Almost 21 million people in the United States have diabetes, and of those, between 90 and 95 percent have type 2. Each day, roughly 4,100 people are diagnosed with diabetes, and there are 1.5 million new cases of diabetes each year. The numbers are staggering, and never before has there been so great a need for treatment.

The pharmaceutical industry is well aware of this, and the result is an intense, high-stakes race between drug companies large and small to create more options for people with type 2. There are currently several new classes of type 2 drugs in development, drugs that work differently from those currently on the market, and one day, you and your doctor may be able to mix and match different drugs to create a diabetes care plan as unique as your fingerprint.

It may take some time, however. Some drugs are further along than others, and each stage of development takes between 1 and 3½ years. (For an explanation of the various stages of development, see “The Long Road To Approval” on page 50.) What’s more, the U.S. Food and Drug Administration (FDA) may take up to 2½ years to review a drug’s safety and effectiveness once it has been submitted for approval—and approval is never guaranteed.

By Terri D’Arrigo

The race is on to bring you more treatment options for type 2 diabetes than ever before.

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That said, each day scientists are discovering more about how diabetes works and thinking of new ways to treat it. Although a complete listing of every compound currently in development is beyond the scope of this article, here’s a snapshot of what’s coming down the pipeline.

**Frontrunners**

**THE GUT DRUGS**

A hot area of research involves drugs that affect naturally occurring gut hormones. One class of gut drugs, called DPP-4 inhibitors, appears to be furthest along in development. DPP-4 inhibitors help to maintain levels of the gut hormone GLP-1. When you eat, the cells lining your small intestines secrete GLP-1, which then promotes insulin production. The enzyme DPP-4 breaks down GLP-1. In people without diabetes, this is a good thing: It stops the pancreas from producing too much insulin. But people with diabetes often have a deficiency in GLP-1. Less GLP-1 means less insulin produced at mealtime and higher blood glucose later. Then the pancreas responds to the higher blood glucose by going into overdrive.

Inhibiting DPP-4—keeping it from breaking down GLP-1 quickly—allows the GLP-1
Different type 2 drugs are in different stages of development. Each product must go through clinical trials before the company submits an application to the U.S. Food and Drug Administration (FDA) for approval. In general, for every 5,000 substances drug companies consider, only about five actually enter clinical trials. Of those five, only one will be approved by the FDA.

**Preclinical testing.** This is the first consideration of a new drug. The company evaluates how a given substance works in test tubes and laboratory animals. It takes from 3 to 3½ years for most companies to decide whether to pursue further testing.

**Investigational new drug application (IND application).** After the company determines that preclinical testing was successful, it will file an IND application with the FDA. Then clinical trials may begin.

**Phase I.** This phase determines the safety and dosage of the drug. There are usually between 20 and 80 healthy volunteers in the trial who do not have the condition the drug is meant to treat. Phase I trials last for 1 year.

**Phase II.** The second phase of clinical trials involves between 100 and 300 volunteers who do have to stick around long enough to prompt the right amount of insulin for your meal. When you finish eating, the small intestine decreases GLP-1 production naturally. The result is that your pancreas will make more insulin when you need it (at meals) and less when you don’t (between meals). This is less taxing on your pancreas than a cycle of falling behind and playing catch-up, so DPP-4 inhibitors are thought to preserve the pancreas, as well.

Two compounds in this class have been submitted for FDA review: sitagliptin (brand name “Januvia”) by Merck & Co., and vildagliptin (brand name “Galyvus”) by Novartis. Other major contenders are saxagliptin (Bristol-Myers Squibb), which is in phase III, and denagliptin (GlaxoSmithKline), which is in phase II.

**Enzymes Interrupted**

**THE LIVER DRUGS**

You might think diabetes is all about the pancreas, but the liver plays a role, too. When someone without diabetes eats, blood glucose rises, and the pancreas releases insulin. Insulin helps muscle cells use glucose, true, but it also helps the liver take in extra glucose and store it as glycogen. Several hours after a meal, as blood glucose drops, the liver breaks down the stored glycogen and releases it back into the body as glucose for the body to use as fuel.

