

Long-Acting HIV Treatment and Prevention Are Coming Preparing for Potential Game Changers



July 2018

**FROM LABORATORY
TO MARKETPLACE**

amfAR
MAKING AIDS HISTORY

The Foundation for AIDS Research

Innovative products for treating and preventing HIV infection are under development. Sometimes called long-acting agents, such products may take different forms ranging from injections to implants to oral medications. If determined to be safe and effective, what could make these new products transformative is that they would not require daily dosing. Some products may require monthly dosing and others may require administration only a few times a year. Taking an idea and turning it into a desirable, effective, affordable, and accessible product is a long and difficult process. To facilitate the analysis and policy decisions needed to advance the process, we describe here some of the issues that must be considered to make durable new HIV treatment and prevention options available for individuals.

FROM LABORATORY TO MARKETPLACE

Several pharmaceutical manufacturers are actively engaged in developing innovative new therapies both to treat and prevent HIV infection. If successful, new long-acting products that do not require daily oral dosing could make their commercial debut within the next few years. The Food and Drug Administration (FDA) must first approve the products for sale and marketing in the United States. The FDA is the federal agency responsible for ensuring the safety, efficacy, and security of drugs, biological products, and medical devices. To obtain FDA approval, a manufacturer of a proposed new product must conduct laboratory, animal, and clinical testing on its safety and effectiveness and submit that information to the FDA. Then the FDA will review the data and may approve the product if the agency determines that it is safe and effective for its intended use and that the benefits outweigh the risks. The FDA approval processes used for drugs, biological products, and medical devices vary and can be difficult to understand, with different classes and tiers of approval.

While the FDA has well-established procedures, long-acting products for HIV treatment and prevention may raise new questions and challenges. For products that remain in the body and bioactive for long periods of time, different chemistry, manufacturing, and control (CMC) measures will be required to assess long-term safety and effectiveness. The FDA also may

Long-Acting HIV Treatment and Prevention: Bringing Innovative Therapies to Market

The Food and Drug Administration (FDA) will have to determine that new products are safe and effective, both in HIV-positive and HIV-negative individuals. The FDA also will need to consider unique questions related to long-acting products, such as the potential to spur drug resistance.

Policy planning should begin now:

- ▶ **Pharmaceutical manufacturers, prescribers, and consumers should work to prepare the FDA for prospective HIV treatment and prevention options.**
- ▶ **Congress should provide adequate funding to support development and review of long-acting products for HIV treatment and prevention.**
- ▶ **Policy makers should begin planning to bring together relevant parts of the FDA to consider the range of potential delivery mechanisms (e.g., pills, injectables, implants, intravaginal rings) and work to expeditiously review new drug applications and provide clear guidance for manufacturers and the public on key issues.**

need to consider questions about the potential for the use of long-acting antiretroviral therapy (ART) to spur drug resistance.

The complexity of issues related to long-acting products creates substantial obstacles to efficient FDA review.

Moreover, long-acting products are being formulated in a variety of delivery mechanisms, such as pills, injections, implants, and intravaginal rings (IVRs). While pills and injections would be classified as drugs, implants and IVRs may contain both drug and device components. These so-called combination products present unique challenges for the FDA. Not only is their classification as a drug or medical device not always clear, but such products also necessitate additional regulatory considerations. Although some products are clearly a drug or a medical device, an implant that intuitively seems to be a medical device may, in fact, be classified as a drug. Classification ultimately determines the regulatory center within the FDA to which the product is assigned. This center has primary jurisdiction over the review of the combination product, but multiple centers and discipline review areas are involved in and can complicate the review process. Combination products can further present unique risks and benefits compared with non-combination products for similar uses.

Beyond the aforementioned products, innovative multi-purpose technologies (MPTs) also are in development. MPTs may contain more than one drug with different indications and aim to address multiple sexual and reproductive health needs (HIV, sexually transmitted infections, and contraception) in one product. To date, MPTs in development include gels and long-acting drug delivery systems, such as IVRs, designed to prevent HIV and unintended pregnancy. The inclusion of long-acting agents for HIV treatment or prevention within MPTs has the potential to increase product uptake, adherence, and satisfaction.

