The Role of the FDA in the Effort Against AIDS

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Synopsis

The Food and Drug Administration has instituted several pro-active measures to expedite the review of treatments, diagnostics, and vaccines for AIDS and related conditions. In particular, the agency has established a special designation—1-AA—for a potential AIDS product which gives top priority to its review.

This special expedited review process for AIDS products has provided for greater cooperation between their sponsors and FDA's reviewers. AIDS products also receive prompt consideration for orphan product status—a status providing financial incentives to the developers of treatments for certain rare and complex diseases.

FDA's special procedures for AIDS drugs have resulted in several major advances in available AIDS treatments. Foremost among these was the FDA's review and approval of zidovudine (commonly known as AZT) as the first effective palliative for AIDS within 107 days—an agency record.

Similarly, the agency quickly evaluated and approved ELISA and Western blot diagnostic kits for detecting the presence of HIV antibody. These test kits have made an important contribution to safeguarding the nation's blood supply.

The agency has also instituted new "treatment" investigational new drug regulations to allow earlier pre-approval distribution of promising experimental treatments to patients with immediately life-threatening conditions, including persons with AIDS. Under this system and its earlier prototype, eligible AIDS patients were able to receive pre-approval treatment with zidovudine and trimetrexate (an experimental drug for the treatment of AIDS patients with Pneumocystis carinii *pneumonia who have experienced severe adverse reactions using standard approved therapies).*

The agency has made institutional reforms to effectively streamline the review of candidate AIDS treatments and vaccines. Two new centers within the agency have been established for the processing of drug and biologics. In addition, reviewing divisions have been created within these centers to give specialized attention to drugs and biologics designed to treat AIDS or related conditions.

These efforts and the other aforementioned reforms, in part, have lead to the initiation of more than 100 ongoing clinical studies of potential drugs for AIDS and related conditions, as well as the clinical testing of two candidate vaccines against HIV.

In other areas, FDA has increased inspections of the manufacturing and processing of condoms and begun a surveillance and sampling program to insure the quality of latex surgical gloves. The agency has worked with other authorities to move against quack AIDS products and to educate the public concerning this health fraud.

FDA hopes that through all these efforts it can help researchers in government, academia, and industry advance the development, testing, and review of safe and effective therapies, preventatives, and diagnostics for AIDS and related conditions.

AIDS POSES AN ENORMOUS CHALLENGE to the societal institutions charged with addressing the disease and its destructive consequences. The Food and Drug Administration (FDA) is meeting this challenge, and it has adopted a pro-active approach to helping the development of treatments, diagnostics, and vaccines for AIDS and related conditions. Through this determined approach,

FDA, working with its sister Public Health Service agencies, industry, and academia, has made many significant advances against AIDS.

FDA has gained a well-deserved reputation for ensuring the safety and efficacy of drugs and medical devices commercially marketed in the United States. Proper clinical studies and thorough review of the resulting clinical data by FDA's physicians and scientists are indispensable to achieving this mission.

FDA leaders realized very early that we could not be content with a "business as usual" approach to this disease, and that we must do everything possible to speed the development and widespread availability of beneficial AIDS diagnostic, therapeutic, and preventive products.

Speeding the Drug Review Process

To accomplish this goal, FDA has established a special designation—1-AA—for all AIDS treatments. This designation ensures them first place in the review process, promises that all decisions on new drug applications (NDAs) will be reached in 180 days or less, and encourages their sponsors to get early consultations with agency staff to facilitate more timely, effective, and efficient clinical studies and FDA reviews.

Under the 1-AA designation, all AIDS drugs are also assured prompt consideration for orphan drug status, a status that is generally valued by the sponsor, since developers of orphan drugs may be entitled to certain tax and other financial incentives. Proposed drugs for AIDS and AIDS-associated conditions that have been designated for this status (on the condition that a new drug application for their approval is granted) include trimetrexate, eflornithine, interferon alfa-nl, BW B759U, diethyl dithio carbamate, HPA-23, interferon alfa 2b, and 2′-3′-dideoxyadenosine. In addition, two drugs already approved—pentamidine, for the treatment of *Pneumocystis carinii* pneumonia and zidovudine, for the treatment of AIDS—have been granted orphan drug status.

FDA has worked as rapidly as possible on AIDS drugs at every level of the new drug review process. FDA has approved more than 100 ongoing clinical studies to test drugs for AIDS or AIDS-associated conditions. Often the agency has granted permission for AIDS drug sponsors to begin clinical testing of their drug on humans within 5 days of receiving a completed application.

