Report to Congress on the Timeliness and Effectiveness of Device Premarket Reviews

Prepared for:

Committee on Commerce, Subcommittee on Health and the Environment and
Committee on Health, Education, Labor and Pensions

Prepared By:

The Secretary of the Department of Health and Human Services

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Executive Summary

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), Public Law 107-250, was passed by Congress on October 26, 2002. Section 205 of MDUFMA requires the Secretary of Health and Human Services to report on the following:

> …the timeliness and effectiveness of device premarket reviews by centers other than the Center for Devices and Radiological Health. Such report shall include information on the times required to log in and review original submissions and supplements, times required to review manufacturers' replies to submissions, and times to approve or clear such devices. Such report shall contain the Secretary's recommendations on any measures needed to improve performance including, but not limited to, the allocation of additional resources. Such report also shall include the Secretary's specific recommendations on whether responsibility for regulating such devices should be reassigned to those persons within the Food and Drug Administration who are primarily charged with regulating other types of devices, and whether such a transfer could have a deleterious impact on the public health and on the safety of such devices.

I want to thank the Congress for this opportunity to report on review of medical devices by the Food and Drug Administration (FDA). I appreciate the help that the Congress has provided to enable FDA to improve its performance in review of medical devices through the provisions of the MDUFMA. Additionally, I appreciate the contribution that was made to this effort by the industry stakeholders who provided honest criticism of past review practices, and thereby helped show us a way forward to make improvements.

Medical devices play a key role in our health care system. I am committed to ensuring that safe and effective devices are approved in a timely manner. I am pleased to report that there has been substantial improvement in device reviews by FDA. Under MDUFMA, FDA has begun to hire new employees because of user fees provided in the legislation and to implement measures that improve device review without compromising safety. Although most devices are reviewed by the Center for Devices and Radiological Health (CDRH), a small proportion of devices that are mostly critical to ensuring the safety, purity, and potency of biological products, including ensuring the safety of our nation's supply of blood and human tissue products, are reviewed at the Center for Biologics Evaluation and Research (CBER). Additionally, CBER regulates diagnostic tests for retroviruses, including Human Immunodeficiency Virus (HIV), as well as devices used in the manufacture of cell and gene therapies for which CBER is responsible.

I am pleased to report that CBER has put to use the initial MDUFMA resources and reallocated base resources to make substantial investments in training and management. These investments, combined with an outstanding effort on the part of the review staff, have resulted in substantial and striking improvements in device review performance. This report provides information on the timeliness and effectiveness of device review in CBER. This report shows that for the devices received thus far, not only has CBER met the MDUFMA performance goals (Appendix 1) for

FY2003, CBER has already met or exceeded the goals for FY2005[1] (see table below). Because of the impressive improvements in the timeliness of device review and the critical role these devices play in ensuring the safety, purity, and potency of biological products, in particular the safety and availability of the nation's blood supply and human tissues, I am recommending that review of these devices remain at CBER. While FDA (including CBER) is committed to enhancing device review, it is important to realize that, in the absence of continued and adequate funding, the improvements achieved to date cannot be sustained.

SUMMARY OF CBER PERFORMANCE IN MEETING MDUFMA GOALS

Marketing Application	***Number of Applications***	***FY'05 Goals Met in FY'03 (%)***
PMAs, Panel-Track Supplements, PDPs, PMRs	***2***	***100***
Expedited PMAs	***0***	***N/A***
180-Day PMA Supplements	***2***	***100***
510(k)s	***45***	***100***
BLAs, BLSs, and Resubmissions	***77***	***100***

[1] It should be noted that some of the numbers in the report are small, due to the relatively few applications received in CBER during this reporting period.

Secretary's Recommendations

The review performance reported herein for CBER is evidence of the positive effect that CBER's commitment to improvement accompanied by continued and expanded Congressional support of MDUFMA can exert on timeliness and effectiveness of medical device reviews at FDA. Improvement is seen in review times at both CBER and CDRH as will be evident in the MDUFMA Annual Report (pending). CBER and CDRH both apply medical device regulations, and the implementation of MDUFMA has supported improved and more consistent processes at both Centers. Because the approach applied by CBER integrates policy development, device review, and oversight of the blood and tissue establishments, and cell and gene therapies, it is important for public health and patient safety that devices used in testing and manufacturing biological products should remain the responsibility of CBER.

CBER has instituted organizational and cultural changes under MDUFMA in response to positive interactions with, and input from, the regulated industry and other stakeholders, and has committed itself to continue this process. Through its implemented changes, CBER has demonstrated that it has the ability to provide timely review of device submissions, consistent with the MDUFMA goals, with the value added of integration into the blood system in a paradigm that is also applied to the regulation of cellular and tissue products. Additionally, CBER has shown improved performance in review and approval of HIV-related diagnostic tests. However, it must be noted that, without the additive resources provided by the MDUFMA program, these results would not have been possible. The additional resources from MDUFMA remain critical in order to sustain and build upon these improvements. I therefore offer the following recommendations:

1. The responsibility for devices currently regulated by CBER should remain at CBER.

2. The resources from MDUFMA should be used to facilitate electronic processing of submissions, continue and expand training in device regulation, including new MDUFMA related policies, and further the development of Quality Control/Quality Assurance programs for the review process.

Timeliness and Effectiveness of Medical Device Review at CBER

I. Overview of Medical Device Review at CBER

As Congress noted, the majority of devices reviewed by FDA are reviewed by CDRH. A smaller proportion of devices that are critical to ensuring the safety, purity, and potency of biological products, including the nation's supply of blood products, retroviral (e.g., HIV) diagnostics, and human tissues used for transplantation are regulated by CBER.

Because CBER is responsible for the oversight of blood and tissue products as well as the devices used in the testing and manufacture of these biological products, the Center can use an integrated approach to their regulation. This integrated approach incorporates review of the products, the devices and development of policies applied to use of the devices, and the marketing of critical biological products, such as blood and tissues, in a risk-based manner, to ensure their continued safety and effectiveness. CBER's regulation of devices related to blood safety illustrates how this integrated approach can contribute to good outcomes for public health. Because the devices regulated by CBER are used to manufacture biological products such as red blood cells, platelets or plasma for transfusion, plasma for the manufacturing of blood derivatives or further manufacture, or devices to be used in the donor screening setting to ensure that blood products are safe, there are different considerations in reviewing and approving these particular products compared to devices typically regulated by CDRH. For example, CBER not only approves the HIV tests used to ensure the safety of blood products, but also requires that blood establishments and tissue establishments use appropriate FDA-approved donor screening tests to ensure blood safety. CBER's review of these tests, the determination of their needed specificity and sensitivity, and whether or not they should be used nationally for blood or tissue screening, are all part of the development of blood policy and help to ensure the widespread use of high quality devices that keep our blood supply safe.

CBER also regulates the collection practices of blood establishments through review of their Standard Operating Procedures and by inspection. CBER evaluates and clears for use the devices used to collect blood products, such as red blood cells, platelets, and plasma. The performance characteristics of these collection devices are critical to ensuring that the blood they are used to collect is safe, pure, and potent.

The continued regulation of *in vitro* diagnostic tests (IVDs) for screening of blood and plasma donors by CBER is crucial to its mission to prevent the entry of transfusion-transmitted infectious agents into the blood supply. Recent potential threats to the blood supply, such as West Nile Virus (WNV) have further illustrated the need for, as well as effectiveness and capacity of, CBER as a regulator of donor screening assays to respond rapidly to emerging infectious diseases affecting the safety of blood and blood products. During the epidemic of WNV in summer 2002 and following demonstration of transfusion transmission, DHHS rapidly called for and facilitated the development of donor screening tests under the investigational new drug (IND) exemption to screen for WNV in blood and plasma donors. FDA worked closely with the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and blood organizations to study the risk of WNV from blood transfusion and worked with device manufacturers and industry organizations to promote rapid development of candidate donor screening tests. For example, FDA sponsored a

public workshop in November 2002 to identify and remove barriers to rapid test development. Also, FDA is developing reagent standards that will be used to ensure appropriate sensitivity of WNV donor screening tests that may become licensed. As a result of all of these efforts and partnerships, two device manufacturers began shipping investigational test kits to blood establishments in June 2003 in order to allow for widespread screening of blood under IND by July 2003. Positive test results in some donors already have resulted in preventing exposure of blood recipients to WNV, a remarkable achievement by industry and the FDA in less than a year after the identification of a new and unexpected threat.

