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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Establishment of Prescription Drug User Fee Rates for Fiscal Year 2005

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the rates for prescription drug user fees for fiscal year (FY) 2005. The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Prescription Drug User Fee Amendments of 2002 (PDUFA III), authorizes FDA to collect user fees for certain applications for approval of drug and biological products, on establishments where the products are made, and on such products. Base revenue amounts for application fees, establishment fees, and product fees for FY 2005 were established by PDUFA III. Fees for applications, establishments, and products are to be established each year by FDA so that revenues from each category will approximate the levels established in the statute, after those amounts have been first adjusted for inflation and workload. This notice establishes fee rates for FY 2005 for application fees ($672,000 for an application requiring clinical data, and $336,000 for an application not requiring clinical data or a supplement requiring clinical data), establishment fees ($262,200), and product fees ($41,710). These fees are effective on October 1, 2004, and will remain in effect through September 30, 2005. For applications and supplements that are submitted on or after October 1, 2004, the new fee schedule must be used. Invoices for establishment and product fees for FY 2005 will be issued in August 2004, using the new fee schedule.

FOR FURTHER INFORMATION CONTACT: Frank Claunts, Office of Management (HFA–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4427.

SUPPLEMENTARY INFORMATION:

I. Background

Sections 735 and 736 of the act (21 U.S.C. 379g and h), establish three different kinds of user fees. Fees are assessed on: (1) Certain types of applications and supplements for approval of drug and biological products, (2) certain establishments where such products are made, and (3) certain products (21 U.S.C. 379h(a)). When certain conditions are met, FDA may waive or reduce fees (21 U.S.C. 379h(d)).

For FY 2003 through 2007 base revenue amounts for application fees, establishment fees, and product fees are established by PDUFA III (title 5 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002). Base revenue amounts established for years after FY 2003 are subject to adjustment for inflation and workload. Fees for applications, establishments, and products are to be established each year by FDA so that revenues from each category will approximate the levels established in the statute, after those amounts have been first adjusted for inflation and workload. The revenue levels established by PDUFA III continue the arrangement under which one-third of the total user fee revenue is projected to come from each of the three types of fees: Application fees, establishment fees, and product fees.

This notice establishes fee rates for FY 2005 for application, establishment, and product fees. These fees are effective on October 1, 2004, and will remain in effect through September 30, 2005.

II. Revenue Amount for FY 2005, and Adjustments for Inflation and Workload

A. Statutory Fee Revenue Amounts

PDUFA III specifies that the fee revenue amount for fiscal year 2005 for each category of fees (application, product, and establishment) is $84,000,000, for a total of $252,000,000 from all three categories of fees (21 U.S.C. 379h(b), before any adjustments are made.

B. Inflation Adjustment to Fee Revenue Amount

PDUFA III provides that fee revenue amounts for each fiscal year after 2003 shall be adjusted for inflation. The adjustment must reflect the greater of: (1) The total percentage change that occurred in the consumer price index (CPI) (all items; U.S. city average) during the 12-month period ending June 30 preceding the fiscal year for which fees are being set, or (2) the total percentage pay change for the previous fiscal year for Federal employees stationed in the Washington, DC, metropolitan area. PDUFA III provides for this annual adjustment to be cumulative and compounded annually after FY 2003 (see 21 U.S.C. 379h(c)(1)).

The inflation increase for FY 2004 was 4.27 percent. This was the greater of the CPI increase during the 12-month period ending June 30 preceding the fiscal year for which fees are being set (June 30, 2003—which was 2.11 percent) or the increase in pay for the previous fiscal year (2003 in this case) for Federal employees stationed in the Washington, DC, metropolitan area (4.27 percent).

The inflation increase for FY 2005 is 4.42 percent. This is the greater of the CPI increase during the 12-month period ending June 30 preceding the fiscal year for which fees are being set (June 30, 2004—which was 3.27 percent) or the increase in pay for the previous fiscal year (2004 in this case) for Federal employees stationed in the Washington, DC, metropolitan area (4.42 percent).

Compounding these amounts (1.0427 times 1.0442) yields a total compounded inflation adjustment of 8.88 percent for FY 2005.

The inflation adjustment for each category of fees for FY 2005 is the statutory fee amount ($84,000,000) increased by 8.88 percent, the inflation adjuster for FY 2005. The FY 2005 inflation-adjusted revenue amount is $91,459,200 for each category of fee, for a total inflation-adjusted fee revenue amount of $274,377,600 in FY 2005.

