been made possible by the fees we have collected under this Act. We are pleased that PDUFA has been amended and extended for another five years under the FDA Modernization Act of 1997 (P.L. 105-115). The new provisions not only improve upon many aspects of the PDUFA, but they also provide a greater level of resources over the next five years. These new resources will enable FDA to meet an even more challenging set of new goals. We look forward to further reducing drug development times as we strive to meet these new goals over the coming five years.



Michael A. Friedman, M.D.
Lead Deputy Commissioner of Food and Drugs

AUTHORITY FOR USER FEES IN 1997

The Act contains three conditions that must be met in order to implement user fees. These conditions are presented in Appendix A. FDA did meet all necessary criteria in FY 1997.

The first condition is that FDA's Salaries and Expenses Appropriation, excluding user fees, for FY 1997 must exceed FDA's FY 1992 Salaries and Expenses Appropriation, as adjusted for inflation according to the Act. FDA's FY 1997 Salaries and Expenses Appropriation, excluding user fees, was $819,971,000. FDA's FY 1992 Salaries and Expenses Appropriation, after adjustment, was $761,120,340. Therefore, the first condition was met.

The second condition is that user fees be provided for in FDA's appropriation. For FY 1997, the basic appropriation act specifying amounts authorized to be collected from fees (Public Law 104-180) was signed by the President August 6, 1996. The appropriation provided funding of $87,528,000 from PDUFA fees collected to augment FDA's Salaries and Expenses Appropriation. The appropriation act specified that the fees collected could remain available until expended. Thus, the second condition was met.

The third condition in the Act is that all user fees collected under the Act may be used only for increases in the costs of resources allocated for the process for the review of human drug applications, compared with FY 1992 adjusted obligations. The $147,959,689 obligated from traditional appropriations in FY 1997, exceeded the $125,872,166 obligated for this purpose in FY 1992, as adjusted. Thus, the third condition has been met. In addition to traditional appropriations, $84,289,046 of user fees collected were obligated and spent in FY 1997, all for costs related to the process for the review of human drug applications, as required by the Act.

USER FEE REVENUES AND OBLIGATIONS

The Act specifies the user fee revenues to be collected from product, establishment, and application fees. Only half of the application fee is due upon submission of an application to the Agency. The remainder of the application fee is due 30 days from the date FDA issues an invoice after issuance of an action letter related to the application. Thus, fee revenue related to submissions received in one year may come due and be collected in succeeding years.

FOOD AND DRUG ADMINISTRATION
STATEMENT OF USER FEE REVENUES AND RELATED OBLIGATIONS

As of September 30, 1997

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997	TOTAL
Revenues:						
Fees Collected FY 1993	$28,531,996					$28,531,996
Fees Collected FY 1994	5,707,994	$48,022,250				53,730,244
Fees Collected FY 1995	1,153,500	6,466,800	$63,333,200			70,953,500
Fees Collected FY 1996	416,000	1,774,200	12,253,800	$67,874,400		82,318,400
Fees Collected FY 1997	24,000	190,200	2,037,600	17,640,185	$73,342,140	93,234,125
Total Fees Collected	35,833,490	56,453,450	77,624,600	85,514,585	73,342,140	328,768,265
Accounts Receivable	140,000	244,000	48,800	4,014,950	6,191,800	10,639,550
Total Revenues:	**35,973,490**	**56,697,450**	**77,673,400**	**89,529,535**	**79,533,940**	**339,407,815**
Obligations:						
Fees Obligated FY 1993	(8,949,000)					(8,949,000)
Fees Obligated FY 1994	(25,290,990)	(14,660,030)				(39,951,020)
Fees Obligated FY 1995	(1,153,500)	(39,829,020)	(33,081,495)			(74,064,015)
Fees Obligated FY 1996	(416,000)	(1,774,200)	(42,505,505)	(40,357,325)		(85,053,030)
Fees Obligated FY 1997	(24,000)	(20,750)	(2,037,600)	(44,365,675)	(37,841,021)	(84,289,046)
Total Obligations:	**(35,833,490)**	**(56,284,000)**	**(77,624,600)**	**(84,723,000)**	**(37,841,021)**	**(292,306,111)**
Balance as of 09/30/97	**$140,000**	**$413,450**	**$48,800**	**$4,806,535**	**$41,692,919**	**$47,101,704**

Total revenues of $35,973,490 in FY 1993 represent user fees collected or receivable during FYs 1993, 1994, 1995, 1996, and 1997 related to applications received in 1993. Total revenues of $56,697,450 in FY 1994 represent user fees collected or receivable during FYs 1994, 1995, 1996, and 1997 related to applications received in 1994. Total revenues of $77,673,400 in FY 1995 represent user fees collected or receivable during FYs 1995, 1996, and 1997 related to applications received in FY 1995. Total revenues of $89,529,535 in FY 1996 represent user fees collected or receivable during FY 1996 and FY 1997 related to applications received in FY 1996. Total revenues of $79,533,940 in FY 1997 represent user fees collected or receivable during FY 1997.