Similar circumstances apply to the regulation of cell, tissue, and gene therapy products. On October 1, 2002, CBER formed the Office of Cellular, Tissue, and Gene Therapies (OCTGT), due to the increase in activities in the areas of cellular and tissue-based products, gene therapies, xenotransplantation, and combination products containing living cells or tissues providing the primary mode of action. Since devices often play a very important role related to cell or tissue products, it is important that OCTGT have oversight of these devices to ensure the safety and, if appropriate, the effectiveness of novel cell and tissue products. Keeping review of these products in one Office allows coordination and consistency so that regulatory decisions are risk-based and do not place unnecessary burdens on manufacturers of innovative products. OCTGT draws on its expertise and experience in molecular and cell biology, tissue and organ regeneration, and developmental biology in order to work closely with academia, industry, and consumers to provide flexible regulation in such a swiftly evolving and promising field. Consolidation of these products, including the devices, into one Office allows seamless and transparent coordination, communication, and regulation. The continuing regulation of devices used in processing cells, tissues, or cellular or tissue-based products by CBER is necessary to ensure the safety of these products which are commonly used in cellular transplants and to treat a number of diseases. Increased and routine teamwork and collaboration with CDRH and training in device review principles (e.g., least burdensome) is already underway to enhance consistency and quality of device review in OCTGT.

II. Increased Effectiveness and Timeliness of Medical Device Reviews in CBER

The increased effectiveness of device review in CBER is illustrated by the product approvals and clearances in the first three quarters of FY2003 (applications received through June 30) listed in Appendix 2 of this document. In many cases, these approvals relate directly to innovations that enhance the safety and efficacy of blood and tissue products. Timely approvals included the implementation of modular Premarket Approval Applications (PMA). Examples of recent timely approvals that have had a significant impact on public health included two rapid HIV tests (OraQuick and Reveal); Clinical Laboratory Improvement Act (CLIA) waiver of the OraQuick rapid HIV test; approval of Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) nucleic acid tests (NAT) for donor screening; rapid development and implementation under IND of donor screening for WNV by NAT; and two quality control devices for detection of bacterial contamination in platelets.

Additionally, CBER expertise in retrovirus marker detection and related fields has contributed to effective regulation of HIV diagnostic tests. Recent approval of rapid tests for HIV and tests to

monitor HIV drug resistance are recent examples of successful regulation at CBER under the frameworks established by the MDUFMA.

Devices Critical to Safety, Quality, and Effectiveness of Biological Products

Medical devices may be critical to ensuring the safety, purity, and potency of related biological products. In particular, blood and tissue safety have broad public health impact with high public interest and scrutiny. Each year, approximately 14 million units of blood are collected from about 8.5 million donors for transfusion into about 4.5 million recipients. The public has come to rely on critical life-saving transfusions. The safety of the blood supply is particularly important to those with weakened immune systems, including the elderly, HIV and cancer patients, and organ transplant recipients. An additional one million units of blood are collected for autologous transfusion. Also, approximately 14 million units of Source Plasma are collected from about 1.5 million donors for further manufacture into plasma derivatives, such as clotting factors to treat hemophilia, immune globulins to treat immune deficiencies, and many other life saving or enhancing products. In addition, about 48,000 donors of ocular tissues, such as corneas, and about 20,000 donors of other "conventional" tissues, such as bones, tendons, ligaments, and vascular tissues provide products that are transplanted into about 850,000 recipients per year. Also, there are about 6,000 recipients annually of unrelated stem cells. These transplantations are life enhancing and/or life saving. Assuring availability of safe blood and tissue products is also important in the medical response to terrorist events and combat situations.

Devices that CBER regulates include devices used by blood establishments to collect different cell types for transfusion or transplantation, tests used by blood establishments for typing blood to allow safe transfusion, tests used by blood and tissue establishments for infectious agents, such as HIV or HCV, blood bank software, and blood and fractionation equipment, such as apheresis machines and their filters used by blood establishments to collect blood or by manufacturers to make blood derivatives. CBER has also had a prominent role in the regulation of cell separators/selectors/purging/expansion devices and cell or blood freezing containers. These medical devices directly affect recipients of the final biological products and tissues, such as red blood cells, bone marrow, stem cells, umbilical cord blood cells, mesenchymal cells, and other cells and tissues. Although many examples are from blood and its products, the numbers of notifications and applications for devices related to tissue and cell products are increasing, and CBER expects that similar considerations will apply to those products as they develop.

Integrating the review of blood- and tissue-related devices helps to address the high public health interest in safe products. For example, FDA uses a multi-layer approach to ensuring the safety of the 14 million units of blood collected each year, including the following:

- Blood donors are screened for risk factors for infectious agents through a detailed questionnaire designed to screen out donors who might have exposure to infectious disease agents.

- Then these apparently healthy low risk donors are tested for certain infectious diseases, including HIV and hepatitis viruses. Tests for blood donor screening must be extremely sensitive and specific to detect infectious agents in a low risk population.

Tests designed to perform properly in the donor collection setting have different design and performance considerations than diagnostic tests used in a doctor's office. The donor screening tests used in blood collection that are reviewed by CBER must perform to a very high level in a "low risk" population of about 8.5 million blood donors per year to prevent infected blood or tissues from being used, while avoiding unnecessarily excluding needed donors or discarding these life-saving or life-enhancing products. Diagnostic tests, which are generally reviewed by CDRH, are typically performed in a doctor's office, or under a physician's orders, where there is a one-to-one medical relationship, and when there is a medical suspicion or symptoms that suggest testing is warranted. The results of these tests are then used in the context of the patient's entire clinical picture. In these settings, a diagnosis is made with awareness of the total information available to the doctor. In some cases, the doctor's decisions are made based on test values (quantity) and a comparison with subsequent results may also be used. Retesting may also be warranted if the diagnosis is unclear. In the blood or tissue donor setting, if the donor passes the donor screening and testing procedures, the blood or tissue is then used to treat a patient. There are usually no second chances. Tests designed to perform properly in a diagnostic setting may not be appropriate for the blood bank setting.

Integrated Decision Making System

Because CBER regulates both the entities that collect blood and tissues and related devices, CBER utilizes an integrated approach to decision-making where performance and availability of the devices helps develop the policies used to regulate the industry.

For example, CBER requires that blood establishments or tissue establishments use test kits approved, cleared, or licensed by the FDA. Current regulations require that "one or more tests" be used as adequate and appropriate to ensure that blood is safe. These regulations provide flexibility so that technological advances and newly approved tests with better performance characteristics replace older tests. CBER recently issued a draft guidance document stating that the agency interpreted "adequate and appropriate" blood donor testing to require testing with newly approved HIV and HCV nucleic acid tests to screen blood donors. With implementation of these nucleic acid tests, blood establishments will no longer be required to use the far less sensitive HIV p24 antigen test, thereby achieving cost and time savings. By facilitating the development of nucleic acid testing technology to the point that it has become an approved product, FDA helped bring more sensitive technology to bear on closing the "HIV window." The result is a safer blood supply and the elimination of requirements for a less effective test. The clearance of a new test, the removal of the requirement for a less sensitive test, and proper implementation at blood establishments demonstrates the value of the integrated approach to biological products and their related devices. This approach also helps encourage innovation and speed implementation of quality and safety improvements. Other examples are:

- Blood screening tests are also used for donor management decisions, such as re-entry after a false positive screen, and for product management decisions, such as in-process testing, quarantine, and "lookback" product retrieval. Managing the entire blood system approvals in one administrative unit permits CBER to integrate results from a new test into algorithms or guidance for blood establishments making licensed blood products.

- CBER has promoted improvements in blood donor screening tests by requiring that newly approved tests perform at least as well as, if not better than, existing tests.

- CBER approves or clears the devices used to collect blood products, such as red cells, platelets, or plasma (apheresis). The device design and performance bears directly on the identity and quality of the licensed product.

- CBER uses product reviews, scientific workshops, standards development, and advisory committee recommendations to integrate IVDs into the blood system for maximum public health benefit.

