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FDA Approves New Inhaled Insulin: Afrezza® (Technosphere® Insulin)

Benjamin Finley, fifth-year pharmacy student from East Sparta, Ohio; Christina Ciccone, fourth-year pharmacy student from Pickerington, Ohio; Kimberly Loughlin, fifth-year pharmacy student from Mishawaka, Ind.; Michelle Musser, PharmD, BCPS, assistant professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-14-216-H01-P

Objectives
After completion of this program, the reader should be able to:

1. Identify the different types of diabetes and each of their pathophysiology.
2. Name several investigative methods for insulin administration.
3. Describe the pharmacokinetics and pharmacodynamics of Technosphere® insulin.
4. Explain the advantages and disadvantages of inhaled insulin compared to injectable insulin.
5. Evaluate the efficacy and safety of Technosphere® insulin based on data from clinical trials.

Abstract
Diabetes is an endocrine disease caused by deficiency or malfunction of insulin that results in high blood glucose levels and places patients at higher risk for a number of complications. This chronic disease is difficult to manage and affects millions of people in the United States, costing the healthcare system billions of dollars a year. Of a variety of antidiabetic agents used to control blood glucose, insulin is perhaps the most effective, but until recently it was only available in injectable form. As of June 27, 2014, a new inhaled insulin called Afrezza® (Technosphere® insulin) was approved by the U.S. Food and Drug Administration (FDA) and will soon be coming to market. This rapid-acting insulin is administered through the lungs and offers an alternative to traditional dosage forms. This article further explores some background about Technosphere® insulin, its mechanism of action and literature regarding its efficacy.

Key Terms
Administration, Inhalation; Blood Glucose; Chronic Disease; Diabetes Mellitus; Disease Management; Endocrine System; Diseases; Humans; Hyperglycemia; Hypoglycemic Agents; Insulin; Insulin, short-acting; Review Literature

Introduction
According to the 2014 National Diabetes Statistics Report, approximately 29.1 million people (9.3%) in the United States have diabetes.1 Direct and indirect health care costs related to diabetes are estimated to total about $245 billion a year, placing a large burden on patients and providers alike.

Disease State
Diabetes mellitus (DM) is an endocrine disease that results in high blood glucose levels due to deficiency or malfunction of the hormone, insulin, that is responsible for most of glucose absorption from the blood stream.1 Patients with diabetes are at higher risk than nondiabetics for a number of other health complications including hypoglycemia or hyperglycemia, hypertension, cardiovascular problems, blindness and kidney disease. Diabetes is usually classified into type I, type II and gestational diabetes (GDM). Type I DM (approximately 5% of diabetes cases) is caused by the body’s immune system destroying the insulin-producing beta cells in the pancreas, resulting in an insulin deficiency without cure or prevention. Type I DM usually appears in young adults, although it can happen at any age. Patients diagnosed with type I DM require exogenous insulin to survive. Type II DM (90 to 95% of diabetes cases) starts with insulin resistance in various tissues, placing an increased demand for insulin on the beta cells of the pancreas. The increased stress on these cells eventually reduces their ability to produce enough insulin to meet the demand. Treatment for type II DM depends on the patient’s individual combination of insulin resistance and reduced insulin secretion. Gestational diabetes develops during pregnancy when increased blood glucose levels cause the mother to develop intolerance to glucose. During pregnancy, high blood glucose is dangerous for the mother and fetus and requires treatment. Even after birth, both mother and child are at increased risk for type II DM.

Treatment
Type I DM requires insulin therapy to maintain normal blood glucose levels.1 Type II DM has a wider variety of progressive treatment options including oral agents (such as metformin, glucagon-like peptide-1 agonists and others) and insulin.2 These agents can be used in conjunction to maintain glycemic control.

Although insulin replacement therapy is acknowledged as the most effective glucose-reducing treatment, its administration by injection is a considerable barrier to many patients.3 A study performed by Cramer and Pugh estimated that subjects taking insulin used 77 percent of their prescription on average.4 Although this average indicates an intention to take the insulin as prescribed, there was still an underuse of insulin and this often resulted in poor glycemic control. Peyrot and colleagues suggested that reasons for nonadherence with insulin therapy were often related to discomfort or inconvenience of the injection.3 Of 502 subjects studied, 23 to 25 percent reported the injections interfered
with various daily activities, 22 percent had to mentally prepare themselves before each injection and 33 percent experienced a level of dread toward taking their insulin injections.3