User fees are obligated as necessary for the process for the review of human drug applications and unobligated balances continue to be available without FY limitation. Thus, the $35,833,490 of user fees collected for FY 1993 in FYs 1993, 1994, 1995, 1996, and 1997 were obligated in FY 1993 ($8,949,000), FY 1994 ($25,290,990), FY 1995 ($1,153,500), FY 1996 ($416,000) and FY 1997 ($24,000). Of the $56,453,450 of user fees collected for FY 1994 in FYs 1994, 1995, 1996, and 1997 ($14,660,030) were obligated in FY 1994, ($39,829,020) were obligated in FY 1995, ($1,774,200) were obligated in FY 1996 and ($20,750) were obligated in FY 1997. Of the $77,624,600 of user fees collected for FY 1995, ($33,081,495) were obligated in FY 1995, ($42,505,505) were obligated in FY 1996, and ($2,037,600) were obligated in FY 1997. Of the $85,514,585 of user fees collected in FY 1996, ($40,357,325) were obligated in FY 1996 and ($44,365,675) were obligated in FY 1997. Of the $73,342,140 of user fees collected in FY 1997, ($37,841,021) were obligated in FY 1997. The unobligated balance of $47,101,704 (including $10,639,550 of estimated receivables) remains available to the Agency for future expenses.

STATEMENT OF USER FEE REVENUES BY FEE CATEGORY

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997	TOTAL
FEES COLLECTED:						
Product Fees	12,946,000	19,836,200	25,900,600	27,720,000	28,182,000	114,584,800
Establishment Fees	11,700,000	18,291,000	25,542,000	31,389,600	27,420,890	114,343,490
Application Fees	11,187,490	18,326,250	26,182,000	26,404,985	17,739,250	99,839,975
TOTAL FEES COLLECTED:	35,833,490	56,453,450	77,624,600	85,514,585	73,342,140	328,768,265
FEES RECEIVABLE:						
Product Fees	30,000	56,400	48,800	289,800	1,848,000	2, 273,000
Establishment Fees	60,000	187,600	0	3,111,900	3,933,800	7,293,300
Application Fees	50,000	0	0	613,250	410,000	1,073,250
TOTAL FEES RECEIVABLE:	140,000	244,000	48,800	4,014,950	6,191,800	10,639,550
TOTAL USER FEE REVENUES:	35,973,490	56,697,450	77,673,400	89,529,535	79,533,940	339,407,815
Additional Unbilled Fees	0	0	0	2,499,000	17,073,500	19,572,500
TOTAL PROJECTED REVENUES:	**35,973,490**	**56,697,450**	**77,673,400**	**92,028,535**	**96,607,440**	**358,980,315**
Appropriations	$36,000,000	$56,284,000	$79,423,000	$84,723,000	$87,528,000	$343,958,000

Additional estimated receivables of $2,499,000 for FY 1996 submissions and $17,073,500 for FY 1997 submissions were not billed or billable as of September 30, 1997, and have not been included in total revenues for FYs 1996 or 1997. These represent application fees to be billed and collected upon completion of the first review action on applications filed in FYs 1996 and 1997. Therefore, the total projected revenues, before estimated waivers and reductions, related to 1993 submissions are $35,973,490, total estimated revenues related to 1994 submissions are $56,697,450, total estimated revenues related to 1995 submissions are $77,673,400, total estimated revenues related to 1996 submissions are $92,028,535 ($89,529,535 + $2,499,000), and total estimated revenues related to 1997 submissions are $96,607,440 ($79,533,940 + $17,073,500). As of September 30, 1997, collections have exceeded appropriations in Fiscal Years 1994 ($169,450) and 1996 ($791,585). Surplus collections will be accumulated by the Agency until further collections of fees from each FY are unlikely. At that point, the Agency will refund surplus collections, or provide credits, in proportion to the total fees paid for that FY by each component.

Through FY 1997, fees were waived in the amounts of $1,126,000 for FY 1993, $2,078,350 for FY 1994, $5,077,400 for FY 1995, $4,208,700 for FY 1996, and $2,458,000 for FY 1997. All waivers are applied to the fiscal year in which the application was submitted. A reserve for additional waivers and reductions of $140,000, $244,000, $48,800, $3,503,700, and $1,956,800 has been recorded by the Agency for FYs 1993, 1994, 1995, 1996, and 1997, respectively. This represents Accounts Receivable for which collections have been deferred, pending final resolution of waiver requests.

A summary of waiver actions taken for FYs 1993, 1994, 1995, 1996, and 1997 is included in Appendix B.

OBLIGATION OF USER FEE REVENUES

User fee revenue can be expended only for increases in the costs of resources allocated for the process for the review of human drug applications, compared with 1992 adjusted obligations. Allowable and excludable costs for the process for the review of human drug applications are defined in Appendix C.

STATEMENT OF USER FEE OBLIGATIONS

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
Personnel Compensation and Benefits	$2,135,000	$16,157,000	$33,294,000	$51,383,000	$62,039,000
Building Alterations	2,085,000		471,000		
Travel And Transportation		555,005	2,541,000	2,011,000	2,270,000
Communications	157,000	291,317	584,000	902,000	1,183,000
Contract Services	667,000	12,895,312	18,222,000	23,033,000	13,637,000
Equipment and Supplies	3,864,000	10,045,606	18,715,000	7,601,000	5,094,000
Other	41,000	6,780	237,015	123,030	66,046
TOTAL OBLIGATIONS:	**$8,949,000**	**$39,951,020**	**$74,064,015**	**$85,053,030**	**$84,289,046**

FDA continued to improve and expedite the activities involved with the process for review of human drug and biologic applications in FY 1997. During FY 1997, the Agency obligated $84,289,046 of the user fees collected.

In FY 1997, FDA continued to hire additional personnel to expedite the drug application process. FDA dedicated 1,277 FTE (Full Time Equivalents or staff years) to the review of human drug applications in the baseline. A time reporting study was undertaken in 1993 to determine the percentage of time each division devotes to user fee related activities. This allowed calculation of FTE related costs. The percentages are updated quarterly through additional time studies. The development of these user fee related costs associated with the review of human drug applications is described in Appendix D. Throughout FY 1997, the Agency financed with user fees 696 more FTE for PDUFA activities than were utilized in 1992.