- Since blood-related screening tests are generally designed for automation in handling, high throughput, and non-subjective readouts compatible with blood establishments, a working knowledge of the blood manufacturing process is necessary for the adequate and efficient review of these medical devices and their successful incorporation into the blood system.

- CBER also recommends or requires certain tests to be used in manufacturing biological products. The same advisory committee that would be consulted for recommendations for required tests would also be consulted on development of needed tests and, if appropriate, charged as a device panel for device recommendations.

CBER Expertise in Blood and Blood Borne Infectious Diseases

CBER has specific laboratory expertise in retroviral and hepatitis testing and test kit performance. This expertise has allowed CBER to assist device manufacturers in blood screening test development and even widespread use of experimental test technologies. Recent examples concerning nucleic acid testing for HIV and screening tests for WNV have already been discussed. In addition, CBER participates twice weekly in conference calls with CDC on monkeypox and other emerging diseases to monitor possible transmission by blood transfusion. Through its scientific collaborations, CBER is ready and able to recommend steps to ensure blood safety, including, where needed, blood-screening protocols, as has been shown by its responses to the recent outbreaks of anthrax, WNV, and SARS.

CBER's test kit-related laboratory expertise has been significant in working with partners to resolve public health problems. For example:

- When necessary to protect the public health, CBER laboratories performed infectious disease lot release testing to prevent transmissions of HCV through plasma derivatives. This

testing was performed until CBER could assist manufacturers in implementing the scientific methods necessary to perform their own lot release testing.

- CBER has been engaged in infectious disease testing when needed to ensure the safety of products as a result of reports of possible contamination or as part of investigations. For example, CBER scientists performed tests to rule out possible contamination of polio vaccine by HIV or its simian variant, SIV.

- CBER has established panels of serum samples used to set performance standards for product approval when this was the most efficient approach to approve a product critical to blood safety. For example, CBER led a multi-laboratory scientific effort to approve the Human T-Lymphotropic Virus (HTLV) test kits based on HTLV samples provided by different research laboratories. A similar effort is presently ongoing to establish standards for WNV.

- CBER has established lot release panels to ensure test kit performance. The World Health Organization adopted some of these standards as international standards.

- CBER used the lot release panels to ensure that all test kits perform at levels comparable to those achievable by contemporary technology.

III. Program Improvements in Device Review at CBER under MDUFMA

CBER recognized that increased performance in device review is crucial to ensuring the safety of blood and tissue products and to facilitating innovation and improvement. MDUFMA offers the promise of increased resources to facilitate these performance enhancements. In order to improve performance and to best implement those increases resulting from user fees and appropriations, CBER has focused on improving its management of review performance with regard to devices. The passage of the Prescription Drug User Fee Act (PDUFA) in 1992 spurred improvements in the management of the review of covered products. Over the past 2 years, CBER, in particular blood and tissue review components, has made efforts to apply improvements in the management of device review using many of the principles of product review originally developed to facilitate the implementation of PDUFA.

Better Management

The leadership of CBER is committed to the improvement of device review in the Center and has taken steps to facilitate that improvement. An improved management structure was implemented after an organizational review by an outside consultant (including interviews with industry stakeholders) followed by strategic operational changes, team building, and individual coaching. As a result, the role of Division Directors, Lab/Branch Chiefs, and review staff were better defined, and internal processes were enhanced for greater efficiency. Project management techniques that were first employed in the review of PDUFA products were implemented for device review with cooperation from the Director's office. These techniques involved improvements in tracking systems and implementation of intermediate target dates for all reviews as well as clarification of

roles and responsibilities documented in written procedures. The Office of the Center Director instituted a regular reporting schedule on device review performance. This oversight provides CBER upper level management the information to identify potential problems and intervene to avoid them should it prove necessary. It also facilitates the quality control and quality assurance of the review process. The Office of the Center Director also placed a priority on the hiring of device reviewers using MDUFMA resources.

In recognition of the importance of the communication between FDA and those who develop important medical devices, CBER has increased its interactions with regulated industry. These interactions include meetings with individual developers themselves as well as communication with representative organizations. For example, CBER recently participated in the AdvaMed Medical Device Submissions Workshop, the Orange County Regulatory Affairs IVD Workshop, the IVD Industry Roundtable, the IVD Professional Society Roundtables, the IVD Roundtable 510(k) Workshop, and the Association for Medical Diagnostics Manufacturers Annual Meeting.

Paradigm Shift in the Review Process

The CBER Director has challenged CBER staff to make a commitment to the improvement of both the timeliness and the quality of device review within the Center. The results presented in this report indicate the willingness of CBER staff to accept that challenge. An important component of improved performance is an improved perspective on the type of interactions between FDA and the regulated industry. CBER reviewers are now strongly encouraged to emphasize problem solving, not just problem finding. The new staff message is to be problem solvers by finishing reviews earlier in the cycle to inform their supervisors, and to plan problem solving teleconferences or meetings. CBER implemented interim review targets in an effort to complete the reviews early in order to permit a major focus on problem solving within the later part of the review cycle (e.g., 30-day review meetings and 60-day action targets for 510(k)s, day-100 meetings with PMA sponsors). Despite the fact that some of the submissions are complex and may pose new challenges to clearing/approving/licensing them in one cycle because of deficiencies, the new approach has resulted in sharply reduced review times.

Management and Reviewer Training

In order to implement these changes, all reviewers and managers need to know their roles and the expectations regarding their performance in device review. As part of the commitment to the improvement of device review in CBER, Center management has been and continues to be involved in the development of various training programs designed to provide this information to managers and reviewers. All current device reviewers and managers received training in managed review procedures, least burdensome policies, and 510(k) review paradigms. A special segment of the Center's Basic Training for New Reviewers will address these principles.

More Efficient Document Handling

CBER review staff is located in a number of different sites. In the past, the time required to deliver applications to the appropriate reviewers was seen as an impediment to efficient review. Center management established a blue ribbon panel to identify possible approaches to these issues. As a

result, CBER improved the administrative processing of documents by initiating a new courier service for device submissions and counter-terrorism documents, and implementing a new comprehensive bar coded tracking of submission delivery. These improvements reduced FDA log-in time and improved tracking capabilities. The use of electronic submissions also contributed to decreased administrative processing and review times. The effectiveness of these measures is reflected in Section IV of this report.

Harmonization of Regulatory Practices with CDRH

In order to manage an effective medical device review program, CBER has dedicated significant staff time to harmonize device review and regulatory policies with CDRH to the extent practicable. Examples of harmonization for devices reviewed under the Medical Device authorities include:

- Least Burdensome Training. In the last year, all CBER device reviewers and managers of device reviews received training in the Least Burdensome approach to device review.

- MDUFMA guidances are issued jointly by both Centers.

CBER uses the 510(k) review paradigm. Data for traditional, abbreviated, and special 510(k)s are reported in Section IV.

- CBER participated with CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) in reviewing pre-investigational device exemption (IDE) questions and answers to assist sponsors in preparing IDEs.

- In June 2003, CBER's Office of Blood Research and Review (OBRR) and CDRH's OIVD held their second annual internal Best Practices Workshop addressing common issues.

- CBER has used the statutory mechanisms under Initial Classification and Reclassification of Certain Devices *"de novo* process" to classify a new medical device as a Class II device.

CBER has implemented CDRH PMA policies such as Day-100 Meetings (FDAMA), and modular PMAs.

  - Eight of the last nine original PMAs submitted were modular; and,

  - The last two PMAs having all modules submitted had day-100 meetings. In one case, this enabled the applicant to amend its application immediately, resulting in an approval on the 1st cycle. The second case was still pending in the first cycle when this report was written.

IV. The Timeliness of Medical Device Reviews in CBER

CBER used the multi-pronged approach (described above) during the first year of MDUFMA to reduce review times while maintaining high scientific standards during a time of additional

challenge from emerging infectious diseases and counter-terrorism concerns. Collectively, the activities described in Section III will provide, in fact have provided, a framework for CBER to meet the MDUFMA goals and enhance review timeliness. These activities also constitute a cultural paradigm shift towards more timely and effective communication and problem solving.

