Just a few years shy of a century ago, a group of Canadian researchers discovered a viable method of extracting insulin, filling a large and critical gap in the therapeutic treatment of diabetes (1). Since then, insulin and its associated delivery devices have become an integral part of the care and management of patients living with diabetes. Shortly after the first insulin injection was successfully delivered, vials of insulin became available commercially. At this time, large glass syringes were used to administer insulin, and each injection required sterilization of the syringe, as well as sharpening of the syringe needle with a pumice stone. Through the years, insulin syringes modernized, but it was not until the 1970s that an alternate delivery system—the insulin pump, used in continuous subcutaneous insulin infusion (CSII) regimens—became available. Fifteen years later, the first insulin pen was introduced to the marketplace, providing evidence that, as time progresses, there is no shortage of innovation in the diabetes arena.

The first two rapid-acting inhaled insulins on the market—Exubera in 2006 and Afrezza in 2014—represented yet another innovation milestone. In theory, inhaled insulin completely eliminated the psychological barriers associated with subcutaneous insulin delivery, such as needle phobia and incorrect injection technique. However, in October 2007, Pfizer withdrew Exubera from the market, and in January 2016, Sanofi withdrew from a $925 million marketing agreement with MannKind for Afrezza; both withdrawals were due to poor sales volume. Although patients and providers have been searching for years for alternatives to injecting insulin, Exubera has already failed, and Afrezza’s destiny is uncertain.

**The Exubera Experience**

In 2006, Exubera was the first inhaled insulin approved by the U.S. Food and Drug Administration (FDA). It showed noninferiority in efficacy with regard to A1C lowering in both type 1 diabetes (2) and type 2 diabetes (3) compared to mixed regular/NPH insulin. Exubera was indicated as combination therapy in patients with type 1 diabetes, to be used in conjunction with a longer-acting insulin (4). In patients with type 2 diabetes, Exubera could be used either as monotherapy or in combination with a longer-acting insulin or oral antidiabetic agents.

Contraindications included smokers and patients who had stopped smoking within the past 6 months. Because of an increased risk of hypoglycemia with smoking, patients who resumed smoking while on Exubera were advised to immediately discontinue using the product. Because of changes in pulmonary lung function affecting absorption of the drug and potentially leading to increased hypoglycemia risk, Exubera was also contraindicated in patients with unstable or poorly controlled lung
disease such as asthma or chronic obstructive pulmonary disease.

Hypoglycemia was demonstrated to be the most common side effect, and frequent glucose monitoring was recommended. Because of the route of administration, many respiratory adverse effects were reported, including increased risks of respiratory infection, cough, pharyngitis, and rhinitis. Studies illustrated a statistically greater decline in pulmonary function compared to placebo, and this decline lasted for the duration of therapy (2 years) (4). These findings led to increased monitoring requirements, including spirometry assessment before initiation of Exubera and at regular intervals thereafter. A safety label change was issued regarding lung cancer when six newly diagnosed cases of lung malignancies were found in patients in the Exubera arm compared to only one case in the comparator arm (5). These results were not robust enough to determine a correlation with Exubera but nonetheless instilled fear in patients and providers.

**The Afrezza Experience to Date**

Although commercialization of Exubera was ultimately unsuccessful, innovation with regard to inhaled insulin continued, and in 2014, Afrezza was launched. The AFFINITY-1 study concluded that, in patients with type 1 diabetes receiving basal insulin, A1C reduction with Afrezza was noninferior to insulin aspart and significantly fewer patients experienced hypoglycemia (6). The AFFINITY-2 study confirmed that, in patients with type 2 diabetes uncontrolled on oral agents, the addition of prandial Afrezza was effective, significantly lowering A1C ($P < 0.0001$) (7).

Afrezza appears to have key advantages over Exubera. Its delivery system is small, sleek, and dosed in units and provides a simple dosing conversion chart, whereas Exubera’s delivery system was large, awkward, and dosed in milligrams. The modifications implemented with Afrezza allow for a more discreet administration process and a dosing regimen that is easier for both prescribers and patients to comprehend.

However, Afrezza’s safety profile resembles that of Exubera, with a decline in pulmonary function and a slight increased incidence of lung cancer. New concerns were brought forward after Afrezza’s approval, prompting the FDA to require a risk evaluation and mitigation strategy and a “black-box” warning informing patients of an increased risk of acute bronchospasm in those with chronic lung disease (8). Diabetic ketoacidosis (DKA) was also found to be more common in patients in the Afrezza cohort.

How have Afrezza’s improvements on and remaining similarities to Exubera situated it for the future? Sanofi’s withdrawal from a marketing agreement with Afrezza manufacturer Mannkind left the product’s fate hanging in the balance of imminent critical business decisions. For a time, Mannkind’s hands were tied while transition teams worked to acquire development and commercialization rights from Sanofi (9). Now that the transition is finalized, MannKind is allowed to market Afrezza, negotiate with insurers, and file for regulatory approval in new jurisdictions. Teams will be activated to ensure that Afrezza does not suffer the same fate as Exubera. The transition date was 5 April 2016; however, Sanofi will continue to distribute Afrezza through June 2016.