FDA's total expenditures for payroll from user fee funds in FY 1997 were $62,039,000. This amount includes costs for the additional staff hired, as well as payroll cost increases for the 1,277 FTE dedicated to the review of human drug applications.

The FDA continued to strengthen and build an electronic information infrastructure directed to the drug approval process and administrative support.

- Information Systems Infrastructure. The FDA continued to improve and enhance the information and communication infrastructure necessary to support the technology to both the FDA reviewer as well as industry. These improvements include office automation, electronic messaging, international electronic exchange of information and end user computing environments.

- Electronic Document Room. This enables the Agency to receive, inspect, load, store and archive electronic submissions in the format of case report tabulations and case report forms of new drug applications. Pilot testing and an industry workshop was complete and the Agency has begun receiving applications electronically.

- Administrative Management of Files. This is an automated means for creating, managing, electronic signing, and archiving internally generated documents for the drug review process. This project is currently operational in two drug review offices and further implementation is scheduled.

- Establishment Evaluation System (EES). This electronic application was designed to enable the tracking of establishments for the pre-approval inspection program. It also enables the ability to request an establishment inspection and have the results from the inspection returned to the drug review office. This is all a paperless process.

- Regulatory Management System (RMS). RMS is an information system designed to provide CBER reviewers an automated means to view and manage data and documents related to regulatory submissions and executive documents. RMS provides data entry and query tools as well as review-related document generation, storage, and routing. This system is currently implemented for 60 users across all review offices. Further implementation throughout the Center is planned.

YEAR END BALANCE

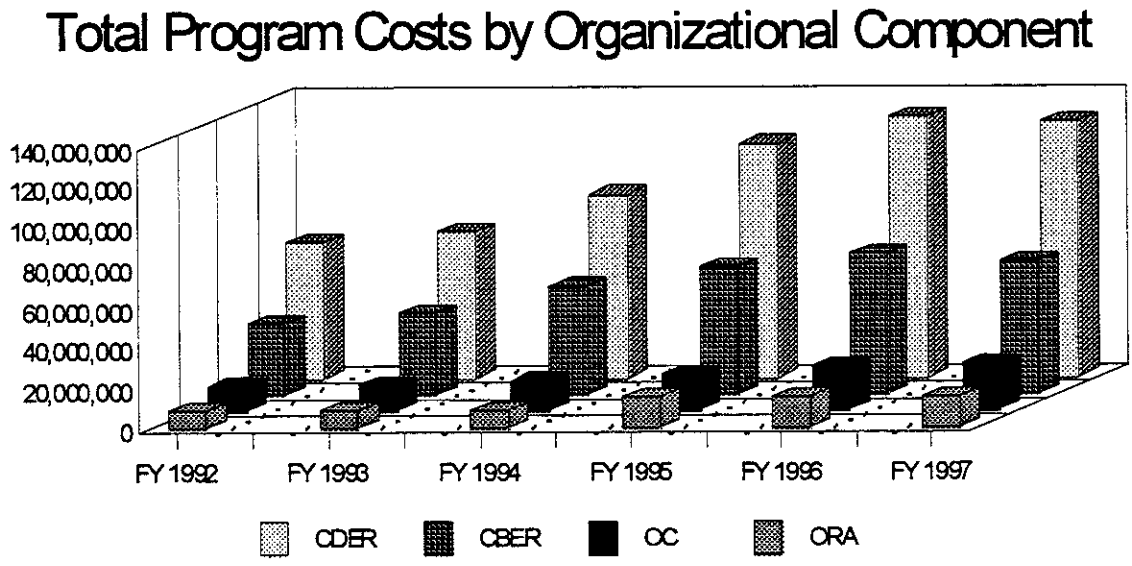
At the end of FY 1993, FDA had cash collections totaling $19,582,996, unbilled receivables totaling $3,555,506, and billed receivables of $732,494 for a total of $23,870,996. At the end of 1994, the total balance FDA carried forward to the next FY was $34,146,420, consisting of cash collections of $33,362,220, and receivables of $784,200. At the end of FY 1995, the total balance FDA carried forward to the next FY was, $31,860,205, consisting of cash collections of $30,251,705, and receivables of $1,608,500. At the end of FY 1996, the total balance FDA carried forward to the next FY, $29,520,175, consisted of cash collections of $27,517,075, and receivables of $2,003,100. At the end of FY 1997, the total balance FDA is carrying forward to the next FY is $47,101,704, consisting of cash collections of $36,462,154, and accounts receivable of $10,639,550. The net result of operations in FY 1997 increased the balance carried forward by $17,581,529. However, this unobligated balance includes a reserve for waivers and reductions that represents Accounts Receivable for which collections have been deferred pending final resolution of waiver requests. If these waivers are approved, and there is a strong possibility that they will, the unobligated balance could be reduced by as much as $6,000,000. The Agency will be revising its Financial Operating Plan annually to reflect current expenditure levels and updated support and investment requirements.

TOTAL PROGRAM COSTS FOR THE PROCESS FOR THE REVIEW OF HUMAN DRUG APPLICATIONS

The following table presents the costs for the review of human drug applications for FYs 1992, 1993, 1994, 1995, 1996, and 1997 by organizational component. This conveys the full cost of the process for the review of human drug applications, including costs paid from traditional appropriations, and, in 1993, 1994, 1995, 1996, and 1997, amounts from user fee revenues. The amounts are based upon obligations recorded as of the end of each FY. Over 81 percent of amounts obligated are expended within one year, and 96 percent within two years. Thus, obligations represent an accurate measure of costs.

