U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Division of Drug Information
10001 New Hampshire Ave.
Silver Spring, MD 20993-0002

December 4, 2018

Samantha Reyes
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Dear Ms. Samantha Reyes,

Thank you for writing to Commissioner Dr. Scott Gottlieb at the Food and Drug Administration (FDA). This is in response to your letter dated August 5, 2018, relayed to us by Professor Anna Matthews on October 15, 2018, regarding the cost of insulin drug products. Your letter was forwarded to the Division of Drug Information in FDA's Center for Drug Evaluation and Research (CDER) for a response. We are responding by email because Professor Matthews provided her email address in her letter.

We understand that high drug prices, including the cost of insulin products, have a direct impact on patients. Please know the FDA has no legal authority to investigate or control the prices set by manufacturers, distributors and retailers, or the extent of coverage provided by insurers; however, the agency is committed to facilitating increased competition in the market for prescription drugs through the approval of lower-cost, generic medicines.

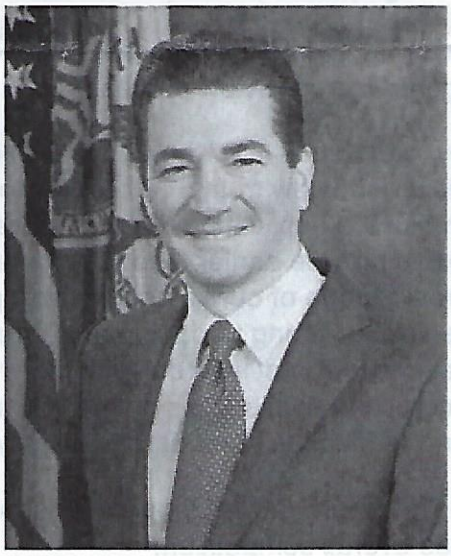
Please read about our Drug Competition Action Plan (DCAP) (online at https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm612018.htm) to learn more about the steps FDA has taken, and plans to take, to facilitate increased competition on the market for prescription drugs. FDA Commissioner Scott Gottlieb, M.D., provided an update on our progress in June 2018, including new infrastructure to support robust generic drug competition. We have attached the update, but it is also available online at https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm611892.htm.

To date, we've taken a number of steps as part of DCAP to help remove barriers to generic drug development and market entry in an effort to spur competition that results in lower drug prices for patients, and greater access. One key aspect of our role is to strengthen and enhance the overall generic drug review process. We've committed to timelier generic drug reviews to reduce the cycles of review that generic applications typically undergo. In 2017, we approved a record number of generic drug applications—more than 1,000 full or tentative approvals. We expect to beat that goal this year. And although the FDA doesn't have a direct role in drug

Budget Matters: Infrastructure to Support Robust Generic Drug Competition

June 18, 2018

By: Scott Gottlieb, M.D.



FDA Commissioner Scott Gottlieb, MD

The FDA launched its Drug Competition Action Plan more than a year ago, with the aim of advancing policies that would promote robust generic drug entry as a way to foster competition and lower drug prices. Access to drugs is a matter of public health. And among the best ways to help consumers get broader access to medicines is through policies that help ensure branded drugs are subject to timely generic competition.

Our work is far from finished. But the policies we've advanced are already showing benefits toward these goals. The benefits we've seen reinforce the fact that policy can be used as a vehicle to advance these purposes.

New resources have also helped advance our work. Owing in large measure to the FDA's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA), which funded critical enhancements to FDA's generic drugs program, our staff eliminated the backlog of generic drug applications. In 2017, we also approved the **largest number of generic drugs (https://blogs.fda.gov/fdavoice/index.php/2018/02/2017-was-another-record-setting-year-for-generic-drugs/)** in the FDA's history.

As part of GDUFA, as well as through our own new efforts, the FDA also has put policies in place to promote generic drug development in areas where there's inadequate competition. This includes a focus on developing new guidance aimed at promoting development of generic versions of complex drugs. These are drugs that are often

harder to copy. By advancing clear, objective, science-based guidance for developing generic copies of complex drugs, we hope to foster more competition.

And the FDA also has improved the efficiency and predictability of the generic drug review process to help promote more robust generic drug competition. For example, we're prioritizing the review of generic drug applications for which there are no blocking patents or exclusivities. The aim is to promote competition so that there are at least four approved applications for each product (including the brand drug). Our data shows that there are significant price decreases once there are at least three generic drugs on the market. Our new policy will help ensure that there is robust competition across the market that will drive down drug costs to consumers.