The FDA has significant experience with long-acting and extended-release products for other conditions, including long-acting injectable antipsychotics for schizophrenia and a variety of long-acting products for contraception. Nonetheless, there is often an unavoidable level of uncertainty involved in the FDA's determinations, especially with

respect to novel classes of products. While consumers may want to bring long-acting HIV treatment and prevention to market as quickly as possible, the complexity of issues related to long-acting products creates substantial obstacles to efficient FDA review. Establishing clear standards for how the FDA will evaluate different products, as well as the standards that these products will be required to meet, is critical to ensuring a review and approval process that is both efficient and rigorous.

FDA Review and Product Approval

Drug Approval Process: Drugs are regulated by the Center for Drug Evaluation and Research (CDER) of the FDA.¹ Developing a new drug can take 10 or more years and begins with preclinical testing in rigorous *in vitro* and animal studies. The FDA actively engages manufacturers during preclinical studies and early CMC development to ensure that the appropriate data are generated to support clinical trials in humans. Before any human testing is done, the manufacturer must submit an Investigational New Drug (IND) application to the FDA. An IND application includes preclinical study data for review by CDER physicians, statisticians, chemists, pharmacologists, and other scientists, along with information about the chemical composition of the drug, an account of the manufacturing process, and proposals for testing the drug in humans. When reviewing preclinical study data, CDER is looking for three things: (1) the pharmacological profile of the drug, (2) the acute toxicity of the drug in at least two species of animals, and (3) the short-term (two weeks to three months) toxicity

Safety, Efficacy, and Effectiveness

Safety determines the highest tolerable dose or optimal dose needed to achieve the desired clinical effect and potential adverse effects in that exposure range.

Efficacy is a measure of a drug's positive clinical benefit over placebo or other intervention under ideal or strictly controlled conditions.

Effectiveness describes a drug's clinical benefit in a "real world" situation, such as when people have comorbid conditions or take other medications that interact with the drug, or when drug administration may not follow study guidelines.

in animals, to support the proposed duration of use in the first human trials. These data points serve as the basis for an FDA determination as to the reasonableness and safety of proceeding to human clinical trials.

Clinical trials are usually conducted in three, and sometimes four, phases that build on one another.

After preclinical studies, drug approval requires human clinical trials to establish the safety and efficacy of new drugs. Clinical trials are usually conducted in three, and sometimes four, phases that build on one another. Each phase is initiated via a manufacturer's submission of an IND to the FDA. The manufacturer may begin proposed trials 30 days after submitting an IND, as long as the FDA does not object within that time.

Phase I trials are designed to identify potential side effects at different dosages of the drug, as well as to determine the distribution, metabolism, and pharmacological actions of the drug in humans. Potential therapeutic activity is a secondary concern. The trials usually study fewer than 100 people and take less than a year. The success of these trials is predicated on showing that the drug is safe and well tolerated among healthy people at the doses studied. Approximately 70% of drugs in Phase I trials move to the next phase.

Phase II trials have three primary goals: (1) determine drug dose ranges; (2) evaluate the efficacy of the drug; and (3) continue to identify short-term side effects and associated risks. These trials enroll hundreds of people and take one to two years to complete. The trials are usually randomized, which means participants are assigned by chance either to a group receiving the study drug or to a reference or control group receiving standard treatment or, if there is no standard treatment, a dummy medication called a placebo. In some trials, neither the participants nor their health care providers know who is getting the study drug or the placebo. This is called a double-blinded study. The success of Phase II trials is predicated on determining whether the drug has any efficacy and side effects for people who have a certain disease or condition. Approximately 33% of drugs in Phase II trials move to the next phase.

Phase III trials can study up to a few thousand people and often last for two years or more. These trials are usually randomized and blinded. By the time they reach Phase III trials, the investigational drugs have demonstrated preliminary evidence of efficacy and safety, and these trials seek to collect more data on a drug's efficacy and side effects, using the dose selected in earlier trials, and to evaluate the overall benefit-risk profile of the drug. Before applying for approval to sell the new drug, a manufacturer generally meets with reviewers from CDER to present a summary of clinical studies and to talk through any issues, problems, or deficiencies that have arisen. The success of Phase III trials is predicated on demonstrating whether the drug offers a treatment benefit to the population with the disease or condition. Approximately 25–30% of drugs in Phase III move to the next phase or are approved.

Phase IV trials are known as “post-marketing studies” because they take place after the FDA approves the marketing of a new drug. If conducted, the trials can monitor the long-term effects of new drugs and treatments over a longer period and among a greater number of people. Post-marketing success is achieved through documentation and persuasive demonstration of long-term safety, efficacy, and effectiveness.

Phases of Clinical Trials

Preclinical Trials assess biological activity and preliminary safety; they include *in vitro* studies and animal studies.