FOR THE FISCAL YEARS ENDED SEPTEMBER 30,

	Base year 1992 Adjusted Through 9/30/97	1993 Actuals	1994 Actuals	1995 Actuals	1996 Actuals	1997 Actuals
Costs for the Center for Drug Evaluation and Research (CDER)	$68,764,807	$72,618,726	$91,422,027	$117,065,219	$130,129,983	$127,686,288
Costs for the Center for Biologic Evaluation and Research (CBER)	35,739,726	40,511,011	53,805,952	63,103,088	69,818,032	66,102,113
Field Inspection and Investigational Costs (ORA)	8,805,534	9,054,944	9,038,316	15,053,823	15,362,362	14,849,704
Agency General and Administrative Costs (OC)	12,562,099	13,279,896	15,021,863	18,672,203	22,032,040	23,610,630
Total Cost for the Review of Human Drug Applications	$125,872,166	$135,464,577	$169,288,158	$213,894,333	$237,342,417	$232,248,735



MANAGEMENT CHALLENGES FOR FY 1998

The Prescription Drug User Fee Act has provided significant additional revenue to expedite the review of human drug applications. These additional resources have been used to achieve the performance goals of reducing the average time between the submission of an application and the delivery of a first action. With the enactment of the Food and Drug Modernization Act of 1997 (the FDAMA), Public Law 105-115, FDA expects to continue to apply user fees to assure that new performance goals are also attained. FDA will also continue aligning its incremental resources to changing workload requirements to ensure that a reasonable balance and real value for expenditures are maintained. The Agency is dedicated to ensuring that user fee revenues help FDA contribute to reduced drug development times and effective therapies made available more quickly to the American people.

Among the most pressing challenges facing the Agency is the need to continue to hire, equip, and train qualified reviewers. Access to qualified, highly motivated reviewers is essential to continued improvement in the human drug application review process.

Multi-year investments in information technologies and management systems will continue. Both CDER and CBER have placed a high priority on and are making substantial investments in new technologies to improve the management of the application process and to support electronic submissions of applications. Investments such as these are necessary now in order to achieve our five year goal of a paperless review process.

Without the availability of funds derived from user fees, the substantial progress in improving and expediting the review of human drug applications could not have been achieved. The challenge for FY 1998 will be to sustain and advance this achievement through the continued judicious use of these resources.

CONDITIONS FOR ASSESSMENT AND USE OF FEES

The Prescription Drug User Fee Act (The Act) enumerates three major conditions that must be met each year before fees can be collected and spent that year for the human drug review process. Each of these conditions is reviewed below, along with an explanation of how the condition was met in 1997.

The **first condition** comes from section 736(f)(1) of the Act. It states:

> Fees may not be assessed under subsection (a) for a FY beginning after FY 1993 unless appropriations for salaries and expenses of the FDA for such FY (excluding the amount of fees appropriated for such FY) are equal to or greater than the amount of appropriations for the salaries and expenses of the FDA for the FY 1992 multiplied by the adjustment factor applicable to the FY involved.

The Act requires that the 1992 Salaries and Expenses appropriation for FDA will be adjusted each year by an "adjustment factor", which is defined in section 735(8) of the act. It states:

> The term 'adjustment factor' applicable to a FY is the lower of-
>
> (A) the Consumer Price Index for all urban consumers (all items; United States city average) for August of the preceding FY divided by such Index for August 1992, or
>
> (B) the total of discretionary budget authority provided for programs in the domestic category for the immediately preceding FY (as reported in the Office of Management and Budget sequestration preview report, if available, required under section 254(d) of the Balanced Budget and Emergency Deficit Control Act of 1985) divided by such budget authority for FY 1992 (as reported in the Office of Management and Budget final sequestration report submitted after the end of the 102d Congress, 2d Session).

The first calculated factor (change in consumer price index since August of 1992) is 11.6%. The second calculated factor (change in domestic discretionary spending since 1992) is 4.843%. Since the latter is lower, FDA used the second calculated factor, 4.843%. Applying this to the FY 1992 appropriation of $725,962,000 the adjusted FY 1992 appropriation is $761,120,340. FDA's FY 1997 Salaries and Expenses Appropriation, excluding user fees, was $819,971,000. Since this latter figure is higher, the first condition was met.

The **second condition** comes from Section 736 (g) (2) (A). It states that fees shall be collected in each year in an amount specified in appropriation Acts for that FY. Without a specific appropriation, no fees may be collected.

The basic appropriation act specifying amounts collectable from fees during FY 1997 (Public Law 104-180) was signed by the President August 6, 1996. This appropriation provided that $87,528,000 in funding was to come from fees collected under the Act, and specified that the fees collected could remain available until expended. Thus, the second condition was met.

The **third condition** in the Act, in Section 736 (g) (2) (B), states that fees:

> "shall only be collected and available to defray increases in the costs of the resources allocated for the process for the review of human drug applications (including increases in such costs for an additional number of full-time equivalent positions in the Department of Health and Human Services to be engaged in such process) over such costs for FY 1992 multiplied by the adjustment factor."

As a first step, it is necessary to adjust FDA's 1992 base obligations. In 1992, FDA's actual obligations for the process for the review of human drug applications was $120,057,253. Applying the adjustment factor derived above (4.843%), FDA's 1992 adjusted costs for the process for the review of human drug applications is $125,872,166.

The following table compares the FDA costs (obligations) for the process for the review of human drug applications for 1992 (adjusted) with 1997 actuals. It shows that, since the 1997 amount spent from base appropriations exceeded the 1992 adjusted amount, the third condition was met.