In addition, we're taking other new steps to curtail various forms of "gaming" by brand companies, where some sponsors sometimes adopt tactics that seek to delay entry of generic competition.

But we know that we need to do even more to promote access and competition. And so we've put forward a broader plan, as part of the President's Budget, to achieve these aims.

Toward these goals, the President's fiscal year 2019 Budget Request included $37.6 million to fund two initiatives that will help modernize aspects of our generic drug review process.

The first initiative will create a new review platform — the Knowledge-aided Assessment & Structured Application (KASA) platform — to modernize generic drug review from a text-based to a data-based assessment. The KASA will enable a structured review that will make the application review process more efficient, and allow deficiencies to be spotted earlier. This will allow the FDA to provide earlier feedback to generic drug makers that will, in turn, help to reduce multiple cycles of application review, one of our key aims and a primary focus of our overall efforts to speed market access to new generic medicines. Going through multiple review cycles is one of the primary reasons why the approval of generic drug applications is sometimes delayed many years. The new KASA system will help sponsors submit high-quality and more complete applications on the first submission. It will decrease the risk that applications will be refused for receipt and reduce the number of review cycles that applications undergo.

We anticipate that the new platform will allow more generic applications to be approved after the first cycle. This will promote timely generic entry and increase overall competition.

The new platform will also enable more efficient and robust knowledge management across different aspects of the FDA's review process, helping reviewers capture and manage all of the information about products allowing for more seamless and effective product surveillance based upon quality and risk. This system will benefit both the agency and generic drug sponsors by increasing overall speed and efficiency of the pre- and post-market processes.

Having a structured template that completely replaces the current largely narrative-based review will allow for more consistent and predictable entry and analysis of data. Current assessments require manual review of the entire application. KASA will enable automated analysis of some portions of the application, which will save time, and ensure consistency.

The second initiative is aimed at promoting the more widespread use of existing generic drugs by looking for ways to keep generic drug labeling up-to-date with the latest information about each medicine's risks and benefits. Generic drugs are generally required to have the same labeling as the brand drug they reference. And the burden to update the labeling with new safety and effectiveness information is typically born by the brand company.

However, when brand reference drug companies voluntarily withdraw their marketing applications, they also stop updating their labeling. When this happens, the FDA loses a key mechanism that the agency relies on as a way to update generic labeling. This can stymie the ability to modernize generic labels. In turn, when labels become out-of-

date, providers may not have complete information about the full range of benefits and risks of the product. This can serve to diminish the use of these lower cost alternatives.

Consistent with our current authorities, which allow for certain types of labeling changes to continue to be made for generic drugs after the brand drug is withdrawn, this budget request will provide the funding to allow the FDA to assume more responsibility to help bring these drug labels up to date. We intend to launch this initiative initially for oncology products.

Our goal is to help ensure that doctors and patients have up-to-date information for these products. This will better inform clinical decisions regarding these medicines, and help promote more widespread use of low-cost, generic alternatives. By ensuring generic product labels are up to date, we'll promote wider and more clinically optimal use of these drugs, which can save patients money.

We appreciate that the appropriations committees of both chambers of Congress supported this budget request in their appropriations bills. Congress has long recognized the need for — and importance of – investments in our generic drug program and efforts to promote generic drug use. The benefits of these initiatives are significant to the FDA's modernization and efficiency. They'll help advance a robust generic drug market that drives product competition and lowers drug prices.

Scott Gottlieb, M.D., is Commissioner of the U.S. Food and Drug Administration

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FDA News Release

FDA approves Admelog, the first short-acting "follow-on" insulin product to treat diabetes

Note: This press release was corrected on December 14, 2017 to reflect that health care providers should monitor potassium levels in patients taking Admelog who are at risk of hypokalemia, a serious and potentially life-threatening condition in which the amount of potassium in the blood is too low. (Not hyperkalemia.)

For Immediate Release

December 11, 2017

Release

Español (/NewsEvents/Newsroom/ComunicadosdePrensa/ucm588782.htm)

The U.S. Food and Drug Administration today approved Admelog (insulin lispro injection), a short-acting insulin indicated to improve control in blood sugar levels in adults and pediatric patients aged 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus. Admelog is the first short-acting insulin approved as a "follow-on" product (submitted through the agency's 505(b)(2) pathway).