These efforts have already produced some major accomplishments. Zidovudine, commonly known as AZT, was approved as the first effective palliative for AIDS in March 1987. The drug was clinically tested, reviewed, and approved 2 years after its initial *in vitro* testing against the human immunodeficiency virus (HIV) had been started by researchers at FDA, the National Cancer Institute, and the Burroughs Wellcome Co. (zidovudine's sponsor) in early 1985. In fact, the drug's completed new drug application was thoroughly reviewed and approved in 107 days—the fastest approval up to that time under the 1968 drug amendments.

Because of the high degree of cooperation among FDA's medical reviewers and researchers at the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and Burroughs Wellcome Co. during the preliminary and clinical testing of zidovudine, the agency could more readily evaluate the definitive clinical data which emerged during the Phase 2 stage of efficacy testing. That data, along with subsequent long-term data obtained from the monitoring of these patients after the placebo control portion of the efficacy testing was discontinued, indicated that the drug could prolong the survival of patients with AIDS who had experienced *Pneumocystis carinii* pneumonia, as well as those patients with advanced ARC (AIDS related complex) who had severely reduced immune systems (as measured by T cell counts below 200/mm^3). These data were used in determining the indications for which the drug was approved.

It is believed that approximately 80 percent of all persons diagnosed with AIDS may fit into the medical criteria set under zidovudine's approved indication. Extensive clinical studies are now being conducted by the National Institute of Allergy and Infectious Diseases to determine whether the drug might be effective for the treatment of patients with other AIDS associated conditions, such as Kaposi's sarcoma or AIDS-related dementia.

Although the agency's work in the review and approval of zidovudine has been one of its more dramatic successes, there have been other less publicized accomplishments like the swift approval of injectable pentamidine as a treatment for *Pneumocystis carinii* pneumonia—one of the most common life-threatening conditions associated with AIDS.

Beyond these drug approvals, FDA has facilitated hundreds of clinical studies on nearly a hundred different candidate AIDS drugs at research centers across the country. These experimental drugs include anti-infective, anti-neoplastic,

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and immunomodulating agents for direct treatment or prophylaxis of AIDS, or both, as well as for the cancers and opportunistic infections associated with the disease.

Similarly, FDA has worked diligently to review and approve testing kits to detect the presence of HIV antibodies in blood. FDA licensed the first enzyme-linked immunosorbent assay (ELISA) designed to detect HIV antibodies in March 1985, about 3 months after receiving the completed application. In April 1987, FDA licensed a Western blot testing kit used for validating initial ELISA screenings. The universal use of both kinds of kits by blood establishments in the United States to screen blood for HIV antibodies has served to safeguard the nation's blood supply.

Paralleling these accomplishments, FDA has continued to expedite and improve its system of review for new candidate drugs in general, and for drugs with the potential for treating life-threatening conditions in particular. To this end, FDA issued a series of regulations in the summer of 1987 to streamline the process for conducting the clinical testing of certain drugs and to expand and expedite the access of desperately ill patients to promising experimental drugs. Such patients, of course, include those who suffer from AIDS.

FDA's "treatment" regulations for investigational new drugs (IND) provide a mechanism for drug developers to provide promising experimental drugs to patients with immediately life-threatening or certain serious conditions before complete data on the drug's efficacy or toxicity are available to enable approval for full commercial distribution. They became effective in June 1987 following the highly successful use of a treatment IND-type mechanism for the early distribution of zidovudine to some 4,000 AIDS patients in 1986. FDA granted this treatment IND request within 5 working days of its submission.

These new treatment IND regulations have already produced significant results. A treatment IND protocol by FDA in February 1988, for example, allowed for expanded, pre-approval distribution of the experimental drug trimetrexate for certain patients with *Pneumocystis carinii* pneumonia.

This treatment IND was granted on the basis of clinical trial studies of the drug conducted by the National Cancer Institute which strongly indicated that the drug might be effective in AIDS patients with *Pneumocystis carinii* pneumonia who had severe or life-threatening adverse reactions to the two conventional approved treatments for this indication—injectable pentamidine and trimethoprim/sulfamethoxazole.

Under the terms of this protocol, trimetrexate, along with the drug leucovorin (the two drugs must be used in combination because leucovorin protects human cells from the potentially lethal effects of trimetrexate), were made available to physicians with eligible patients through a distribution system administered by the National Institute of Allergy and Infectious Diseases.