OBLIGATIONS FOR THE PROCESS FOR THE REVIEW OF HUMAN DRUG APPLICATIONS

	Adjusted FY 1992	FY 1997
Base Appropriations	**$125,872,166**	**$147,959,689**
User Fee Funds	$0	$84,289,046
Total Obligations	**$125,872,166**	**$232,248,735**

APPENDIX B

WAIVERS AND EXEMPTIONS

The Act directs FDA to waive or reduce fees in five different circumstances:

- when a waiver is necessary to protect the public health;
- when a fee is a significant barrier to innovation;
- when the fees paid exceed FDA's costs of reviewing a person's human drug application;
- when imposition of the fee creates an inequity between certain 505(b) (1) and 505(b) (2) human drug applications and;
- when a sponsor withdraws a pending human drug application after FDA has filed it, but before FDA has performed substantial work on the marketing application.

All fees may be waived or reduced under these waiver provisions. Many of the waiver requests FDA receives pertain to orphan products; products indicated for diseases or conditions affecting fewer than 200,000 patients in the United States. FDA reviews waiver requests on a case by case basis, taking into account, among other things, the patient population for which a drug product is indicated.

The Act also directs FDA to permit qualified small businesses to defer payment of application fees for one year after submission of a human drug application, and to reduce the application fee by 50 percent. To qualify for the small business exemption, a business must have fewer than 500 employees, and have no prescription drug products introduced into interstate commerce.

The following table summarizes the waiver actions taken by FDA for FYs 1993, 1994, 1995, 1996, and 1997:

APPROVED WAIVERS

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
APPLICATIONS:					
Waivers Approved	10	7	21	15	6
Value of Waivers Approved	$700,000	$789,750	$3,594,000	$2,550,000	$922,500
PRODUCTS:					
Waivers Approved	21	37	37	35	35
Value of Waivers Approved	$126,000	$350,600	$451,400	$441,000	$474,600
ESTABLISHMENTS					
Waivers Approved	5	10	8	9	8
Value of Waivers Approved	$300,000	$938,000	$1,032,000	$1,217,700	$1,060,900
TOTAL VALUE OF WAIVERS APPROVED:	**$1,126,000**	**$2,078,350**	**$5,077,400**	**$4,208,700**	**$2,458,000**

PENDING WAIVERS

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
APPLICATIONS:					
Waivers Pending	1	0	1	1	15
Allowance for Pending Waivers	$50,000	$0	$0[1]	$102,000	$0[2]
PRODUCTS:					
Waivers Pending	5	6	4	23	8
Allowance for Pending Waivers	$30,000	$56,400	$48,800	$289,800	$105,600
ESTABLISHMENTS:					
Waivers Pending	1	2	2	23	16
Allowance for Pending Waivers	$60,000	$187,600	$0[3]	$3,111,900	$1,851,200
TOTAL ALLOWANCE FOR PENDING WAIVERS:	**$140,000**	**$244,000**	**$48,800**	**$3,503,700**	**$1,956,800**

1 No allowance was established for the pending waivers because, for the firms who submitted waiver requests, there were no outstanding accounts receivable.

2 IBID

3 IBID

ALLOWABLE AND EXCLUDED COSTS FOR THE PROCESS FOR THE REVIEW OF HUMAN DRUG APPLICATIONS

The Prescription Drug User Fee Act of 1992 and the related House of Representatives Report 102-895 ("House Report") define, for the first time, the process for the review of human drug applications and the costs which may be included in that process. Using these definitions (and further refinements as necessary) and the methodologies described in this report, the Agency identified those activities which were applicable to the process for the review of human drug applications. The costs of resources allocated to the process for the review of human drug applications are based on FY 1992 and 1997 obligations, which are consistent with the FY 1992 and 1997 appropriations referenced in the Act. Over 96 percent of amounts obligated are expended within two years. Therefore, obligations represent an accurate measure of costs.

User Fee Related Costs

Section 735(6) of the Act defines in general terms the activities necessary for the review of human drug applications (the "human drug review process"). In summary, costs related to the following process activities have been attributed to the process for the review of human drug applications.

- All investigational new drug (IND) review activities (including amendments), after an IND exemption has become effective pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act.
- All new drug application (NDA) and product license application (PLA) review activities (including supplements and amendments).
- All review activities for establishment license applications (ELAs) and amendments.
- Regulation and policy development activities related to the review of human drug applications.
- Development of product standards for products subject to review and evaluation.
- Meetings between the Agency and the sponsor of a covered application or supplement.
- Review of labeling prior to approval of a covered application or supplement and the review of the initial pre-launch advertising.
- Review of post-marketing studies that have been agreed to by sponsors as a condition for approval.
- Inspections of facilities undertaken as part of the review of pending applications or supplements.
- Lot release activities for covered biological products.
- Assay development and validation to ensure batch-to-batch consistency and reliability for covered biological products.

- Monitoring of clinical and other research conducted in connection with the review of human drug applications.
- User Fee Act implementation activities.
- Research related to the human drug review process.

All user fee related costs represented by the above activities are collectively referred to in this report as costs for the process for the review of human drug applications.

Section 735(7) of the Act defines the "costs of resources allocated for the process for the review of human drug applications" as the expenses incurred in connection with this process for:

(A) officers and employees of the FDA, employees under contract with the FDA who work in facilities owned or leased for the FDA, advisory committees, and costs related to such officers, employees, and committees including, travel, education, recruitment, and other personnel related activities;
(B) management of information, and the acquisition, maintenance, and repair of computer resources;
(C) leasing, maintenance, renovation, and repair of facilities and acquisition, maintenance, and repair of fixtures, furniture, scientific equipment, and other necessary materials and supplies; and
(D) collecting user fees under section 736 of the Act and accounting for resources allocated for the review of human drug applications and supplements.