According to the **Centers for Disease Control and Prevention (https://www.cdc.gov/)**, more than 30 million people in the U.S. have diabetes, a chronic disease that affects how the body turns food into energy and the body's production of natural insulin. Over time, diabetes increases the risk of serious health complications, including heart disease, blindness, and nerve and kidney damage. Improvement in blood sugar control through treatment with insulin, a common treatment, can reduce the risk of some of these long-term complications.

"One of my key policy efforts is increasing competition in the market for prescription drugs and helping facilitate the entry of lower-cost alternatives. This is particularly important for drugs like insulin that are taken by millions of Americans every day for a patient's lifetime to manage a chronic disease," said FDA Commissioner Scott Gottlieb, M.D. "In the coming months, we'll be taking additional policy steps to help to make sure patients continue to benefit from improved access to lower cost, safe and effective alternatives to brand name drugs approved through the agency's abbreviated pathways."

Admelog was approved through an abbreviated approval pathway under the Federal Food, Drug, and Cosmetic Act, called the 505(b)(2) pathway. A new drug application submitted through this pathway may rely on the FDA's finding that a previously approved drug is safe and effective or on published literature to support the safety and/or effectiveness of the proposed product, if such reliance is scientifically justified. The use of abbreviated pathways can reduce drug development costs so products can be offered at a lower price to patients. In the case of Admelog, the manufacturer submitted a 505(b)(2) application that relied, in part, on the FDA's finding of safety and effectiveness for **Humalog (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020563)** (insulin lispro injection) to support approval. The applicant demonstrated that reliance on the FDA's finding of safety and effectiveness for Humalog was scientifically justified and provided Admelog-specific data to establish the drug's safety and efficacy for its approved uses. The Admelog-specific data included two phase 3 clinical trials which enrolled approximately 500 patients in each.

Admelog is a short-acting insulin product, which can be used to help patients with diabetes control their blood sugar. Short-acting insulin products are generally, but not always, administered just before meals to help control blood sugar levels after eating. These types of insulin products can also be used in insulin pumps to meet both background insulin needs as well as mealtime insulin needs. This is in contrast to long-acting insulin products, like insulin glargine, insulin degludec and insulin detemir, which are generally used to provide a background level of insulin to control blood sugars between meals, and are administered once or twice a day. While both types of insulin products can play important roles in the treatment of types 1 and 2 diabetes mellitus, patients with type 1 diabetes require both types of insulin while patients with type 2 diabetes may never need a short-acting insulin product.

"With today's approval, we are providing an important short-acting insulin option for patients that meets our standards for safety and effectiveness," said Mary T. Thanh Hai, M.D., deputy director of the Office of New Drug Evaluation II in the FDA's Center for Drug Evaluation and Research.

Admelog can be administered by injection under the skin (subcutaneous), subcutaneous infusion (i.e., via insulin pump), or intravenous infusion. Dosing of Admelog should be individualized based on the route of administration and the patient's metabolic needs, blood glucose monitoring results and glycemic control goal.

The most common adverse reactions associated with Admelog in clinical trials was hypoglycemia, itching, and rash. Other adverse reactions that can occur with Admelog include allergic reactions, injection site reactions, and thickening or thinning of the fatty tissue at the injection site (lipodystrophy).

Admelog should not be used during episodes of hypoglycemia (low blood sugar) or in patients with hypersensitivity to insulin lispro or one of its ingredients. Admelog SoloStar prefilled pens or syringes must never be shared between patients, even if the needle is changed.

Patients or caregivers should monitor blood glucose in all patients treated with insulin products. Insulin regimens should be modified cautiously and only under medical supervision. Admelog may cause low blood sugar (hypoglycemia), which can be life-threatening. Patients should be monitored more closely with changes to insulin dosage, co-administration of other glucose-lowering medications, meal pattern, physical activity and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness.

Accidental mix-ups between insulin products can occur. Patients should check insulin labels before injecting the insulin product.

Severe, life-threatening, generalized allergic reactions, including anaphylaxis, may occur.

Health care providers should monitor potassium levels in patients at risk of hyporkalemia, a serious and potentially life-threatening condition in which the amount of potassium in the blood is too low.

Admelog received tentative approval from the FDA on Sept. 1, 2017 and is now being granted final approval.

The approval of Admelog was granted to Sanofi-Aventis U.S.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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