In type 2, however, this cycle is disrupted, and the liver can release too much glucose, which will make your blood glucose too high. One drug currently available, metformin, helps to keep the liver from producing too much glucose, but other drugs in development may provide new ways to do this by targeting different enzymes than metformin does.

Two compounds in development (CS-917 and MB07803, both by Metabasis Therapeutics) target one such enzyme, called FBPase. These compounds constitute a new class of drugs called FBPase inhibitors. CS-917 is in phase II and MB07803 is in phase I.

Another enzyme involved in the cycle is glycogen phosphorylase. A class of drugs called glycogen phosphorylase inhibitors target this enzyme and include compounds in preclinical studies by Sanofi Aventis.

**Thinking Of Volunteering?**

_Do you want to be part of medical history? The National Institutes of Health has an online database of clinical trials that includes recruitment criteria and contact information for trials that are looking for volunteers. If you’re interested in participating in a clinical trial, talk to your doctor first. Then check out www.clinicaltrials.gov._
have the condition the drug is meant to treat. Researchers evaluate the drug’s effectiveness and look for side effects. This phase lasts about 2 years.

**Phase III.** In the third phase, researchers evaluate the drug’s effectiveness in 1,000 to 3,000 volunteers who have the condition the drug is meant to treat. This phase takes about 3 years and gives researchers a chance to see if there are any adverse effects from long-term use.

**New drug application (NDA).** If a drug company is satisfied that its product is safe and effective, it will file an NDA with the FDA to request approval to sell the drug in the United States. Review may take as long as 2½ years, unless the FDA decides to “fast-track” the drug. When a drug is fast-tracked, it has priority review, and the FDA may render a decision in as little as 6 months.

**Phase IV.** In the final phase, also known as the post-marketing phase, the company tracks the drug once it’s out on the market.

Adapted from “The Long Road To Approval,” appearing in “The Future Of Insulin,” by Terri Kordella, in the March 2003 issue of Diabetes Forecast.

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**Something Completely Different**

**THE KIDNEY DRUGS**

Healthy kidneys play a role in maintaining normal blood glucose levels, too. The kidneys filter your blood. They remove waste, which is then removed from the body through your urine. The kidneys also process the glucose that’s in your blood and send it back out into the bloodstream. (The exception is when blood glucose is very high: Then the kidneys retain some of the glucose and you excrete it in your urine.)

One class of drugs in development, SGLT-2 inhibitors, would interfere with the way healthy kidneys return glucose to the blood. Instead, they would prompt the kidneys to retain some glucose so that you excrete it in your urine. The theory is that this will help normalize blood glucose.

Several companies are investigating compounds in this class, including GlaxoSmithKline and Sanofi Aventis, which both have drugs in phase II studies.

**Tricky Mixes**

**DUAL ACTION DRUGS**

A class of drugs known as dual PPAR agonists, or “glitazars,” stood poised to burst onto the market at the end of 2005 when an FDA advisory committee recommended that the FDA approve muraglitazar (brand name “Pargluva,” by Bristol-Myers Squibb). Glitazars are designed to lower blood glucose and regulate HDL (“good”) cholesterol and triglycerides.

After the advisory committee recommended approval, however, a study appearing in the *Journal of the American Medical Association* revealed cardiovascular risks associated with the drug. Researchers in Ohio found that people who took Pargluva were twice as likely to have heart trouble or stroke or die as those who took dummy pills. The FDA then delayed approval of the drug.

As *Forecast* went to press, the drug was still on hold. The FDA has requested additional safety information from the manufacturer, and the company has been in contact with the FDA about what may be required.

Pargluva’s woes haven’t stopped other companies from developing drugs in this class, however. Tesaglitazar (brand name “Galida,” by AstraZeneca) is in phase II trials, and GlaxoSmithKline’s yet-unnamed glitazar is in phase I.

Scientists understand type 2 better each day. As researchers unlock the cellular secrets of diabetes, there will no doubt be more treatments to come. ▲

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