Phase I Trials are initial safety and activity evaluations to determine a safe dosage range, identify side effects, and study the toxicity profile of the drug; they include 20–80 healthy subjects.

Phase II Trials determine drug dose ranges, evaluate efficacy, and continue to identify short-term side effects and associated risks; 100–300 subjects with the target condition participate.

Phase III Trials are a final confirmation of safety and efficacy; 1,000–3,000 subjects with the target condition are studied.

Phase IV Trials are any trials conducted after FDA approval of the drug. They monitor long-term efficacy, safety, and side effects.

Expedited Programs

Typically, a manufacturer submits a New Drug Application (NDA), a formal proposal requesting approval to market a new drug in the United States, after completing Phase III trials. To ensure the submission of a well-organized and readily reviewable NDA, a manufacturer may benefit from a pre-NDA meeting with the FDA. CDER often convenes advisory panels of experts to review clinical data and usually follows the panel's recommendations. The FDA also evaluates drug samples, inspects the production facilities, and checks proposed labeling before making a determination of approval status. Approval may include specific conditions, such as requiring the manufacturer to complete Phase IV trials to assess efficacy or safety concerns or to address quality of life or cost-effectiveness.

A New Drug Application (NDA) is the formal proposal requesting approval to market a new drug in the United States.

The FDA determines whether a drug meets criteria to qualify for expedited programs for serious conditions: fast track, breakthrough therapy, accelerated approval, and priority review.² The purpose of these four programs is to help ensure that therapies for serious conditions are approved and available to individuals as soon as it can be concluded that the therapies' benefits justify their risks. To qualify for an expedited program, the drug must be intended to treat a serious condition and must address an unmet medical need, such as a condition whose treatment or diagnosis is not addressed adequately by available therapy. A drug may qualify for more than one expedited program.

The FDA's determinations about expedited programs tend to be made before the manufacturer submits an NDA, and the manufacturer must request some program designations. Ideally, a request for breakthrough therapy designation is submitted no later than the end of Phase II clinical trials, and a request for a fast track designation is submitted no later than the pre-NDA meeting. The FDA must respond to all fast track and breakthrough designation requests within 60 days.

Expedited Programs for Drug Review

The Food and Drug Administration (FDA) has developed four distinct approaches to making drugs available as rapidly as possible.

Fast Track: Fast track is a process designed to facilitate the development and expedite the review of drugs that treat serious conditions and fill an unmet medical need. AIDS is specifically listed as a serious condition on the FDA Fast Track website, and certain HIV therapies may qualify for this designation if they fill an unmet medical need (e.g., better therapy than those currently available). The designation must be requested by the manufacturer and entitles the manufacturer to frequent meetings and communication with the FDA throughout the drug approval process, and to eligibility for accelerated approval and priority review, if relevant criteria are met.

Breakthrough Therapy: Breakthrough therapy is a process designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapy. For example, reductions in HIV-RNA levels would likely qualify as an effect on an established surrogate endpoint and may be grounds for breakthrough therapy designation, depending on the level of reduction. Breakthrough therapy designation is requested by the manufacturer, but the FDA may also suggest that a manufacturer consider submitting a request if the manufacturer has not requested breakthrough therapy designation. This designation provides the manufacturer with the features of fast track designation, in addition to more intensive guidance and organization commitment involving senior managers at the FDA.

Accelerated Approval: Under the Food and Drug Administration Safety Innovations Act, the FDA may accelerate approval of drugs for serious conditions that fill unmet medical needs if the drug has an effect on a surrogate or intermediate clinical endpoint.

Priority Review: A priority review designation means the FDA's goal is to take action on an application within six or eight months. This designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. The FDA decides on the priority review designation for every application. However, an applicant may expressly request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics. Manufacturers of HIV drugs may also procure priority review vouchers (PRVs), which have been awarded to other manufacturers that have successfully developed and commercialized treatments for tropical and rare pediatric diseases. Pharmaceutical manufacturers ViiV and Gilead have both purchased PRVs for speeding the review and approval of HIV drugs, including Juluca and Odefsey, respectively.

A drug that qualifies for a fast track or breakthrough therapy designation or the accelerated approval pathway can qualify for, but is not guaranteed, priority review. Only the priority review designation specifies a shorter review timeline. A priority review designation means that the FDA review team plans to take action on the marketing application at least one month prior to the goal date indicated in the Prescription Drug User Fee Act (PDUFA). For all drugs classified as new molecular entities (NMEs), the priority review timeline is within eight months of receipt of the NDA, whereas the standard review timeline is within 12 months of receipt of the NDA. For non-NMEs, the priority review timeline is six months, and the standard review timeline is 10 months.