C. Workload Adjustment to Inflation Adjusted Fee Revenue Amount

For each fiscal year beginning in FY 2004, PDUFA III provides that fee revenue amounts, after they have been adjusted for inflation, shall be further adjusted to reflect changes in workload for the process for the review of human drug applications (see 21 U.S.C. 379h(c)(2)).

The conference report accompanying PDUFA III, House of Representatives report number 107–481, provides additional instructions on how the workload adjustment provision of PDUFA III is to be implemented. Following that guidance, FDA calculated the average number each of the four types of applications specified in the workload adjustment provision (human drug applications, commercial investigational new drug applications (INDs), efficacy supplements, and manufacturing supplements) received over the 5-year period that ended on June 30, 2002 (base years), and the average number of each of these types of applications over the most recent 5-year period that ended June 30, 2004.

The results of these calculations are presented in the first 2 columns of table 1 of this document. Table 1, column 3 of this document, reflects the percent

change in workload over the two 5-year periods and column 4 shows the weighting factor for each type of application, reflecting how much of the total FDA drug review workload was accounted for by each type of application in the table during the most recent 5 years. This weighting factor was developed by averaging data generated in a 2002 KPMG study of FDA's drug review workload and data from FDA's time reporting systems to submission data for the most recent 5-year period. Column 5 of table 1 of this document, is the weighted percent change in each category of workload, and was derived by multiplying the weighting factor in each line in column 4 by the percent change from the base years in column 3. At the bottom right of table 1 of this document, the sum of the values in column 5 is added, reflecting a total change in workload of 1.47 percent for FY 2005.

TABLE 1.—WORKLOAD ADJUSTER CALCULATION

Application Type	Summary of Workload Adjustment Calculations				
	Column 1 5-year Average Base Years	Column 2 Latest 5-year Average	Column 3 Percent Change	Column 4 Weighting Factor	Column 5 Weighted % Change
New drug application/biological licence application	119.6	120.4	0.7%	42.5%	0.28%
Commercial INDs	629.8	626.6	-0.5%	41.7%	-0.21%
Efficacy supplements	159.2	166.8	4.8%	5.9%	0.28%
Manufacturing supplements	2100.6	2336.8	11.2%	9.9%	1.12%
FY 2005 workload adjuster					1.47%

Increasing the inflation-adjusted revenue amount of $91,459,200 for each category of fee by the FY 2005 workload adjuster (1.47 percent) results in an increase of $1,344,450, for a total inflation and workload adjusted revenue amount for each fee category of $92,803,650. The total FY 2005 inflation and workload adjusted fee revenue target for all three fee categories combined is $278,410,950.

III. Application Fee Calculations

PDUFA III provides that the rates for application, product, and establishment fees be established 60 days before the beginning of each fiscal year (21 U.S.C. 379h(c)(4)). The fees are to be established so that they will generate the fee revenue amounts specified in the statute, as adjusted for inflation and workload.

A. Application Fee Revenues and Application Fees

The application fee revenue amount that PDUFA III established for FY 2005 is $92,803,650, as calculated in the previous section. Application fees will be set to generate this amount.

B. Estimate of Number of Fee-Paying Applications and Establishment of Application Fees

For FY 2003 through 2007, FDA will estimate the total number of fee-paying full application equivalents (FAEs) it expects to receive the next fiscal year by averaging the number of fee-paying FAEs received in the 5 most recent fiscal years. This use of the rolling average of the 5 most recent fiscal years is the same method that was applied in making the workload adjustment.

In estimating the number of fee-paying FAEs that FDA will receive in FY 2005, the 5-year rolling average for the most recent 5 years will be based on actual counts of fee-paying FAEs received for FYs 2000 through 2004. For FY 2004, FDA is estimating the number of fee-paying FAEs for the full year based on the actual count for the first 9 months and estimating the number for the final 3 months.

Table 2, column 1 of this document, shows the total number of each type of FAE received in the first 9 months of FY 2004, whether fees were paid or not. Table 2, column 2 of this document shows the number of FAEs for which fees were waived or exempted during this period, and column 3 shows the number of fee-paying FAEs received through June 30, 2004. Column 4 estimates the 12-month total fee-paying FAEs for FY 2004 based on the applications received through June 30, 2004. All of the counts are in FAEs. A full application requiring clinical data counts as one FAE. An application not requiring clinical data counts one-half an FAE, as does a supplement requiring clinical data. An application that is withdrawn or refused for filing counts as one-fourth of an FAE if it initially paid a full application fee, or one-eighth of an FAE if it initially paid one-half of the full application fee amount.