The report will first present FY 2003 performance compared to FY 2005 goals. This is because, although only one performance goal applies to FY 2003, CBER managed the review process to meet the more extensive FY 2005 goals. The results presented are for the time period October 1, 2002, through June 30, 2003, i.e., the first 9 months of FY 2003. Goals for the 5 years of MDUFMA will be presented, followed by charts with the FY 2003 results to date (first 3 quarters). Second, the report will present data on the parameters specified in Sec. 205, i.e., information on the times required to log in and review original submissions and supplements, times required to review manufacturers' replies to submissions, and times (and cycles) to approve or clear such devices.

Timeliness of Document Control Functions

Following are the times (in working days) recorded for device application processing in the Document Control Center (DCC) from Login to Checkout.

Beginning in mid-January 2003, CBER's Document Control Center (DCC) embarked upon streamlined life cycle records management to increase efficiencies and enhance procedures.

The following table documents the impact of enhancements to improve performance regarding device applications, supplements, and amendments received and processed through DCC. The table captures the average number of days between Login and Checkout.

	Total Number	**Average Days Login to Checkout**	**Number applications processed in**				
			1 day	**2 days**	**3 days**	**4 days**	**5 days**
510(k) / PMA / BLA							
Oct. – Dec. 2002	121	1.9	48	45	22	5	1
Jan. – June 2003	259	1.1	241	14	2	2	0

This table demonstrates an improvement in performance for getting new applications logged into the CBER system and sent to reviewers.

Timeliness of Device Review – MDUFMA Goals, Review Times and Cycles

CBER's review times, as well as the number of cycles to final actions, are presented in tables below. In an effort to provide a comprehensive picture of the Center's overall accomplishments in reviewing these applications, data on CBER's performance thus far with regard to the goals

committed to by the Secretary[2] are also provided. The goal data are presented in a manner similar to the reporting format used in the annual *Performance Report to Congress for the Prescription Drug User Fee Act of 1992.*

While most of the goals under MDUFMA are not effective until Fiscal Year 2005, it is notable that CBER is currently exceeding all MDUFMA goals for FY 2005.

The following sections are divided by type of medical device marketing application:

A. PMAs, Panel-Track Supplements, Product Development Protocols (PDPs), and Pre Marketing Reports (PMRs)
B. Expedited PMAs
C. 180-Day PMA Supplements
D. 510(k)s, Premarket Notification
E. Biologics Licensing Applications (BLA), Biologics Licensing Application Supplements (BLS), and Resubmissions

Each section has three subsections, with tables providing information for that type of application (or applications):

1. A summary of the MDUFMA review performance goals
2. CBER's workload (applications received and reviewed) and MDUFMA review performance.
3. CBER's timeliness of application review, including:
    b) Average review times
    c) Average number of review cycles
4. Summary

Note the following with regard to the data provided in the tables:

- All data are for applications <u>received</u> in the first three quarters of fiscal year 2003 (from October 1, 2002, through June 30, 2003). FY 2003 is the ***cohort*** year and includes all applications that have been or will be received during FY 2003, regardless of when actions on those applications occur.

- Because there are separate review performance goals for the different possible interim actions and final actions, a single application that has multiple actions may meet and/or miss more than one goal. *Within Goal* or *Overdue* for an application applies to that goal only, regardless of whether it has met or missed any of the other goals. This means that the total number of goals met and/or missed will usually be larger than the number of applications received. Also, because more than one type of first or second action may be possible for a pending application, it is not possible to state the number of pending actions *Within Goal* or *Overdue* for some of the goals; for these goals, the pending cells have been grayed out in the tables. Cells have also been grayed out where the data are not relevant for the type of submission, e.g., Average Total Time for Applicant Responses in the Review Time tables.

[2] See Secretary Thompson's letter to Senator Kennedy dated November 14, 2002 and the enclosed goals document.

- The "% On Time" in the review performance tables is derived from the number of applications completed *Within Goal* divided by the number of applications completed *Within Goal* **plus** the number of applications completed *Overdue* **plus** the number of applications that are pending but *Overdue* for the goal. These are all of the applications that have reached the goal date, so their fate is known with regard to meeting or missing the goal. The calculation does not include applications pending within goal because it is unknown whether or not they will meet the goal.

- Only applications with final actions are used in calculating average times and cycles. Consequently, these calculations may be affected by the review times and number of cycles for applications received in this cohort year that were pending at the time this report was written and subsequently approved/cleared.

- A list of all medical device applications in the FY 2003 cohort approved through June 30, 2003, are included in Appendix 2.

A. PMAs, Panel-Track Supplements, PDPs, and PMRs

1. Goals - The table below summarizes the review-time performance goals for **PMAs, Panel-Track Supplements, PDPs, and PMRs** from FY 2003 to FY 2007.

Activity	Review Time	Performance Level (by FY) (-- indicates no quantitative goal)				
		2003	2004	2005	2006	2007
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	320 days	--	--	--	80%	90%
• FDA decision - median performance	180 days	--	--	--	--	50%
• First action - "major deficiency" letter	150 days	--	--	75%	80%	90%
• First action - all other first actions (approval, approvable, approvable pending GMP inspection, not approvable, or denial)	180 days	--	--	75%	80%	90%
• Second or later action - "major deficiency" letter	120 days	--	--	75%	80%	90%
• Action on an amendment containing a complete response to a "major deficiency" or "not approvable" letter	180 days	--	--	75%	80%	90%
• Action on an amendment containing a complete response to an "approvable" letter	30 days	90%	90%	90%	90%	90%

2. Workload and Performance in Meeting MDUFMA Goals for **PMAs, Panel-Track Supplements, PDPs, and PMRs**

Number of Applications		Actions	Goal Review Time (days)	Within Goal			Overdue			% On Time
Rec'd	Filed			Comp	Pend	Total	Comp	Pend	Total	
2	**2**	FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	320 days	**1**	**1**	**2**				**100%**
		FDA decision – median performance	180 days							
		First action – "major deficiency" letter	150 days							
		First action – all other first actions	180 days	**1**		**1**				**100%**
		Second or later action – "major deficiency" letter	120 days							
		Action on an amendment containing a complete response to a "major deficiency" or "not approvable" letter	180 days							
		Action on an amendment containing a complete response to an "approvable" letter	30 days							

3. Timeliness of Medical Device Reviews by CBER for **PMAs, Panel-Track Supplements, PDPs, and PMRs**

a) Review Times *in days*

Original Submissions

Submission Type	# Received	# First Actions	Average FDA Time to First Action
PMA	2	1	178
Panel Track Suppl	0	--	--
PDPs	0	--	--
PMRs	0	--	--
Total	**2**	**1**	**178**

Manufacturer Replies

(There have been no manufacturer replies as of June 30, 2003)

Total Approval Times

Submission Type	# Received	# Approvals	Average Total FDA Time	Average Total Time to Approval
PMA	2	1	178	178
Panel Track Suppl	0	--	--	--
PDPs	0	--	--	--
PMRs	0	--	--	--
Total	**2**	**1**	**178**	**178**

b) **Review Cycles**

Submission Type	# Received	# of Final Actions	Average # of Cycles	# Pending without 1st Action	# Pending with 1st Action Completed
PMA	2	1	1	1	0
Panel Track Suppl	0	--	--	--	--
PDPs	0	--	--	--	--
PMRs	0	--	--	--	--
Total	**2**	**1**	**1**	**1**	**0**

4. Summary

Although only 2 PMAs were received during this time period, one was completed in one cycle of 178 days within all goals. The remaining PMA was still pending within the review goal time at the time this report was drafted.

B. Expedited PMAs

1. Goals - The table below summarizes the review-time goals for **Expedited PMAs** from FY 2003 to FY 2007. These goals apply when FDA has granted expedited status; the applicant has attended a pre-filing meeting; manufacturing facilities are ready for inspection; and the PMA is substantively complete as defined at the pre-filing meeting.

Activity	Review Time	Performance Level (by FY) (-- indicates no quantitative goal)				
		2003	2004	2005	2006	2007
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	300 days	--	--	70%	80%	90%
• First action - "major deficiency" letter	120 days	--	--	70%	80%	90%
• First action - all other first actions (approval, approvable, approvable pending GMP inspection, not approvable, or denial)	170 days	--	--	70%	80%	90%
• Second or later action -- "major deficiency" letter	100 days	--	--	70%	80%	90%
• Action on an amendment containing a complete response to a "major deficiency" or "not approvable" letter	170 days	--	--	70%	80%	90%
• Action on an amendment containing a complete response to an "approvable" letter	30 days	90%	90%	90%	90%	90%

2. Workload and Performance in Meeting MDUFMA Goals for **Expedited PMAs**

CBER has received no **Expedited PMAs** in FY 2003 as of June 30, 2003.