To qualify for an expedited program, the drug must be intended to treat a serious condition and must address an unmet medical need.

Drugs given priority review are distinct from those receiving standard review in that they represent a significant advance from currently available therapies. Examples of significant advances may include increased effectiveness in the treatment, prevention, or diagnosis of a condition; elimination or substantial reduction in a treatment-limiting drug reaction; enhancement of patient compliance; or evidence of safety and effectiveness in a new subpopulation of patients. In the case of HIV drugs, those satisfying unmet medical needs are particularly apt for priority review.

Device Approval Process: Devices are regulated by the Center for Devices and Radiological Health (CDRH) of the FDA. Medical devices often go through a less arduous review process than drugs, and most classes of medical devices do not require true clinical trial testing for safety and efficacy. The Food, Drug, and Cosmetic Act requires that the FDA determine the safety and effectiveness of a device by weighing any probable benefit to health from the use of the device against probable risk of injury or illness. The greater the risk, the greater the benefit that needs to be demonstrated to balance the risk. This also means that greater risk comes with greater FDA oversight.

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of

devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

The class of device determines which pathway of premarket review the FDA will require. Class I devices are low-risk products and are generally exempt from premarket review. Most manufacturers of Class I devices, such as toothbrushes and thermometers, do not have to obtain FDA approval before they market their products.

Class II devices pose potentially higher risks and require premarket notification (PMN). The vast majority of devices fall within Class II, and these devices are described as FDA-cleared, not approved. This class of devices includes glucose test strips, electrodes, and monitoring devices, as well as contact lenses, gloves, tampons, and condoms. Injecting pens and related injectors provide an innovative approach to delivering long-acting products, and many injectors are Class II devices. Injectors intended for general use with a wide range of drug or biological products often are regulated as Class II devices, as are injectors intended for use with a certain class or family of products. However, injectors intended for use with a specific drug or biological product, such as those pre-filled with the product, co-packaged with the product, or separately distributed but labeled for

Classes of Medical Devices

The three classes of medical devices provide a risk-based system of regulation.

Class I devices present the least potential for harm to the user and are generally exempt from the regulatory process, meaning premarket notification and FDA clearance are not required prior to marketing.

Class II devices present a greater potential for harm to the user and generally require premarket notification via a 510(k) application. Devices must show equivalence to an existing legally marketed device and are described as FDA-cleared.

Class III devices present the greatest potential for harm to the user and require the most formal review process for devices, known as premarket approval, which stipulates that the product must demonstrate safety and effectiveness.

use together, are typically considered combination products, which have different regulatory requirements from medical devices.

Beyond scientific and technical considerations for premarket review, injectors raise practical considerations related to making them easy to use and accessible. Scientific and technical considerations include injection site (e.g., the area of the body where the product is injected); intended injection tissue and depth of injection (e.g., subcutaneous, intramuscular, intradermal); intended user (e.g., patient, caregiver, health care provider); type of use (e.g., use as a single, disposable, reusable, or refillable injector); and purpose and condition of use (e.g., use with a specific product or a range of products, packaging configuration). One practical consideration is that injectors may have a separate patent from the drug or biological product, which can sometimes lead to cost and access problems, particularly in the first years after marketing begins.

Class III devices have the highest risk potential and are subject to the strictest type of regulation. These devices are said to be FDA-approved. Many implants likely would be classified as Class III devices.

There are essentially two pathways that a new device can follow to gain approval for marketing in the United States: Premarket Notification (PMN, also known as the 501(k) application) or the Premarket Approval (PMA). A PMN is a fast-track process for devices in which the manufacturer demonstrates that the proposed new medical device is “substantially equivalent” to an existing legally marketed device. Products reviewed under this pathway are generally commercialized in 90 days or less. Substantial equivalence is met if, in comparison to a legally marketed device, the proposed new device is (1) as safe and effective, (2) has the same intended use and technological characteristics, and (3) does not raise new questions of safety and effectiveness. Applications may require performance and effectiveness testing, depending on the device’s technological characteristics and risks, and some devices may require clinical evaluation data supporting applications.