TABLE 2.—FY 2004 FAES RECEIVED THROUGH JUNE 30, 2004, AND PROJECTED THROUGH SEPTEMBER 30, 2004

Application or Action	Column 1 Total Received Through June 30, 2004	Column 2 Fee Exempt or Waived Through June 30, 2004	Column 3 Total Fee Paying Through June 30, 2004	Column 4 12 Month Projection
Applications requiring clinical data	78.0	24.0	54.0	72.0
Applications not requiring clinical data	11.5	4.0	7.5	10.0
Supplements requiring clinical data	53.5	5.0	48.5	64.7

TABLE 2.—FY 2004 FAEs RECEIVED THROUGH JUNE 30, 2004, AND PROJECTED THROUGH SEPTEMBER 30, 2004—Continued

Application or Action	Column 1 Total Received Through June 30, 2004	Column 2 Fee Exempt or Waived Through June 30, 2004	Column 3 Total Fee Paying Through June 30, 2004	Column 4 12 Month Projection
Withdrawn or refused to file	0.25	0.0	0.25	0.3
Total	143.25	33.0	110.25	147.0

In the first 9 months of FY 2004 FDA received 143.25 FAEs, of which 110.25 were fee-paying. Based on data from the last seven FYs, on average, 25 percent of the applications submitted each year come in the final 3 months. Dividing 110.25 by 3 and multiplying by 4 extrapolates the amount to the full 12 months of the fiscal year and projects the number of fee-paying FAEs in FY 2004 at 147.

All pediatric supplements, which had been exempt from fees prior to January 4, 2002, were required to pay fees effective January 4, 2002. This is the result of section 5 of the Best Pharmaceuticals for Children Act that repealed the fee exemption for pediatric supplements effective January 4, 2002. Thus, in estimating FY 2004 fee-paying receipts, we must add all the pediatric supplements that were previously exempt from fees prior to January 4, 2002. The exempted number of FAEs for pediatric supplements for FY 2000, FY 2001, and FY 2002, respectively, were 12.5, 19, and 4.5. Since fees on these supplements are paid for pediatric applications submitted in FY 2004 and beyond, the number of pediatric supplement FAEs exempted from fees each year from FY 2000 through 2002 (the years in table 3 of this document when fees were exempted) are added to the total of fee-paying FAEs received each year.

As table 3 of this document shows, the average number of fee-paying FAEs received annually in the most recent 5-year period, assuming all pediatric supplements had paid fees, and including our estimate for FY 2004, is 138.1 FAEs. FDA will set fees for FY 2005 based on this estimate as the number of FAEs that will pay fees.

TABLE 3.—FEE-PAYING FAE—5-YEAR AVERAGE

Year	2000	2001	2002	2003	2004	5-year Average
Fee-paying FAEs	153.0	107.6	127.6	119.5	147.0	130.9
Exempt pediatric supplement FAEs	12.5	19.0	4.5	0.0	0.0	7.2
Total	165.9	126.6	132.1	119.5	147.0	138.1

The FY 2005 application fee is estimated by dividing the average number of full applications that paid fees over the latest 5 years, 138.1, into the fee revenue amount to be derived from application fees in FY 2005, $92,803,650. The result, rounded to the nearest one hundred dollars, is a fee of $672,000 per full application requiring clinical data, and $336,000 per application not requiring clinical data or per supplement requiring clinical data.

IV. Adjustment for Excess Collections in Previous Years

Under the provisions of PDUFA, as amended, if the agency collects more fees than were provided for in appropriations in any year after 1997, FDA is required to reduce its anticipated fee collections in a subsequent year by that amount (21 U.S.C. 379h(g)(4)). In FY 1998, Congress appropriated a total of $117,122,000 to FDA in PDUFA fee revenue. To date, collections for FY 1998 total $117,737,470—a total of $615,470 in excess of the appropriation limit. This is the only fiscal year since 1997 in which FDA has collected more in PDUFA fees than Congress appropriated.

FDA also has some requests for waivers or reductions of FY 1998 fees that have been decided but that are pending appeals. For this reason, FDA is not reducing its FY 2005 fees to offset excess collections at this time. An offset will be considered in a future year, if FDA still has collections in excess of appropriations for FY 1998 after the pending appeals for FY 1998 waivers and reductions have been resolved.