Why has the marketing of Afrezza faced such difficulties? Insurance coverage to date has been poor, new adverse effects and concerns emerged, and competition from therapeutic alternatives is at an all-time high. The following sections delve deeper into these challenges.

**Addressing the Challenges to Afrezza’s Success**

**Insurance Barriers**

It would be wise for MannKind to seek payer buy-in to be successful in 2016 and beyond. Insurance coverage has been a major obstacle for MannKind and for patients who rely on Afrezza for their diabetes management. In 2015, most major commercial insurance companies and pharmacy benefit managers included Afrezza in coverage tiers 3 or 4 (nonpreferred brands). Medications placed in these tiers have higher copayments compared to their preferred brand-name or generic alternatives, or they may not be covered at all. If this was not enough of a deterrent, many patients seeking to use Afrezza also must obtain a prior authorization from their prescribers and insurance company, an additional time-consuming obstacle.

In light of this challenge, one plan would be to price Afrezza competitively enough in the United States to gain favorable payer coverage. To recoup lost revenues through price decreases in the United States, MannKind would have to make strategic deals in foreign markets to ensure significant short-term cash flow (9). Achieving favorable payer coverage is the first crucial step toward successful market uptake.

**Emerging Safety Concerns**

New concerns and side effects, largely focused on Afrezza’s possible negative effects on the respiratory system, have emerged. A simple Google Internet search turns up examples of apprehensions on the part of both patients and providers about introducing insulin (a growth hormone) into the lungs (10,11).

With subcutaneous insulin administration, lipohypertrophy is one complication that can affect patients. The cause is likely multifactorial and could involve poor injection site rotation or poor injection technique, but also the growth factor properties of insulin (12–14). During clinical trials of Afrezza, there were two cases of lung cancer during 2,750 patient-years of exposure. Both cases occurred in smokers exposed to Afrezza; no subjects in the placebo cohorts were diagnosed...
with lung cancer. After clinical trial completion, the investigators reported that two nonsmokers also were diagnosed with the same type of cancer (squamous cell lung carcinoma) (8). Could the growth factor properties of insulin that may be implicated in lipohypertrophy when insulin is administered subcutaneously be the cause of pulmonary malignancy when it is inhaled? Although animal carcinogenicity studies indicate an absence of neoplasias and preneoplastic signals in Afrezza-treated rats, there are not yet enough human data to confidently confirm or dismiss the risk of pulmonary malignancy with inhaled insulin.

Cough is another side effect associated with inhaled insulin. In a 24-month trial conducted by Raskin et al., 27.8% (257/923) of patients in the Technosphere insulin (TI; the insulin used in Afrezza) cohort experienced cough compared to 4.4% (42/949) in the usual care cohort (15). The AFFINITY-1 study documented that 27.1% of subjects in the TI cohorts (94/347) reported cough, leading to a 4.3% (15/347) discontinuation rate (6). Although cough may not directly cause any clinical concerns, it is likely considered an annoyance to most and may impede patients’ quality of life.

All cohorts (TI, usual care, and nondiabetes) in the Raskin trial experienced a decline in FEV1 (a measure of lung function). The mean change in FEV1 between treatment groups at 24 months met the noninferiority criterion (least squares mean of 0.037, 95% CI 0.014–0.060). The initial decline at 3 months was greater in the TI group than in the usual care group and persisted for the duration of therapy (2 years) (8). Visually, the reduction in FEV1 appeared to be -100 mL for TI, -50 mL for usual care, and -50 mL for nondiabetes. Finally, 5.75% of patients receiving TI and 3.28% of those receiving usual care had a ≥15% decrease in FEV1 from baseline at 24 months. However, the investigators determined that only three of the subjects who had a decline in FEV1 of ≥15% had a clinically significant reduction. Again, there are not yet enough data to evaluate the long-term significance of this decline in pulmonary function.

The primary therapeutic effect of insulin is to regulate glucose levels in the blood (8). Both hypo- and hyperglycemia can be dangerous to patients with diabetes, and hyperglycemia is a clear risk factor for inducing complications (16). Therefore, vital endpoints for pivotal trials evaluating insulin-based therapies should include both hypo- and hyperglycemia. Patients with type 1 diabetes experienced less hypoglycemia, whereas patients with type 2 diabetes experienced more hypoglycemia with Afrezza compared to rapid-acting subcutaneous insulin (6,7). However, hyperglycemia and DKA data were not reported in AFFINITY-1, AFFINITY-2, or the supplemental materials. Albeit from a study with a small number of patients and a small absolute risk, the package insert reported a 207% higher incidence of DKA in Afrezza users (0.43%, n = 13) versus comparators (0.14%, n = 3). The pharmacokinetic profile of Afrezza’s TI (particularly its rapid offset) is such that a patient’s meal may be covered initially, but prolonged increases in postmeal glucose may not be adequately managed. This could partially explain why daily basal insulin requirements increased by -5 units in the TI group in AFFINITY-1, helping to attenuate the postmeal glucose excursions (6). Additionally, as diabetes management moves beyond A1C to other measures (i.e., glycemic variability, percentage of time in range, and mean absolute relative difference in glucose sensor readers), having access to both hyperglycemia and hypoglycemia data will be important.