The FDA may determine that the proposed new device is not substantially equivalent to a legally marketed device and refuse the 501(k) application, and then a full PMA will be required. In contrast to the PMN, the PMA requires clinical data providing suitable demonstration of safety and effectiveness for all diagnostic and/or therapeutic claims. To conduct premarket clinical investigations

for devices, the manufacturer must obtain FDA approval, apply for investigational device exemption (IDE), or be exempt from IDE regulation. Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending upon the level of risk. The IDE regulation further distinguishes between significant and non-significant risk device studies. Studies of devices that pose a significant risk (e.g., heart valves, pacemakers, intraocular lenses) require both FDA and Institutional Review Board (IRB) approval prior to initiation of a clinical study, whereas studies of devices that do not pose a significant risk (e.g., contact lenses, cotton menstrual pads, or tampons) require only IRB approval prior to initiation of a clinical study.

Combination Products: Some products regulated by the FDA do not fit exclusively into the category of drug or device, but rather are a combination of a drug and a device. Combination products include some of the delivery systems being formulated for long-acting products, such as HIV drug-eluting implants and, if intended for use with a specific HIV drug, injectors such as injecting pens. The Office of Combination Products within the FDA is responsible for classifying each combination product as a drug, device, or biological product and assigning the review of that product to the most appropriate center. Classification is determined based on the primary mode of action, which is defined as the single mode of action that provides the most important therapeutic action of the combination product.

Combination products include some of the delivery systems being formulated for long-acting products, such as HIV drug-eluting implants and, if intended for use with a specific HIV drug, injectors such as injecting pens.

A combination product is held to the same premarket approval and regulatory processes as a non-combination product regulated under the assigned center. While this center will be assigned as the primary jurisdiction, review of a product with both drug and device components will be performed by a combination of divisions in both CDER and CDRH. In the case of a long-acting product that is a drug-eluting implant, review would likely involve the Antiviral Division and perhaps also other larger divisions and offices within CDER working with an engineering review team and other device experts within CDRH.

Special Considerations for the Development of Long-Acting HIV Treatment and Prevention

In November 2015, the FDA released guidance for industry regarding the development of HIV antiretroviral drugs for treatment.³ This guidance is applicable to the development of long-acting products, but does not address the development of antiretroviral drugs for preventing HIV.

The guidance stresses several important points. HIV antiretroviral drug development should pay close attention to five issues in preclinical studies: (1) mechanism of action; (2) antiviral activity in cell culture; (3) cytotoxicity and mitochondrial toxicity; (4) combination antiviral activity; and (5) resistance and cross-resistance. Drug development in clinical studies should evaluate the drug's effect on reducing HIV-RNA levels from baseline and provide for evaluation of short-term safety considerations.

Because long-acting injectable formulations take longer to clear the body, it can be hard to reverse side effects if they occur.

The guidance divides the HIV patient population in clinical studies into three groups depending on patients' treatment experience and potential drug resistance. These groupings reflect differences in the patient population and help ensure evaluation of a wide range of patients. The groupings also provide a framework for which drugs may qualify for expedited programs, such as fast track and breakthrough designations. For example, new drugs with favorable resistance profiles that retain activity to viral strains resistant to approved drugs are likely to fill an unmet medical need in treatment-experienced patients. For most treatment studies, the primary efficacy endpoint is generally the proportion of patients with HIV-RNA less than the lower limit of quantification (what is colloquially called "undetectable") at 48 weeks (or 24 weeks for drugs with a likely treatment advantage over available options for treatment-experienced patients). For some studies with treatment-experienced patients, the primary efficacy endpoint should be the proportion of patients with HIV-RNA decreases from baseline exceeding 0.5 log₁₀ or greater at an early time point (up to two weeks).

Long-Acting Formulations: Long-acting products, especially injectable formulations, raise considerations over and above those generally applicable to the development of HIV antiretroviral drugs for treatment. In a recent commentary on long-acting injectable antiretroviral therapy,⁴ Linda Mobula and colleagues outline some of these considerations. Compared to standard oral formulations, long-acting injectable formulations typically take more time (several days rather than hours) to reach maximum concentration in the body. While long-acting, injectable ART can be developed in the absence of a lead-in phase of oral medication, this research suggests that a period of oral induction therapy (whereby the drug product is first administered orally) may be necessary to achieve appropriate drug concentrations until maximum concentration is achieved.

Another and a primary reason for oral induction therapy is to gauge hypersensitivity or drug toxicity, so that adverse events can be avoided. This points to a significant safety concern raised by long-acting therapy. Most antiretroviral drugs are not dialyzable (meaning they cannot be removed from the body via dialysis), so once the drug is administered, it may not easily be removed. Moreover, because long-acting injectable formulations take longer to clear the body, it can be hard to reverse side effects if they occur.