User Fee Excluded Costs

The User Fee Act excludes costs related to the following.

Excluded Products

- Generic drugs
- Over-the-counter drugs not associated with an NDA or NDA supplement
- Large volume parenterals approved before 9/1/92
- Allergenic extract products
- Whole blood or a blood component for transfusion
- In vitro diagnostic biologic products
- Certain drugs derived from bovine blood

Excluded Process Activities

- Pre-IND effective activities
- Enforcement policy development
- Post-approval compliance activities
- Advertising review activities once marketing of the product has begun
- Inspections unrelated to the review of covered applications
- Research unrelated to the human drug review process

Since these inclusions and exclusions require an accounting of a subset of FDA activities, it was necessary to develop and implement a methodology that would allow the Agency retrospectively to capture the 1992 costs for the newly defined "process for the review of human drug applications," and apply that same methodology for future year calculations. Arthur Andersen & Company independently reviewed FDA procedures in 1995, and found the methodologies to be reasonable.

APPENDIX D

DEVELOPMENT OF COSTS FOR THE PROCESS FOR THE REVIEW OF HUMAN DRUG APPLICATIONS

GENERAL METHODOLOGY

The costs associated with the process for the review of human drug applications are based upon obligations recorded within the following FDA organizations: the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) (together - "center costs"), the Office of Regulatory Affairs (ORA), and the Office of the Commissioner (OC). These organizations correspond to the cost categories presented on the Statement of Costs for the Process for the Review of Human Drug Applications as follows:

Cost Category	FDA Organization
Costs for the Review of New Drug Applications and Supplements	CDER
Costs for the Review of New Biologic Applications and Supplements	CBER
Field Inspection and Investigation Costs	ORA
Agency General and Administrative Costs	OC

The costs were accumulated using a variety of methods including time reporting, management surveys, and detailed interviews. Using the definitions of costs and activities included in the "process for the review of human drug applications" in the Act, a portion of the costs within the four organizations listed above was identified as part of the human drug review process.

In addition, in 1994, OC established the Strategic Systems Staff as a part of the Office of Management and Systems. This staff was tasked with the development of computer systems designed to provide management information necessary to the proper implementation of the Act.

Center Costs

Costs are accumulated in CDER and CBER in cost centers corresponding to the organizational divisions within the centers. Most FDA divisions involved in the human drug review process perform a mixture of user fee included activities and user fee excluded activities. These

divisions fall into three categories: 1) review and laboratory divisions; 2) indirect review and support divisions; and 3) user fee excluded divisions. Costs are accumulated in division cost centers, as well as cost centers that collect center-wide expenses applicable to some or all of the divisions in a center. The allocation of costs for the three categories of divisions and centerwide expenses are discussed below.

Review and Laboratory Divisions:

The review and laboratory divisions, as organized during FY 1997, have the primary responsibility for the review of human drug applications and supplements. Below is a list of the direct review and laboratory divisions in CDER and CBER.

REVIEW AND LABORATORY DIVISIONS

CDER	CBER
Office of the Center Director	Office of the Center Director
Office of Drug Evaluation I	Office of Vaccines
Neuropharamacological Drug Products	Office of Therapeutics
Oncologic Drug Products	Office of Blood
Cardio-Renal Drug Products	Office of Establishment Licensing and Product Surveillance
Office of Drug Evaluation II	Allergenic Products and Parasitology
Metabolic and Endocrine Drug Products	Bacterial Products
Pulmonary Drug Products	Viral Products
Reproductive and Urologic Drug Products	Vaccines and Related Product Applications
Office of Drug Evaluation III	Cytokine Biology
Gastro-Intestinal and Coagulation Drug Products	Cellular and Gene Therapies
Anesthetic, Critical Care and Addiction Drug Products	Hematologic Products
Medical Imaging and Radiopharmaceutical Drug Products	Clinical Trial Design and Analysis
Office of Drug Evaluation IV	Application Review and Policy
Anti-Viral Drug Products	Transfusion Transmitted Diseases
Anti-Infective Drug Products	Hematology
Special Pathogens and Immunodulatory Drug Products	Blood Applications
Office of Drug Evaluation V	Establishment Licensing
Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products	Biostatistics and Epidemiology
Dermatologic and Dental Drug Products	Biological Product and Quality Control
Over-the-Counter Drug Products	Monoclonal Antibodies
Office of Epidemiology and Biostatistics	Veterinary Services
Quantitative Methods and Research Staff	
Biometrics I, II, III, and IV	
Office of Pharmaceutical Science	
Office of New Drug Chemistry	
Office of Clinical Pharmacology and Biopharmaceutics	

User fee related activities in the direct review and laboratory divisions were measured

using two methodologies. During 1993, a 16-week total time reporting study was conducted in CDER and CBER among all direct review personnel to measure the level of user fee related costs for each of these divisions.

These time reporting data were used to measure user fee related costs in CDER for FY 1994 and FY 1992. In CBER, a workload measurement procedure, in place since 1991 for planning purposes, was conducted among CBER staff to assess level of effort expended by each division on certain pre-defined activities. A total of 43 possible functional activities by 9 product classes were reported. These data were used to determine the user fee related costs for all divisions in CBER in FYs 1992, 1994, and 1995. In FY 1996, the CBER time reporting system was enhanced to collect a total of 69 possible functional activities by 9 product classes.