Competing Products
A myriad of therapeutic options are available to patients with type 1 or type 2 diabetes, and new developments within this disease state are constantly arising. Two notable choices are CSII, an option for all patients with diabetes, and glucagon-like peptide 1 (GLP-1) receptor agonists, a treatment specifically for type 2 diabetes. CSII is rapidly progressing toward a closed-loop system, and multiple GLP-1 receptor agonists that require less frequent dosing are being developed or marketed.

For patients with type 1 diabetes, Afrezza’s rigid dosing options may prove troublesome. These patients have the option of using insulin vials and syringes, insulin pens, or CSII. Dosing adjustments can be made with syringes in increments of 0.5 units; pens allow quick and easy administration typically in 1-unit increments, although pens offering 0.5-unit increments are available; and insulin pump technology can provide small bolus doses in 0.05-unit increments in CSII (17). This is in stark contrast to Afrezza, which allows 4-unit incremental change. This dosing inflexibility may be considered a disservice to and a limitation for patients who require more careful dosing titration.

In lieu of mealtime insulin, patients with type 2 diabetes have the option of using once-daily or once-weekly GLP-1 receptor agonists, which have been shown to decrease A1C by up to 1.9% (18). GLP-1 receptors are found in both the stomach and the brain. By mimicking the effects of the incretin hormone GLP-1, which is released during food intake, these therapies trigger a cascade of physiological effects, including increased insulin secretion, decreased glucagon release (a feature that is crucial in the control of glucose levels and rare to find in the properties of a medication), increased fullness, and slowed gastric emptying. These agents also work only when the body is in a state of hyperglycemia; therefore, they pose a minimal hypoglycemia risk and may preserve β-cell function.
Although GLP-1 receptor agonists are not recommended in patients with gastroparesis, a history of pancreatitis, or a personal or family history of medullary thyroid cell carcinoma or multiple endocrine neoplasia syndrome type 2, the side effect of weight loss is welcomed by many patients. With adherence being one of the more limiting factors in achieving adequate glycemic control, this class of drugs poses a threat to inhaled insulin.

One of the target patient groups for inhaled insulin is those with needle phobia. Many patients have a level of fear of injections that limits their ability to administer the insulin they require and subsequently find it difficult to stay in glycemic control. It has been estimated that 30–50% of patients experience anxiety about and fear of injection-associated pain (19). Unfortunately, Afrezza usually does not solve this problem because it is only a prandial insulin, and patients who require basal insulin will still need to inject their basal doses. Thus, Afrezza use reduces the total number of injections given per day, which is attractive, but it does not completely eliminate injections except for patients requiring only prandial insulin coverage.

Predicting the Future of Afrezza

What will diabetes care look like in the future? One published model predicts a doubling of spending in the next 25 years on diabetes care and complications in the United States (20). As the prevalence and incidence of patients burdened with this endocrine disease escalate, the more important it becomes to work toward a safe, efficacious, easy, and affordable solution to the problem of achieving glycemic control.

As we look to the future, can we expect to see continuing advancements in diabetes management, as we have over the past century since the discovery of insulin? Often, patients with diabetes follow a multiple daily injection (MDI) insulin regimen, and keeping track of when each dose is administered can be a great challenge. A pen cap with digital memory is now available, which can help patients overcome this obstacle and simplify their diabetes self-care. Phase I clinical trials have commenced to study the effects of “smart insulin,” a type of insulin that only acts when blood glucose is elevated and ceases its action when patients become euglycemic (21). Also, researchers at Massachusetts Institute of Technology and Massachusetts General Hospital are researching oral administration of biologics through encapsulated microneedles, an approach that is likely to be applied more for biologics such as monoclonal antibodies but also may provide an alternative route for insulin administration (22). In a recent presentation at the 2016 Advanced Technologies & Treatments for Diabetes conference, Pozzilli took the improvement in glucometrics with CSII compared to an MDI regimen; outlined preliminary data suggesting that CSII positively affects factors associated with progression to complications; and briefly explained how CSII can protect β-cell function in type 2 diabetes (23,24). Finally, the race is on for the introduction of an artificial pancreas into the market, a closed-loop system coupling insulin delivery with continuous glucose monitoring and synchronized to mimic the endogenous insulin release of a well-functioning pancreas (25).

Although Exubera was unable to succeed, Afrezza still has a chance to positively affect patient care, but time is of the utmost importance. As new and emerging therapies and medical devices provide easier, safer, and more discreet options for patients, Afrezza will continue to face an uphill battle for success.

Duality of Interest

Dr. Oleck and Dr. Kassam are postdoctoral fellows in Global Medical Affairs at Becton Dickinson and Company and MCPHS University. Dr. Goldman is a speaker’s bureau member for Novo Nordisk and Sanofi, a consultant to Becton Dickinson, and the academic preceptor for Drs. Oleck and Kassam. No other potential conflicts of interest relevant to this article were reported.

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