There is also an increased risk of prolonged low drug concentrations from missed doses. This is worrying because resistance can develop when drugs remain in the body for significant periods of time, yet in amounts below the level of effectiveness. So while long-acting injectable formulations for HIV treatment and prevention are likely to decrease adherence burden, the consequences of non-adherence may be greater. Therefore, a significant concern of the FDA and treating physicians will be to ascertain the potential for both injectable and non-injectable long-acting products to lead to drug resistance.

Long-acting products may play a larger role in assisting some key populations than others, and understanding who could benefit most should play a role in assessing how to deploy new products for HIV treatment and prevention.

Policy Development Should Begin Now

Below are three ways that federal policy makers and administrators, pharmaceutical manufacturers, consumer advocates, and others can prepare the FDA to consider relevant scientific and policy issues related to long-acting HIV treatment and prevention.

1. **Pharmaceutical manufacturers, prescribers, and consumers should work to prepare the FDA for prospective HIV treatment and prevention options.**

Policy analysis and planning should begin now to lay the groundwork for a future with long-acting products for HIV treatment and prevention. FDA approval of a new product is merely the ultimate goal of the FDA review process. Throughout the process, pharmaceutical manufacturers, consumers, and others usually meet several times to discuss both scientific and regulatory issues and identify potential areas of concern.

It is important that consumers and advocates have an open dialogue with the FDA about community priorities and scientific and policy issues pertaining to long-acting treatment and prevention.

Often meetings between the FDA and manufacturers take place at predefined times, such as right before or right after submission of clinical data or an NDA. But manufacturers can request meetings at other times to discuss product development plans with FDA regulators and clarify interpretations of regulations. Manufacturers should meet with the FDA to get feedback about the appropriateness of proposed trials, sufficiency of clinical data, and adequacy of the format for submitting information.

Some issues that may require more immediate attention concern the standards and the type of review that the FDA will use to assess long-acting products. The benchmark standard for FDA review is based on non-inferiority (which means a drug needs to demonstrate it is no less effective than currently approved products), especially for treatment-naïve patients in treatment studies and for gay and bisexual men in

prevention studies.⁵ In a non-inferiority trial design, patients are randomized to receive either a standard-of-care regimen or the same regimen with the investigational product substituting for one of its components, and they are followed for at least 48 weeks. This design is used to show that the new regimen is not inferior to the standard-of-care regimen as the active control.

For highly treatment-experienced patients, a non-inferiority trial design may not be feasible because there are usually no standard regimens. Depending on the exact patient population to be studied, an active control group will be formulated to serve as a basis of comparison with the new product. The appropriate trial design for a patient population in which drug resistance is present, and for which it is possible to construct a suppressive regimen, is an active-controlled non-inferiority comparison with or without comparisons of multiple doses of the investigational drug. Manufacturers should discuss proposed trial design, especially for non-inferiority trial proposals, with the FDA well in advance of any trial and provide detailed supporting documentation for non-inferiority treatment-experienced trials early in the protocol development stage. Before the completion of clinical trials, manufacturers should also consider whether their new drug applications are eligible for expedited programs, such as fast track and breakthrough designations.

In addition to manufacturers, consumers within the HIV community and consumer advocates also have a role to play in preparing the FDA for long-acting products. The HIV community has a longstanding and strong relationship with leadership and staff at the FDA. This relationship has helped to accelerate effective drug development in the past and saved millions of lives. It is important that consumers and advocates have an open dialogue with the FDA about community priorities and scientific and policy issues pertaining to long-acting HIV treatment and prevention. These may include ascertaining the potential for long-acting products to lead to drug resistance and finding ways to streamline the medical product review process. The use and consideration of background HIV incidence data, for example, could be one way to streamline the development and approval of long-acting products for HIV prevention.

2. Congress should provide adequate funding to support the development and review of long-acting products for HIV treatment and prevention.

The product review and approval process is heavily influenced by funding allocations authorized by Congress. Federal funding to conduct innovative research, ensure appropriate levels of FDA staffing, and support FDA commitments to product review timelines is important and can help deliver on the promise of the 21st Century Cures Act (Cures Act).⁶ Further, learning derived from the development of long-acting formulations for HIV treatment and prevention could also benefit other conditions requiring lifelong or long-term treatment.