C 180-Day PMA Supplements

1. Goals - The table below summarizes the review-time goals for **180-Day PMA Supplements** from FY 2003 to FY 2007.

Activity	Review Time	Performance Level (by FY) (-- indicates no quantitative goal)				
		2003	2004	2005	2006	2007
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	180 days	--	--	80%	85%	90%
• First action - "not approvable" letter	120 days	--	--	80%	85%	90%
• First action - all other first actions (approval, approvable, approvable pending GMP inspection, not approvable, or denial)	180 days	--	--	80%	85%	90%
• Action on an amendment containing a complete response to a "not approvable" letter	160 days	--	--	80%	85%	90%

2. Workload and Performance in Meeting MDUFMA Goals for **180-Day PMA Supplements**

Number of Applications		Actions	Goal Review Time (days)	Within Goal			Overdue			% On Time
Rec'd	Filed			Comp	Pend	Total	Comp	Pend	Total	
2	**2**	FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	180 days	**1**	**1**	**2**				**100%**
		First action – “not approvable” letter	120 days	**1**		**1**				**100%**
		First action – all other first actions (approval, approvable, approvable pending GMP inspection, or denial)	180 days							
		Action on an amendment containing a complete response to a “not approvable” letter	160 days							

3. Timeliness of Medical Device Reviews by CBER for **180-Day PMA Supplements**

a) **Review Times *in days***

Original Submissions

Submission Type	# Received	# First Actions	Average FDA Time to First Action
PMA 180-day Supplement	2	1	90

Manufacturer Replies

(There have been no manufacturer replies as of June 30, 2003)

Total Approval Times

(There have been no approvals as of June 30, 2003)

b). **Review Cycles**

Submission Type	# Received	# of Final Actions	Average # of Cycles	# Pending without 1st Action	# Pending with 1st Action Completed
Original Submissions	2	0	--	1	1

4. Summary

For the two submissions of 180-day PMA supplements, there was one first action within the time goals and the second PMA supplement is still pending within the goal at the time this report was written.

D. 510(k)s

1. Goals - The table below summarizes the review-time goals for **510(k)s (Traditional, Abbreviated, and Special)** from FY 2003 to FY 2007.

Activity	Review Time	Performance Level (by FY) (-- indicates no quantitative goal)				
		2003	2004	2005	2006	2007
• FDA decision (substantially equivalent/ not substantially equivalent)(SE/NSE)	90 days	--	--	75%	75%	80%
• First action -- "additional information" letter	75 days	--	--	70%	80%	90%
• Second or later action	60 days	--	--	70%	80%	90%

2. Workload and Performance in Meeting MDUFMA Goals for **510(k)s (Traditional, Abbreviated, and Special)**

Number of Applications Rec'd	Actions	Goal Review Time (days)	Within Goal			Overdue			% On Time*
			Comp	Pend	Total	Comp	Pend	Total	
45	FDA decision (SE/NSE)*	90 days	**33**	**12**	**45**				**100%**
	First action — "additional information" letter	75 days	**8**		**8**				**100%**
	Second or later action	60 days	**5**	**2**	**7**				**100%**

* Applications withdrawn after initiation of review are counted as an FDA decision.

3. Timeliness of Medical Device Reviews by CBER for **510(k)s (Traditional, Abbreviated, and Special)**

a) Review Times *in days*

Original Submissions

Submission Type	# Received	# First Actions	Average FDA Time to First Action
Traditional	29	20	58.2
Abbreviated	6	6	50.2
Special	10	10	18.9
Total	**45**	**36**	

Manufacturer Replies

Submission Type	# Received	# Actions	Average FDA Time to Action
Traditional	5	3	13
Abbreviated	2	2	31
Special	0	--	--
Total	**7**	**5**	

Total Approval Times

Submission Type	# Received	# Cleared	Average Total FDA Time	Average Total Time to Clearance
Traditional	29	14	61.1	74.6
Abbreviated	6	6	60.5	71.8
Special	10	9	20.6	20.6
Total	**45**	**29**		

b) **Review Cycles**

Submission Type	# Received	# of Final Actions	Average # of Cycles	# Pending without 1st Action	# Pending with 1st Action Completed
Traditional	29	17	1.18	9	3
Abbreviated	6	6	1.33	0	0
Special	10	10	1.00	0	0
Total	**45**	**33**	**1.15**	**9**	**3**

4. Conclusions

Forty five 510(k)s submissions were received.

29 were cleared, i.e., determined to be substantially equivalent (SE), within all goals. Of these, 24 were reviewed within the first cycle. 22.2% of the 510(k) submissions were special 510(k)s, which is within the range of receipts of previous years (10 - 36% in FY99 - FY02).

Twelve submissions are pending; the remaining 4 submissions were withdrawn or found not substantially equivalent (NSE).

E. BLAs, BLSs, and Resubmissions

1. Goals - The table below summarizes the review-time goals for **BLAs, BLSs, and Resubmissions** from FY 2003 to FY 2007.

Activity	Review Time	Performance Level (by FY) (-- indicates no quantitative goal)				
		2003	2004	2005	2006	2007
Biologics Licensing Applications - BLAs						
• Review and act on standard original BLAs (issue "complete action" letter)	10 months	--	--	75%	80%	90%
• Review and act on priority original BLA submissions (issue "complete action" letter)	6 months	--	--	75%	80%	90%
BLA Supplements						
• Review and act on standard BLA efficacy supplements (issue "complete action" letter)	10 months	--	--	--	75%	90%
• Review and act on priority BLA efficacy supplements (issue "complete action" letter)	6 months	--	--	--	75%	90%
• Review and act on BLA manufacturing supplements that require prior approval (issue "complete action" letter)	4 months	--	--	--	75%	90%
BLA Resubmissions, BLA Supplement Resubmissions						
• Review and act on a Class 1 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	2 months	--	--	75%	80%	90%
• Review and act on a Class 2 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	6 months	--	--	75%	80%	90%

2. Workload and Performance in Meeting MDUFMA Goals for **BLAs, BLSs, and Resubmissions**

Application Type	Number of Applications		Actions	Goal Review Time (months)	Within Goal			Overdue			% On Time
	Rec'd	Filed			Comp	Pend	Total	Comp	Pend	Total	
BLAs - Standard	**0**	--	Review and act on standard original BLAs (issue "complete action" letter)	10 months							
BLAs - Priority	**0**	--	Review and act on priority original BLA submissions (issue "complete action" letter)	6 months							
BLSs - Standard Efficacy	**3**	**3**	Review and act on standard BLA efficacy supplements (issue "complete action" letter)	10 months		**3**	**3**				--
BLSs - Priority Efficacy	**0**	--	Review and act on priority BLA efficacy supplements (issue "complete action" letter)	6 months							
BLSs - Prior Approval Manufacturing	**74**	**74**	Review and act on BLA manufacturing supplements that require prior approval (issue "complete action" letter)	4 months	**21**	**53**	**74**				**100%**
BLA/BLS Resubmissions	**2**		Review and act on a Class 1 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	2 months							
			Review and act on a Class 2 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	6 months	**1**	**1**	**2**				**100%**

3. Timeliness of Medical Device Reviews by CBER for **BLAs, BLSs, and Resubmissions**

a) Review Times *in months*

Original Submissions

Submission Type	# Received	# First Actions	Average FDA Time to First Action
BLAs - Standard	0	--	--
BLAs - Priority	0	--	--
Total	**0**	**--**	**--**
BLSs – Efficacy- Standard	3	0	--
BLSs – Efficacy - Priority	0	--	--
BLSs – Manuf. - PAS	74	21	3.48
Total	**77**	**21**	**3.48**

Manufacturer Replies

Submission Type	# Received	# Actions	Average FDA Time to Action
Original Submissions			
BLAs - Standard	2	1	2.60
BLAs - Priority	0	--	--
Total	**2**	**1**	**2.60**
BLSs – Efficacy- Standard	0	--	--
BLSs – Efficacy - Priority	0	--	--
BLSs – Manuf. - PAS	6	6	2.95
Total	**6**	**6**	**2.95**

Total Approval Times

Submission Type	# Received	# Approvals	Average Total FDA Time	Average Total Time to Approval
Original Submissions				
BLAs - Standard	0	--	--	--
BLAs - Priority	0	--	--	--
Total	**0**	**--**	**--**	**--**
BLSs – Efficacy- Standard	3	0	--	--
BLSs – Efficacy - Priority				
BLSs – Manuf. - PAS	74	20	4.39	4.54
Total	**77**	20	**4.39**	**4.54**

b) Review Cycles

Submission Type	# Received	# of Final Actions	Average # of Cycles	# Pending without 1st Action	# Pending with 1st Action Completed
BLAs - Standard	0	--	--	--	--
BLAs – Priority	0	--	--	--	--
Total	**0**	--	--	--	--
BLSs - Efficacy -Standard	3	0	--	3	0
BLSs – Efficacy - Priority	0	--	--	--	--
BLSs - Manuf. - PAS	74	20	1.3	53	1
Total	**77**	**20**	**1.3**	**56**	**1**

4. Summary

For BLAs, BLSs and resubmissions, there were 20 final actions, all of which were for prior approval supplements (PAS). FY'05 goals were met for all of these final actions.