V. Fee Calculations for Establishment and Product Fees

A. Establishment Fees

At the beginning of FY 2004, the establishment fee was based on an estimate that 354 establishments would be subject to and would pay fees. By the end of FY 2004, FDA estimates that 379 establishments will have been billed for establishment fees, before all decisions on requests for waivers or reductions are made. FDA again estimates that a total of 25 establishment fee waivers or reductions will be made for FY 2004, for a net of 354 fee-paying establishments. FDA will use this same number again, 354, for its FY 2005 estimate of establishments paying fees, after taking waivers and reductions into account. The fee per establishment is determined by dividing the adjusted total fee revenue to be derived from establishments ($92,803,650) by the estimated 354 establishments, for an establishment fee rate for FY 2005 of $262,200 (rounded to the nearest one hundred dollars).

B. Product Fees

At the beginning of FY 2004, the product fee was based on an estimate that 2,225 products would be subject to and pay product fees. By the end of FY 2004, FDA estimates that 2,260 products will have been billed for product fees, before all decisions on requests for waivers or reductions are made. Assuming that there will be about 35

waivers and reductions granted, FDA estimates that 2,225 products will qualify for product fees in FY 2004, after allowing for waivers and reductions, and will use this number for its FY 2005 estimate. Accordingly, the FY 2005 product fee rate is determined by dividing the adjusted total fee revenue to be derived from product fees ($92,803,650) by the estimated 2,225 products for a FY 2005 product fee of $41,710 (rounded to the nearest ten dollars).

VI. Fee Schedule for FY 2005

The fee rates for FY 2005 are set out in table 4 of this document:

TABLE 4.

Fee Category	Fee Rates for FY 2005
Applications	
Requiring clinical data	$672,000
Not requiring clinical data	$336,000
Supplements requiring clinical data	$336,000
Establishments	$262,200
Products	$41,710

VII. Implementation of Adjusted Fee Schedule

A. Application Fees

The appropriate application fee established in the new fee schedule must be paid for any application or supplement subject to fees under PDUFA that is received after September 30, 2004. Payment must be made in U.S. currency by check, bank draft, or U.S. postal money order payable to the Food and Drug Administration. Please include the user fee identification (ID) number on your check. Your payment can be mailed to: Food and Drug Administration, P.O. Box 360909, Pittsburgh, PA 15251–6909

If checks are to be sent by a courier that requests a street address, the courier can deliver the checks to: Food and Drug Administration (360909), Mellon Client Service Center, rm. 670, 500 Ross St., Pittsburgh, PA 15262–0001. (Note: This Mellon Bank address is for courier delivery only.)

Please make sure that the FDA post office box number (P.O. Box 360909) is written on the check. The tax ID number of the FDA is 530 19 6965.

B. Establishment and Product Fees

By August 31, 2004, FDA will issue invoices for establishment and product fees for FY 2005 under the new fee schedule. Payment will be due on October 1, 2004. FDA will issue invoices in October 2005 for any products and establishments subject to fees for FY 2005 that qualify for fees after the August 2004 billing.

Dated: July 27, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Mouse Model of PRKAR1A Down-Regulation

Constantine Stratakis *et al.* (NICHD); DHHS Reference No. E–266–2004/0—Research Tool; Licensing Contact: Mojdeh Bahar; 301/435–2950; *baharm@mail.nih.gov.*

The invention represents the first animal model of cyclic AMP (cAMP)-induced tumorigenesis, and the first animal model of protein kinase A (PKA)-related tumorigenesis. The cAMP/PKA system is of seminal importance for cellular function and signaling, and is involved in many systems and diseases. This discovery is expected to facilitate the development of drugs useful in treating endocrine and other tumors.

Compositions and Methods for Diagnosis and Treatment of Chemotherapy-Resistant Neoplastic Disease

John Park (NINDS); U.S. Provisional Application No. 60/571,296 filed 15 May 2004 (DHHS Reference No. E–192–2004/0–US–01); Licensing Contact: Jesse S. Kindra; 301/435–5559; *kindraj@mail.nih.gov.*

The present invention relates to compositions and methods for the treatment of a neoplastic disease state (*i.e.,* tumors) using RNA interference-mediated down regulation of stathmin expression. This invention also discloses methods for determining the presence or predisposition to a neoplastic disease state.

Stathmin is a cytoplasmic protein that is highly expressed in many different types of tumors such as leukemias, lung cancers and brain tumors. Stathmin is believed to be involved in the regulation of the cell cycle via its interactions with microtubules. Lowering the expression of stathmin in tumor cells using RNA interference (RNAi) technology causes a decrease in tumor cell growth and also causes such cells to become more sensitive to the effects of standard chemotherapeutic agents.

Accordingly, the delivery of stathmin RNAi oligonucleotides either alone or in combination with standard chemotherapies may be used to treat patients with various tumors. For example, retroviruses or adeno-associated viruses containing stathmin RNAi oligonucleotides could be delivered to brain tumors in order to