The 21st Century Cures Act

The 21st Century Cures Act (Cures Act) was signed into law in December 2016 to help accelerate medical product development and more quickly bring new innovations and advances to individuals who need them. One provision of the Cures Act enables faster drug approvals by expanding the kinds of evidence, including biomarkers and surrogate endpoints, used to evaluate a product's efficacy. Another provision gives the FDA new authority and funding to hire and retain scientific, technical, and professional experts the agency needs for executing the Cures Act. These provisions underscore issues potentially relevant to the development of long-acting products for HIV treatment and prevention.

In regard to research, the NIH has played a central role in nearly every major HIV scientific advance since the beginning of the HIV epidemic and is currently sponsoring various studies of long-acting injectable and implantable products. While Congress rejected the Trump Administration's proposal to cut the NIH budget by \$7.7 billion, or 22 percent, for fiscal year 2018, increased federal funding is crucial to support NIH research and the development of long-acting HIV treatment and prevention products, so that they enter the review pipeline.

In regard to the FDA, long-acting products require an expanded workforce of experts to guarantee efficient review, let alone expedited review. As the federal budget and appropriations process moves forward, Congress must determine whether the FDA has the staff and resources to provide timely review of product applications and

associated regulatory activities. Progress toward making long-acting HIV treatment and prevention available to the public may be slowed if the FDA does not have adequate funding to carry out its work.

On August 18, 2017, the President signed into law the Food and Drug Administration Reauthorization Act, which includes reauthorization of the Prescription Drug User Fee Act (PDUFA) through September 2022. PDUFA authorizes the FDA to collect fees from manufacturers that produce certain human drug and biological products, and these fees constitute a significant portion of the resources to fund the drug approval process. In addition to Congressional commitment to PDUFA reauthorization beyond 2022, Congress should ensure adequate funding through the appropriations process and ensure the FDA's commitment to stringent regulatory review, whereby safety and effectiveness remain paramount to public health and commercialization practices.

3. Policy makers should begin planning to bring together relevant parts of the FDA to consider the range of potential delivery mechanisms (e.g., pills, injectables, implants, and IVRs) and work to expeditiously review new drug applications and provide clear guidance for manufacturers and the public on key issues.

To make long-acting HIV treatment and prevention available to the public as soon as possible, the FDA will have to efficiently review proposed new products. The President has said his administration will significantly cut the length of time it takes the FDA to approve medical products, and some policy makers in the Trump Administration and Congress have even suggested bypassing Phase III clinical trials or combining Phase II and Phase III clinical trials as a way to speed drug approvals. While the 21st Century Cures Act creates new mechanisms to bring products to market faster, several details, including any applicability to long-acting products for HIV treatment and prevention, remain unclear. The Cures Act vests agencies with broad discretion over whether and how to decrease regulatory burdens and speed innovation. As a result, the FDA has a significant role in deciding what is and is not required for product approvals. The FDA commissioner and other key agency officials should not eliminate Phase III trials as the gold standard for clinical trial methodology, since Phase III trials often provide information beyond that provided by Phase II trials and are therefore essential to confirming a product's safety or efficacy.⁷

As policy makers work to promote an efficient approval process, maintaining rigorous evidence-based standards is important. Under certain circumstances, this may mean granting fast track or breakthrough therapy designations. In the case of the long-acting products for HIV treatment and prevention, not only are Phase III trials likely necessary to sufficiently evaluate safety and efficacy, but further Phase IV trials and/or risk evaluation and mitigation strategies (REMS) may be needed to examine long-term issues, such as adherence in the real world and drug resistance. The FDA should provide clear guidance for manufacturers and the public on these and other key issues concerning long-acting products.

To make long-acting HIV treatment and prevention available to the public as soon as possible, the FDA will have to efficiently review proposed new products.

Policy makers also should make plans now to bring together relevant parts of the FDA to consider the various delivery mechanisms for long-acting products, such as pills, injections, implants, and IVRs. As discussed above, different delivery mechanisms are regulated by different, and in some cases, multiple parts of the FDA. CDER regulates drug products and includes an Office of Antimicrobial Products (OAP) as part of its Office of New Drugs. OAP is comprised of three review divisions: the Division of Anti-Infective Products, the Division of Antiviral Products, and the Division of Transplant and Ophthalmology Products. For long-acting products for HIV treatment and prevention, the Division of Antiviral Products has the most relevant expertise in the range of issues and is the review division and point of contact.