Appendix 1

Performance Goals For The Medical Device User Fee And Modernization Act Of 2002 -- (Senate - November 19, 2002)

[Page: S11549]

Mr. KENNEDY. Mr. President, on October 17, 2002, the Senate passed the Medical Device User Fee and Modernization Act of 2002, "MDUFMA." Included in Title I of this bill is the authorization of medical device user fees.

Performance goals, existing outside of the statute, accompany the authorization of medical device user fees. These goals represent a realistic projection of what the Food and Drug Administration's Center for Devices and Radiological Health and Center for Biologics Evaluation and Research can accomplish with industry cooperation. The Secretary of Health and Human Services forwarded these goals to the chairmen of the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor and Pensions of the Senate, in a document entitled "MDUFMA PERFORMANCE GOALS AND PROCEDURES." According to Section 101 of Title I of MDUFMA, "the fees authorized by this title will be dedicated to meeting the goals set forth in the *Congressional Record*."

Today I am submitting for the **RECORD** this document, which was forwarded to the Committee on Health, Education, Labor and Pensions on November 14, 2002, as well as the letter from Secretary Thompson that accompanied the transmittal of this document.

I ask unanimous consent to print those items.

There being no objection, the material was ordered to be printed in the **RECORD**, as follows:

MDUFMA Performance Goals and Procedures

The performance goals and procedures of the FDA Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the medical device user fee program in the Medical Device User Fee and Modernization Act of 2002, are summarized as follows:

I. REVIEW PERFORMANCE GOALS--FISCAL YEAR 2003 THROUGH 2007

All references to "days" mean "FDA days."

A. ORIGINAL PREMARKET APPROVAL (PMA), PANEL-PMATRACK SUPPLEMENT, AND PREMARKET REPORT SUBMISSIONS

1. The following cycle goals apply to: 75% of submission received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

(a) First action major deficiency letters will issue within 150 days.

(b) All other first action letters (approval, approvable, approvable pending good manufacturing practices (GMP) inspection, not approvable, or denial) will issue within 180 days.

(c) Second or later action major deficiency letters will issue within 120 days.

(d) Amendments containing a complete response to major deficiency or not approvable letters will be acted on within 180 days.

2. Decision Goals:

(a) 80% of submissions received in fiscal year 2006 will have an FDA decision in 320 days.

(b) 90% of submissions received in fiscal year 2007 will have an FDA decision in 320 days.

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3. Subject to the following paragraph, 50% of submissions received in fiscal year 2007 will have an FDA decision in 180 days.

This goal will be re-evaluated following the end of fiscal year 2005. FDA will hold a public meeting to consult with its stakeholders and to determine whether this goal is appropriate for implementation in fiscal year 2007. If FDA determines that the goal is not appropriate, prior to August 1, 2006, the Secretary will send a letter to the Committee on Health, Education, Labor and pensions of the Senate and to the Energy and Commerce Committee, Subcommittee on Health of the House of Representatives stating that the goal will not be implemented and the rationale for its removal.

4. 90% of amendments containing a complete response to an approvable letter received in fiscal years 2003 through 2007 will be acted on within 30 days.

B. EXPEDITED ORIGINAL PMA SUBMISSIONS

1. The following goals apply to PMA submissions where:

(a) FDA has granted the application expedited status;

(b) The applicant has requested and attended a pre-filing review meeting with FDA;

(c) The applicant's manufacturing facilities are prepared for inspection upon submission of the application; and

(d) The application is substantively complete, as defined at the pre-filing review meeting.

2. The following cycle goals apply to: 70% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

(a) First action major deficiency letters will issue within 120 days.

(b) All other first action letters (approval, approvable, approvable pending GMP inspection, not approvable, or denial) will issue within 170 days.

(c) Second or later action major deficiency letters will issue within 100 days.

(d) Amendments containing a complete response to major deficiency or not approvable letters will be acted on within 170 days.

3. Decision Goals:

(a) 70% of submissions received in fiscal year 2005 will have an FDA decision in 300 days.

(b) 80% of submissions received in fiscal year 2006 will have an FDA decision in 300 days.

(c) 90% of submissions received in fiscal year 2007 will have an FDA decision in 300 days.

4. 90% of amendments containing a complete response to an approvable letter received in fiscal years 2003 through 2007 will be acted on within 30 days.

C. 180-DAY PMA SUPPLEMENT SUBMISSIONS

1. The following goals apply to: 80% of submissions in fiscal year 2005; 85% of submissions in fiscal year 2006; 90% of submissions in fiscal year 2007.

(a) First action not approvable letters will issue within 120 days.

(b) All other first action letters (approval, approvable, approvable pending GMP inspection, not approvable or denial) will issue within 180 days.

(c) Amendments containing a complete response to a not approvable letter will be acted on within 160 days.

2. Decision Goals:

   (a) 80% of submissions received in fiscal year 2005 will have an FDA decision in 180 days.

   (b) 80% of submissions received in fiscal year 2006 will have an FDA decision in 180 days.

   (c) 90% of submissions received in fiscal year 2007 will have an FDA decision in 180 days.

3. Current performance for real-time review PMA supplement submissions will be maintained.

D. 510(K) SUBMISSIONS

1. The following goals apply to: 70% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

   (a) First action additional information letters will issue within 75 days.

   (b) Subsequent action letters will issue within 60 days.

2. Decision Goals:

   (a) 75% of submissions received in fiscal years 2005 and 2006 will have an FDA decision in 90 days.

3. Subject to the following paragraph, 80% of submissions received in fiscal year 2007 will have an FDA decision in 90 days.

   This goal will be re-evaluated following the end of fiscal year 2005. FDA will hold a public meeting to consult with its stakeholders and to determine whether this goal is appropriate for implementation in fiscal year 2007. If FDA determines that the goal is not appropriate, prior to August 1, 2006, the Secretary will send a letter to the Committee on Health, Education, Labor and Pensions of the Senate and to the Energy and Commerce Committee, Subcommittee on Health of the House of Representatives stating that the goal will not be implemented and the rationale for its removal, and that the goal for fiscal year 2006 will be implemented for fiscal year 2007.

E. ORIGINAL BIOLOGICS LICENSING APPLICATIONS (BLAS)

   The following goals apply to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

1. Review and act on standard original BLA submissions within 10 months of receipt.
2. Review and act on priority original BLA submissions within 6 months of receipt.

F. BLA EFFICACY SUPPLEMENTS

The following goals apply to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

1. Review and act on standard BLA efficacy supplement submissions within 10 months of receipt.
2. Review and act on priority BLA efficacy supplement submissions within 6 months of receipt.

G. ORIGINAL BLA AND BLA EFFICACY SUPPLEMENT RESUBMISSIONS

The following goals apply to: 75% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

1. Review and act on Class 1 original BLA and BLA efficacy supplement resubmissions within 2 months of receipt.
2. Review and act on Class 2 original BLA and BLA efficacy supplement resubmissions within 6 months of receipt.