FDA's Organizational Changes

In addition to these procedural initiatives, FDA has undergone some important organizational changes in order to review potential treatments for AIDS more expeditiously and efficiently. To ensure more specialized treatment of drugs and biologics under review, the drug and biologic components which made up the old Center for Drugs and Biologics have each been elevated to full Center status (the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research). Through this reorganization FDA hopes to tailor further its reviewing system to meet the specific needs of each of these product types.

To nurture promising AIDS treatments and vaccine candidates, FDA is developing two highly specialized review divisions: the Division of Anti-Viral Drug Products within the Center for Drug Evaluation and Research will concentrate its efforts on candidate AIDS drugs, and the Division of Cytokine Biology within the Center for Biologics Evaluation and Research will help to facilitate applied AIDS research to advance the development of biologic agents that are intended to treat the disease.

Vaccine Research

In this regard, FDA virologists have been heavily involved in research and development efforts in devising a vaccine against HIV. Their work has focused on developing methodologies for standardization, preclinical characterization, clinical testing, and evaluation of safety and efficacy of candidate vaccines. Thanks to the high degree of cooperation among FDA officials, other government researchers, and the private developers of candidate vaccines against HIV, the initial steps toward this objective are already underway.

In August 1987, FDA sanctioned the first human testing of a candidate vaccine against HIV in the United States. The vaccine, developed by MicroGeneSys Inc., is being tested under the auspices of the National Institute of Allergy and Infectious Diseases at its clinical center in Bethesda, MD, and through its AIDS vaccine evaluation units at universities across the country.

Another candidate vaccine, developed by Bristol-Myers Co., was sanctioned for clinical testing in November 1987. This vaccine is composed of vaccinia virus into which has been inserted, through recombinant DNA techniques, genes for the surface or envelope proteins from HIV.

It should be noted that successful development and testing of a vaccine against HIV is likely to be a relatively long and arduous task. The first vaccine against the hepatitis B virus—a virus that had been recognized and studied for decades—took more than 17 years to develop and test. Nevertheless, this early work on a vaccine against the HIV virus represents an encouraging first step in this long-term effort.

Under our system, drug companies, universities, and Federal research organizations, such as the National Institutes of Health, are responsible for the design, development, and evaluation of research leading to the formulation of the application for approval by FDA of AIDS therapies, vaccines, and diagnostics. FDA gives their products expedited treatment through the 1-AA process.

By law, safety and efficacy are the only standards upon which the agency can base its decisions concerning proposed treatments for AIDS or any other disease. In the final analysis, approval of a particular AIDS drug still depends on whether good clinical data have shown it to be safe and effective for its intended use.

Therefore, FDA cooperates to the fullest extent possible with any scientifically sound effort to test and develop AIDS diagnostics, vaccines, and treatments. We are committed to working with all medical and scientific groups within the private and public sectors that are developing potential AIDS therapies, vaccines, and diagnostics.

Actions in Other Areas

FDA has also worked in other ways to help facilitate the PHS effort against AIDS. For example, in keeping with Surgeon General C. Everett Koop's clearly enunciated views on the importance of the proper use of high-quality latex condoms in reducing the spread of AIDS, FDA has increased its inspection of the manufacturing and processing of condoms. This action includes programs for testing both domestic and foreign made condoms to ensure conformance with FDA's current good manufacturing practice regulations. Any condoms out of compliance with FDA standards are recalled from the market.

In a related area, FDA has begun a surveillance and sampling program to ensure the quality of latex surgical gloves, which help to protect health care providers from exposure to infection.

FDA is also working diligently to protect the public against fraudulent and dangerous AIDS "treatments." The agency has worked closely with other Federal, State, and local authorities to take action against those promoting quack AIDS products. The agency has prominently featured examples of AIDS quackery in its ongoing campaign to educate the public about health fraud.

FDA is committed to continuing its fight against AIDS on these several fronts, and particularly to expediting the review of promising candidate AIDS treatments, vaccines, and diagnostics.

The agency is working closely with the other Public Health Service agencies and with researchers in academia and the private sector in this effort. This cooperation has already helped to develop promising approaches to combatting the disease and dealing with many of its consequences. By continuing to work together on this challenge, we can build on the progress already made against AIDS and hasten the day that it will no longer be a threat to mankind.