Indirect Review and Support Divisions

Indirect review and support divisions assist the primary review divisions and provide the infrastructure for the review process. In CDER, these divisions include the Divisions of Information Systems Design, Management and Budget, Drug Information Resources, the Medical Library, and the Office of Compliance. In CBER, these divisions include portions of the Office of the Center Director, Office of Management, Office of Compliance, and the Office of Communications, Training, and Manufacturers Assistance.

In CDER, detailed interviews were conducted with the division directors or their designees for each of the divisions classified as indirect review and support for the human drug review process. The first step of the interviews was to identify the activities in the division and classify these as user fee related or user fee excluded activities based on the definitions in the Act. Then, using information provided by the division directors, the number of full time equivalent employees (FTEs) involved in these activities was estimated. With this information, an overall user fee applicable percentage was calculated for each division.

In CBER, the workload measurement procedures were used to measure the level of effort of user fee related activities in the compliance divisions. Most of the Office of the Director, Office of Management, and the Office of Communications, Training, and Manufacturers Assistance are considered support organizations to CBER, therefore their time is added as overhead to each activity.

User Fee Excluded Divisions

Based on a review of a division's activities and the definitions in the Act, some divisions within the centers were completely excluded from the calculation of costs related to the process for the review of drug applications. Examples of the user fee excluded divisions include the Office of Generic Drugs in CDER. In CBER, all cost

centers perform some PDUFA work, although it can be as little as 5 percent.

Center-wide Expenses

A number of center-wide expenses are collected in central accounts rather than being charged directly to a specific division. These costs include rent, utilities, some computer equipment, facilities repair and maintenance, and extramural and service contracts. Many of these costs could be traced back to the specific division that generated the cost and were assigned the user fee related percentage calculated for the division to which the expenditure related. For the costs that benefited the center as a whole and could not be traced to a specific division, a weighted average user fee percentage was calculated based on the level of user fee related costs to total costs in the center.

TIME REPORTING STUDY

In November 1997, CDER initiated a 100% on-line time reporting survey of each employee within the Center. This two-week survey began on November 30, 1997 and ran through December 13, 1997. Prior to this survey, only those employees involved in PDUFA-related activities participated in direct time reporting; and a few others provided indirect management estimates. This new survey will capture the expenditure of time on PDUFA-related activities and other CDER mission-oriented activities as well. The 100% time reporting survey will be conducted for a two-week period during each quarter.

A total time reporting study was conducted from July 18, 1993, to November 6, 1993, as part of a contract with Arthur Andersen & Company, to measure the level of user fee related activities for the direct review and laboratory divisions in CDER and CBER. Over 1,000 staff participated in the 16-week study. The time sheets were designed to capture information on activities based on the definitions for the process for the review of human drug applications in the Act.

Using the results of the time reporting study, a user fee related percentage was calculated for each participating division and applied to the total FY 1992. The results of the 16-week time reporting exercise are representative of the activities during FYs 1992, 1993, and 1994 in CDER. In CBER, the original workload measurement procedure was used to measure 1992 and 1994 user fee costs. The results of the Arthur Andersen & Company 16-week total time reporting study were used to measure CBER's 1993 user fee costs.

In May 1995, CDER conducted an internal time reporting study of all CDER units previously surveyed by Arthur Andersen in 1993. This internal study enabled CDER to update user fee percentages on a one-time basis. On November 19, 1995, CDER implemented on-line, quarterly time reporting. These quarterly updates will facilitate timely reporting of user fee percentages by the various components of the Center.

In FY 1995, CBER began collecting, quarterly, based on the 1993 Arthur Andersen survey, "all hands" actual hours worked reported over a 2-3 consecutive week period. A total of 43 possible functional activities by 9 product classes were reported. Research activity was reported by specific research project number. These quarterly surveys were used to calculate the Center's PDUFA activity for each quarter and the percentage applied to each cost center. By mid-1995, CBER had begun a pilot computer-based reporting system (mirroring the paper submissions), that was accessed through the network (paperless.) By the end of the fiscal year, CBER designed, with the assistance of Arthur Andersen, an on-line reporting system called the "Resources Reporting System", that made it easier for employees to report and provide more data to management.

Additionally, the Resource Reporting System links direct review time to other Center data systems for application review and to the research project database. CBER has designed downloading capabilities to generate PDUFA percentage reports and other management information for both the Agency and the Center.

RESEARCH COVERED BY THE PRESCRIPTION DRUG USER FEE ACT

The FDA performs research to determine the risks and benefits of pharmaceutical agents and to set appropriate standards and methods for analysis. These activities include research on specific products or product classes that are approved or under review. Research is carried out in biomedical areas to develop expertise necessary to address new technologies, issues and emerging areas, develop and validate testing methodologies, and to establish drug and biologic standards. All of these activities are fundamental to the evaluation of human drugs and biological products. Research activities that directly support the process for the review of drug and biologic applications are described below.

Laboratory activities specified in the legislative history of PDUFA that are associated with the drug review process include activities necessary for the release of lots of biologics under section 351 of the PHS Act, and assay development and validation to ensure batch-to-batch consistency and reliability.

Further, the FDA Fee Management Committee defined research activities associated with the review of new drugs and biologics such as research to facilitate review of clinical and product testing, support policy development, validate assays, and develop standards. These user fee related activities are associated with approved products or product classes, those currently under review as IND's, PLA's, NDA's, or supplements.