H. BLA MANUFACTURING SUPPLEMENTS REQUIRING PRIOR APPROVAL

The following goal applies to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

1. Review and act on BLA manufacturing supplements requiring prior approval within 4 months of receipt.

I. ADDITIONAL EFFORTS RELATED TO PERFORMANCE GOALS

The Agency and the regulated industry agree that the use of both informal and formal meetings (e.g., determination and agreement meetings, informal pre-IDE meetings, pre-PMA meetings, pre-PMA filing meetings) by both parties is critical to ensure high application quality such that the above performance goals can be achieved.

J. MAINTENANCE OF CURRENT PERFORMANCE

It is the intent of the Agency that in review areas where specific performance goals have not been identified, current performance will be maintained.

K. APPLICATION OF USER FEE REVENUES

The Agency intends to apply significant user fee revenues to support reviewer training and hiring and/or outside contracting to achieve the identified performance goals in a responsible and efficient manner.

L. MODULAR PMA REVIEW PROGRAM

The Agency intends to issue guidance regarding the implementation of new section 515(c)(3) of the Federal Food, Drug, and Cosmetic Act. It is the intent of the Agency that once this program is implemented, the Agency will work with its stakeholders to develop appropriate performance goals for this program. Until such time, the Agency intends to review and close complete modules that are submitted well in advance of the PMA submission as expeditiously as possible.

M. "FOLLOW-ON" LICENSED DEVICES

The Center for Biologics Evaluation and Research will, if feasible, identify a category of "follow-on" licensed devices and collect information to determine whether alternative performance goals for such a category are appropriate.

N. BUNDLING POLICY

The Agency will, in consultation with its stakeholders, consider the issue of bundling for products with multiple related submissions. After such consultation, the Agency will either issue guidance on bundling or publish a notice explaining why it has determined that bundling is inappropriate.

O. ELECTRONIC REVIEW OF APPLICATIONS

The Agency will continue its efforts toward development of electronic receipt and review of applications, as expeditiously as possible, acknowledging that insufficient funding is included in the user fee program for this effort.

P. PREAPPROVAL INSPECTIONS

The Agency will plan to improve the scheduling and timeliness of preapproval inspections. The Agency will monitor the progress of these efforts and provide such information in the annual performance report.

II. ANNUAL STAKEHOLDER MEETING

Beginning in fiscal year 2004, FDA will hold annual public meetings to review and evaluate the implementation of this program in consultation with its stakeholders.

III. DEFINITIONS AND EXPLANATION OF TERMS

A. For original PMA submissions, Panel-Track PMA supplement submissions, expedited original PMA submissions, 180-day supplement submissions, and premarket report submissions, issuance of one of the following letters is considered to be an FDA decision:

1. approval
2. approvable
3. approvable pending GMP inspection
4. not approvable
5. denial

B. For 510(k) submissions, issuance of one of the following letters is considered to be an FDA decision:

1. substantially equivalent (SE)
2. not substantially equivalent (NSE)

C. Submission of an unsolicited major amendment to an original PMA submission, Panel-Track PMA supplement submission, expedited original PMA submission, 180-day supplement submission, or premarket report submission extends the FDA decision goal date by the number of days equal to 75% of the difference between the filing date and the date of receipt of the amendment. The submission of the unsolicited major amendment is also considered an action that satisfies the first or later action goal, as applicable.

D. For BLA (original, efficacy supplement, or manufacturing supplement) submissions, the term "review and act on" is understood to mean the issuance of a complete action letter after the complete review of a filed

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complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

E. For original BLA and BLA efficacy supplement resubmissions:

1. Class 1 resubmitted applications are applications resubmitted after a complete response letter that include the following items only (or combinations of these items):

(a) Final printed labeling

(b) Draft labeling

(c) Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new

information including important new adverse experiences not previously reported with the product are presented in the resubmission)

(d) Stability updates to support provisional or final dating periods

(e) Commitments to perform Phase 4 studies, including proposals for such studies

(f) Assay validation data

g) Final release testing on the last 1-2 lots used to support approval

(h) A minor reanalysis of data previously submitted to the application (determined by the agency as fitting the Class 1 category)

(i) Other minor clarifying information (determined by the Agency as fitting the Class 1 category)

(j) Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry.

2. Class 2 resubmissions are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

THE SECRETARY OF HEALTH AND
HUMAN SERVICES,
Washington, DC, November 14, 2002.
Hon. **EDWARD KENNEDY,**
U.S. Senate,
Washington, DC.

DEAR MR. CHAIRMAN. As you are aware, the Medical Device User Fee and Modernization Act of 2002 was signed by the President on October 26, 2002. Under Title I, the additional revenues generated from fees paid by the medical device industry will be used to expedite the medical device review process, in accordance with performance goals that were developed by the Food and Drug Administration (FDA) in consultation with the industry.
FDA has worked with various stakeholders, including representatives from consumer, patient, and health provider groups, and the medical device industry to develop legislation and goals that would enhance the success of the device review program. Title I of the Medical Device User Fee and Modernization Act of 2002 reflects the fee mechanisms and other improvements developed in these discussions. The performance goals referenced in Section 101 are specified in the enclosure to this letter, entitled "Performance Goals and Procedures." I believe they represent a realistic projection of

what FDA can accomplish with industry cooperation and the additional resources identified in the bill.

This letter and the enclosed goals document pertain only to title I (Fees Related to Medical Devices) of Public Law 107-250, Medical Device User Fee and Modernization Act of 2002. OMB has advised that there is no objection to the presentation of these views from the standpoint of the Administration's program. We appreciate the support of you and your staffs, the assistance of other Members of the Committee, and that of the Appropriations Committees, in the authorization of this vital program.

Sincerely,

TOMMY G. THOMPSON.

Appendix 2

List of MDUFMA Approved/Cleared Applications (Cohort FY03 as of June 30, 2003)

Does not include: 510(k) – Withdrawals (3), Refusals to Accept (1), Not Substantially Equivalent (1); 180-Day Supplements - Not Approved (1)

1. CBER APPROVED PMA, PTS, PDP, PMR DEVICE APPLICATIONS (COHORT FY03)

Subm ID	Supp ID	Received Dt	Subm Type	Subm Subtype	Product/Device Description	Corporate Name	Total Time in Days	Action	Goal Met?
BP020066	0	10-Dec-2002	PMA	Traditional	HIV Detection Test	BioMerieux, Inc.	178	Approved	Y

2. CBER APPROVED EXPEDITED PMAS (COHORT FY03)

Subm ID	Received Dt	Product/Device Description	Corporate Name	Total Time in Days	Action	Goal Met?
None Approved Cohort FY03 as of June 30, 2003						

3. CBER 180-DAY APPROVED SUPPLEMENTS (COHORT FY03)

Subm ID	Supp ID	Received Dt	Product/Device Description	Corporate Name	Total Time in Days	Action	Goal Met?
None Approved Cohort FY03 as of June 30, 2003							

4. CBER 510(K) DEVICE CLEARED APPLICATIONS (COHORT FY03)

Subm ID	Received Dt	Subm Subtype	Product/Device Description	Corporate Name	Total Time in Days	Action	Goal Met?
BK020046	29-Oct-02	Abbreviated	Stand alone Blood Bank Software	Mediware Information Systems, Inc.	108	FDA First Action: 50 (AI) Sponsor Response: 28 FDA Second Action 30 (SE)	Y Y
BK020058	18-Nov-02	Abbreviated	Stand alone Blood Bank Software	Fifth Dimension Information Systems	77	SE	Y
BK020042	8-Oct-02	Special	Software, Blood Virus Application	Visible Genetics, Inc.	30	SE	Y
BK020043	11-Oct-02	Traditional	Warmer, Blood Non-electromagnetic Radiation	Level 1 Technologies, Inc	248	FDA First Action: 70 (AI) Sponsor Response: 159 FDA Second Action: 19 (SE)	Y Y