While the FDA's Office of Combination Products will ultimately determine whether to classify a long-acting implant as a drug or a device, a likely classification as a drug would involve CDER and also

require collaboration with device reviewers, divisions, and offices within the CDRH. For multi-purpose technologies, such as IVRs, the Division of Antiviral Products would likely be the primary review division, but might work closely with the Division of Anti-Infective Products, the Division of Bone, Reproductive and Urologic Products, and other drug divisions, as well as with device reviewers, divisions, and offices within CDRH. Policy makers need to begin planning to prepare the respective parts of the FDA, so that the agency does not face unnecessary delays in reviewing impending results from clinical and nonclinical trials of long-acting products.

Conclusion

FDA approval of long-acting products is a critical first step in a long chain of policy decisions that will be needed to offer people with HIV and people at risk for HIV infection new treatment and prevention options. Beyond the long-acting products currently in development, multipurpose technologies, which combine protection against multiple risks such as unintended pregnancy, HIV, and other sexually transmitted infections, are also on the horizon. Multipurpose technologies could include long-acting agents and have the potential to address more effectively the comprehensive prevention needs of vulnerable groups and communities, including gay and bisexual men, transgender people, and women of color.

The diversity of products under development likely will offer individuals and providers a variety of new choices, yet a range of scientific and regulatory issues in the FDA review process must be considered, as well as complexities of balancing access to these important, innovative products while continuing to ensure their safety and effectiveness. These new products are generating excitement for their potential to save lives and avert new infections. Therefore, policy actions must be taken now to reduce the risk of roadblocks and setbacks that could delay the introduction of long-acting products into the marketplace.

Prepared for amfAR by Sean E. Bland and Jeffrey S. Crowley
O'Neill Institute for National and Global Health Law, Georgetown Law, July 2018

The authors thank and acknowledge the following individuals who offered insights into relevant policy issues or reviewed drafts of documents produced for this project: Rivet Amico, Dawn Averitt, Lindsey Dawson, Rick Elion, David Evans, Michael Horberg, Tim Horn, Naina Khanna, Ann Lefert, Britten Pund, Ace Robinson, Andrea Weddle, along with numerous federal agency staff members.

REFERENCES

1. Certain products that replicate natural substances such as enzymes, antibodies, or hormones in the body, known as biologics, are regulated by the Center for Biological Evaluation and Research (CBER); but in 2003, the regulation of biopharmaceuticals, such as interferon and monoclonal antibodies that are used for therapeutic purposes, was transferred from CBER to CDER. Most biological products meet the definition of drugs and are regulated like drugs. Whereas a new drug application (NDA) is used for drug products subject to the approval provisions of the Food, Drug and Cosmetic Act, a biologics license application (BLA) may be required for biological products subject to licensure under the Public Health Service Act. FDA form 356h is used for both NDA and BLA submissions. FDA approval to market a biologic is granted by issuance of a biologics license. For more information, see Frequently Asked Questions About Therapeutic Biological Products. Food and Drug Administration Website. <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm>. Updated July 7, 2015. Accessed May 14, 2018.
2. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. Food and Drug Administration Website. <https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm>. Updated February 23, 2018. Accessed May 14, 2018.
3. Food and Drug Administration Center for Drug Evaluation and Research. *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment—Guidance for Industry*. November 2015. Available at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf>.
4. Mobula L, Barnhart M, Malati C, et al. Long-acting, injectable antiretroviral therapy for the management of HIV infection: An update on a potential game-changer. *J AIDS Clin Res*. 2015;6:466. Available at: <https://www.omicsonline.org/open-access/longacting-injectable-antiretroviral-therapy-for-the-management-of-hiv-infection-an-update-on-a-potential-gamechanger-2155-6113-1000466.php?aid=54755>.
5. For high-risk women, prevention studies are designed as superiority trials because a non-inferiority margin is not possible to construct based on past trial results. This trial design for women, however, could change as a subsequent prevention regimen gets approved.
6. 21st Century Cures Act. Pub. L. No. 114-255, 130 Stat. 1033 (2016). Available at: <https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>.
7. Food and Drug Administration. *22 Cases Studies Where Phase 2 and Phase 3 Trials Had Divergent Results*. January 2017. Available at: <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf>

amfAR

MAKING AIDS HISTORY

www.amfar.org

amfAR Public Policy Office 1100 Vermont Avenue, NW • Suite 600
Washington, DC 20005 • T: +1 202.331.8600 F: +1 202.331.8606