Laboratory activities that are associated with generic drugs, OTC monographs, allergenic extracts, in-vitro diagnostics, whole blood or blood components, or large volume parenterals are not considered user fee related activities. Activities associated with the review of these

products are excluded from coverage as described in the Act.

The time reporting study undertaken in 1993 determined the extent of resources expended on research covered by PDUFA. Time was reported to individual research projects and each project was reviewed to determine whether it met the criteria for coverage by the user fee program. These related costs were aggregated and included in the appropriated baseline for PDUFA. Periodic time surveys are undertaken to update these costs. In FY 1995, CBER implemented a program, as a part of their time reporting system, to capture research time by individual research project.

Types of Research

User fee related research could be categorized based on its impact on the drug approval process:

Review of the Manufacturing Process

The evaluation of new biological and drug products requires a careful review of the manufacturing process. The process of manufacture can potentially result in subtle changes in the product characteristics which could affect safety and efficacy of the product. This review is especially critical in the evaluation of new products manufactured using new technologies.

Development and Validation of Test Methodologies

Standards for testing must be set for each drug or biologic product in order to ensure its identity, purity, and potency prior to approval. Frequently, test methods are developed and validated in FDA laboratories. These tests are used for lot release and for characterizing qualification lots of products submitted for approval.

Safety and Toxicity

New drugs and biological products must be evaluated for safety and toxicity. Frequently, a product will represent a new class whose toxicity profile is not well established. In these cases, it may be necessary for the Agency to conduct studies to gain information in order to establish policy and safety standards for similar products in the new product class.

Pharmacology

The pharmacology of drugs and biological products must be understood in order to evaluate potential toxicities and measures of potency. In some cases a detailed understanding of the mechanisms of action, metabolism, distribution, and excretion is

critical to establish tests for potency and to better understand toxicity. It may also be necessary for pharmacodynamic endpoints to establish appropriate product dosing and to develop in-vivo and in-vitro standards for evaluating manufacturing changes.

Clinical

The study of drugs and biological products in human subjects is an important component of FDA research. Many important questions related to the optimal use of a given drug in human subjects or patients may not be part of the standard drug development process. However, such data would facilitate more optimal use of the product. Further, some of these research questions impact on regulatory review policy for the product class being studied. Examples of such research include the study of drugs in special populations (i.e. women, the elderly, patients with renal or hepatic impairment), evaluation of drug interactions and the development of pharmacokinetic/pharmacodynamic correlations, or safety of combination vaccines.

FIELD INSPECTION AND INVESTIGATION COSTS

All field inspection and investigation costs are generated by FDA's Office of Regulatory Affairs (ORA). ORA costs are incurred in both the ORA administrative office and the district offices (the "field"). The primary human drug review activities performed in the field are inspections of manufacturing facilities, investigations of clinical studies, and analytical testing of samples. The Agency accumulates ORA fee related cost data through the use of the Program Oriented Data System (PODs). PODs is a time tracking system which captures both CDER and CBER pre-approval inspection, investigation, and analytical hours.

The ORA user fee related costs are calculated from the amount of FTEs (full time equivalents, or staff years of effort) used in the human drug review process. Based upon a description of the work performed in PODs (which is tracked by Program Assignment Code), the Agency accumulates total direct hours incurred on pre-approval activities related to the human drug review process. Total direct hours are used to calculate the total number of FTEs required by ORA to perform these activities. In addition to the direct FTEs, an allocation of support FTEs is also included to represent the work done by the ORA administrative/management personnel. The Agency then applies the total number of user fee related FTEs to the average salary cost in ORA to arrive at ORA user fee related salary costs. The final step is to allocate ORA obligations for operations and rent to the human drug review process based upon the level of user fee related FTEs to total ORA FTEs. The following table summarizes the calculation for the FYs ended September 30, 1992, 1993, 1994, 1995, 1996, and 1997.

PROCESS RELATED COSTS FOR THE OFFICE OF REGULATORY AFFAIRS

	Adjusted 1992	1993	1994	1995	1996	1997
	126.51	134.36	126.4	184.06	185	171
Average Salary and Benefits in ORA	$46,023	$47,713	$51,083	$54,654	$56,435	$60,585
Process Related Salary and Benefits	5,822,403	6,410,696	6,456,849	10,059,623	10,440,549	10,360,041
Process Related Operations and Rent	2,572,314	2,644,248	2,281,468	4,994,200	4,912,813	4,489,663
FY 1992 Adjustment	410,817					
ORA PROCESS RELATED COSTS	$8,805,534	$9,054,944	$9,038,316	$15,053,823	$15,362,362	$14,849,704

AGENCY GENERAL AND ADMINISTRATIVE COSTS

The agency general and administrative costs are generated in the FDA's Office of the Commissioner (OC). OC is comprised of the following offices:

- Immediate Office of the Commissioner
- Office of Policy
- Office of External Affairs
- Office of Management and Systems

The OC costs applicable to the process for the review of human drugs was calculated per a method developed by the Division of Cost Determination Management, Office of Finance, Office of the Secretary, Department of Health and Human Services. The method calls for an allocation based on the total salary obligations of the Agency's operations. The calculated allocation rate is applied to the combined salaries applicable to the process for the review of human drugs in CDER, CBER, and ORA to arrive at the OC allocation.

Accordingly, $12,562,099 and $23,610,630 in OC obligations were allocated to the human drug review process in FYs 1992, as adjusted, and 1997 respectively. Although the OC costs applicable to the process have increased, this is due to the large increase in salary costs for CDER, CBER, and ORA, the actual rate of Agency General and Administrative costs to total costs for CDER, CBER, and ORA is 11% in FY 1997, the same percentage it was in FY 1992.