4. CBER 510(K) DEVICE CLEARED APPLICATIONS (COHORT FY03) (cont.)							
Subm ID	**Received Dt**	**Subm Subtype**	**Product/Device Descripti on**	**Corporate Name**	**Total Time in Days**	**Action**	**Goal Met?**
BK020055	28-Oct-02	Traditional	Qualitative Test for HLA, Non-diagnostic	One Lambda, Inc.	99	FDA First Action: 64 (AI) Sponsor Response: 22 FDA Second Action: 13 (SE)	Y Y
BK020051	4-Nov-02	Traditional	Blood Bank Supplies	Cascade Medical Enterprises, LLC	46	SE	Y
BK020053	13-Nov-02	Traditional	Automated Blood Grouping and Antibody Test Systems	Immucor, Inc.	75	SE	Y
BK020054	13-Nov-02	Traditional	Quality Control Kits for Blood Banking Reagents	Immucor, Inc.	75	SE	Y
BK020056	18-Nov-02	Traditional	Automated Blood Cell Separators	Baxter Healthcare Corporation	32	SE	Y
BK020060	18-Nov-02	Traditional	Quality Control Kits for Bloodborne Pathogen Testing of Donors	BioMerieux, Inc.	30	SE	Y
BK020059	20-Nov-02	Traditional	Automated Blood Cell Seporators	Baxter Healthcare Corporation - Fenwal Division	64	SE	Y
BK020063	27-Nov-02	Traditional	Quality Control Kits for Blood Banking Reagents	Beckman Coulter, Inc.	68	SE	Y
BK030001	23-Dec-02	Traditional	Blood Specimen Collection Devices - Vacuum	Greiner Bio-One GmbH	65	SE	Y
BK030003	31-Dec-02	Traditional	Qualitative Test for HLA, Non-diagnostic	Pel-Freez Clinical Systems, LLC	56	SE	Y
BK030005	15-Jan-03	Special	Assay, Genotype, HIV Drug Resistance, In Vitro	Celera Diagnostics	14	SE	Y
BK030006	4-Feb-03	Abbreviated	Blood Mixing and Weighing Devices	Sarstedt, Inc.	23	SE	Y
BK030007	7-Feb-03	Special	Test, Syphilis, Treponema (For Donor Testing)	Fujirebio Diagnostics, Inc.	14	SE	Y
BK030008	5-Feb-03	Traditional	Blood Transfusion Microfilters	Maco Pharma	86	FDA First Action: 71 (AI) Sponsor Response: 8 FDA Second Action: 7 (SE)	Y Y

4. CBER 510(K) DEVICE CLEARED APPLICATIONS (COHORT FY03) (cont.)							
Subm ID	**Received Dt**	**Subm Subtype**	**Product/Device Description**	**Corporate Name**	**Total Time in Days**	**Action**	**Goal Met?**
BK030009	11-Feb-03	Special	Automated Blood Grouping and Antibody Test Systems	Olympus America Inc., Diagnostic Systems Division	20	SE	Y
BK030011	13-Feb-03	Abbreviated	Blood and Plasma Warming Devices	Thermogenesis	117	FDA First Action: 45 (AI) Sponsor Response: 40 FDA Second Action: 32 (SE)	Y Y
BK030015	21-Feb-03	Special	Software, Blood Virus Application	Visible Genetics, Inc.	21	SE	Y
BK030018	24-Feb-03	Abbreviated	Stand alone Blood Bank Software	Soft Computer Consultants Inc.	52	SE	Y
BK030020	4-Mar-03	Traditional	Automated Hemoglobin System	HemoCure, Incorporated	44	SE	Y
BK030021	6-Mar-03	Traditional	Stand alone Blood Bank Software	Gambro BCT, Inc.	56	SE	Y
BK030023	21-Mar-03	Abbreviated	Automated Blood Grouping and Antibody Test Systems	Micro Typing Systems Inc.	54	SE	Y
BK030030	14-May-03	Special	Stand alone Blood Bank Software	Rubin & Poor, Inc.	9	SE	Y
BK030033	21-May-03	Special	Assay, Genotype, HIV Drug Resistance, In Vitro	Celera Diagnostics	21	SE	Y
BK020068	19-Dec-2002	Special	Qualitative Test for HLA, Non-diagnostic	Pel-Freez Clinical Systems, LLC	26	SE	Y
BK020045	22-Oct-2002	Special	Stand alone Blood Bank Software	Gen-Probe	30	SE	Y

5. CBER APPROVED STANDARD AND PRIORITY BLAS (COHORT FY03)							
Subm ID	**Received Dt**	**Application Type**	**Product/Device Description**	**Corporate Name**	**Total Time in Months**	**Action**	**Goal Met?**
None Approved Cohort FY03 as of June 30, 2003							

6. CBER APPROVED STANDARD AND PRIORITY EFFICACY SUPPLEMENTS (COHORT FY03)							
Subm ID	**Supp ID**	**Received Dt**	**Product/Device Description**	**Corporate Name**	**Total Time in Months**	**Action**	**Goal Met?**
None Approved Cohort FY03 as of June 30, 2003							

7. CBER APPROVED LICENSED DEVICE PRIOR APPROVAL MANUFACTURING SUPPLEMENTS (COHORT FY03)							
Subm ID	**Supp ID**	**Received Dt**	**Product/Device Description**	**Corporate Name**	**Total Time in Months**	**Action**	**Goal Met?**
BL102129	5010	2-Oct-2002	Anti-A(Murine Monoclonal)	Gamma Biologicals, Inc.	3.47	Approved	Y
BL102130	5008	2-Oct-2002	Anti-B(Murine Monoclonal)	Gamma Biologicals, Inc.	3.47	Approved	Y
BL102131	5009	2-Oct-2002	Anti-A and B (Murine Monoclonal); Anti-A,B (Murine Monoclonal	Gamma Biologicals, Inc.	3.47	Approved	Y
BL103067	5004	22-Oct-02	Anti-Human Globulin	Ortho-Clinical Diagnostics, Inc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y
BL103068	5007	22-Oct-02	Anti-Human Globulin (Rabbit/Murine Monoclonal)	Ortho-Clinical Diagnostics, I nc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y
BL103075	5004	12-Nov-2002	Anti-Fya	Ortho-Clinical Diagnostics, Inc.	2.31	Approved	Y
BL103079	5004	18-Nov-2002	Anti-k	Ortho-Clinical Diagnostics, Inc.	3.56	Approved	Y
BL103088	5003	22-Oct-02	Anti-A (Murine Monoclonal)	Ortho-Clinical Diagnostics, I nc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y

BL103089	5003	22-Oct-02	Anti-B (Murine Monoclonal)	Ortho-Clinical Diagnostics, I nc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y

7. CBER APPROVED LICENSED DEVICE PRIOR APPROVAL MANUFACTURING SUPPLEMENTS (COHORT FY03) (cont.)							
Subm ID	**Supp ID**	**Received Dt**	**Product/Device Description**	**Corporate Name**	**Total Time in Months**	**Action**	**Goal Met?**
BL103090	5003	22-Oct-02	Anti-A and B (Murine Monoclonal); Anti-A,B (Murine Monoclonal)	Ortho-Clinical Diagnostics, Inc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y
BL103098	5004	18-Nov-2002	Anti-Cw	Ortho-Clinical Diagnostics, Inc.	3.56	Approved	Y
BL103108	5006	4-Mar-2003	Anti-E (Monoclonal)	Ortho-Clinical Diagnostics, Inc.	2.96	Approved	Y
BL103100	5004	22-Oct-02	Anti-D	Ortho-Clinical Diagnostics, I nc.	7.59	FDA First Action: 3.98 (CR) Sponsor Response: .66 FDA Second Action: 2.95 (Approved)	Y Y
BL103111	5004	17-Dec-2002	Anti-Leb(Murine Monoclonal)	Ortho-Clinical Diagnostics, Inc.	2.6	Approved	Y
BL103688	5006	3-Feb-2003	Human T-Lymphotropic Virus Types I & II	bioMerieux, Inc.	3.66	Approved	Y
BL103778	5008	19-Dec-2002	Reagent Red Blood Cells	Ortho-Clinical Diagnostics, Inc.	3.95	Approved	Y
BL103865	5006	4-Mar-2003	Anti-E (Human/Murine Monoclonal) (For Further Manufacturing Use)	Serologicals LTD	2.96	Approved	Y
BL103966	5012	6-Feb-2003	Human Immunodeficiency Virus Type 1 and/or Hepatitis C Virus	Gen-Probe Incorporated	2.31	Approved	Y
BL103091	5005	7-Oct-2002	Anti-M	Ortho-Clinical Diagnostics, Inc.	3.47	Approved	Y
BL103092	5004	7-Oct-2002	Anti-N	Ortho-Clinical Diagnostics, Inc.	3.47	Approved	Y