Due to these barriers for insulin administration, the pharmaceutical industry continues to search for alternative insulin delivery methods. Potential alternatives such as oral, nasal or transdermal insulin often have low bioavailability.5 Exubera® (insulin inhalation), produced by Pfizer, was approved by the FDA on Jan. 27, 2006, and became the first inhaled insulin to make it to market.6 Insulin inhalation was shown to be as effective as short-acting injectable insulin, although it had to be administered in conjunction with an injectable long-acting basal insulin.7 Despite its efficacy, Pfizer decided to withdraw insulin inhalation from the market in 2007 due to poor sales and low demand.8

Afrezza (Technosphere® insulin, abbreviated TI) is a new inhaled insulin developed by MannKind Corporation and was approved by the FDA for marketing as of June 27, 2014.9 It is a very rapid-acting insulin dispensed as a powder from a DreamBoat® inhaler (Figure 1). The DreamBoat® inhaler is small, portable and easy to use, giving TI an edge in convenience over previous inhaled insulin. Technosphere® insulin does not replace long-acting basal insulin, but it could potentially reduce the number of injections that a patient has to take. Clinical studies indicate promising efficacy results, but patients and prescribers may hesitate to use TI due to the negative impression left by the withdrawal of Exubera® (insulin inhalation). The purpose of this article is to evaluate the mechanism of action and clinical significance of TI, supported by data from clinical trials, and to educate pharmacists about this new medication.

About Technosphere® Insulin
Technosphere® insulin is an inhaled, prandial, very rapid-acting insulin product.10,11 The specially-formulated powder is available for absorption via the lung and achieves 37 percent of the bioavailability of subcutaneous insulin administration. The formulation method involves the use of an excipient, fumaryl diketopiperazine (FDKP), which self-assembles via hydrogen bonds in a slightly acidic environment. The hydrogen bonding forms microspheres, which are optimally sized for inhalation deep into the lung. The FDKP microsphere formation can be used to incorporate peptides and proteins (such as insulin) into a solution. The newly formed microspheres containing the drug product are freeze-dried to create the powder used in the inhalers for administration. When a patient inhales this product, the microspheres are introduced into the neutral pH of the lungs allowing for the rapid and extensive absorption of insulin into systemic circulation. Once the insulin is absorbed via the lung mucosa into systemic circulation, the insulin mechanism of action is the same as with subcutaneous and intravenous administration.
methods: acting as a hormone that helps the body utilize glucose by pulling glucose from the blood into the cells to use for energy.

As a mealtime insulin, TI reaches peak levels of insulin concentration within 15 minutes of administration, much quicker than current rapid-acting injected insulin products (e.g., aspart, lispro, glulisine insulin reach peak levels between 30 and 90 minutes). This quick time-to-peak also leads to higher maximum concentrations relative to injected insulin. Technosphere® insulin has faster elimination from the body and, coupled with the fast onset of action, this more closely resembles endogenous prandial insulin release than currently available rapid-acting injected insulin.

Studies show that patients with chronic obstructive pulmonary disease (COPD) and those who smoke do not show evidence of decreased efficacy with the use of this product, including mean peak insulin levels, median time to achieve maximum concentrations and mean insulin exposure time from zero to 240 minutes post-dose.

Adverse effects with TI include hypoglycemia and cough (25% and 19%, respectively). Other adverse effects discovered were anemia and suspected hypersensitivity. Another concern with inhalation administration is that there can be accumulation or deposition of the excipient FDKP and insulin in the lungs. Evidence shows that both FDKP and insulin concentrations in the lung decline to minimal levels (from 12% to 0.3%) over a 12-hour period after taking a dose.

**Comparison**

A study by Rave and colleagues, which compared TI versus subcutaneously injected normal human insulin in postprandial coverage, indicated that peak blood glucose levels were significantly lower with the use of TI. Technosphere® insulin also showed improved results with lower postprandial blood glucose (PPG) levels compared to that of regular insulin 30 to 120 minutes following a meal. Several studies show that TI and biphasic insulin (biphasic insulin is a human insulin analogue suspension containing 70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin]) produced similar decreases of the patient's glycosylated hemoglobin (HbA1c) (at one year, -0.58% and -0.70%, respectively). However, TI was shown to impact fasting plasma glucose (FPG) levels more than biphasic insulin (one year average=171 versus 208 mg/dL, respectively, p=0.0001).

**Patient Counseling/Education Points**

One limitation seen in the past with inhaled insulin products (such as Exubera®) was ensuring proper use of the special inhaler, which was produced specifically for inhalation of insulin. With the past product, the inhaler was larger and difficult to use. The Exubera® inhaler also had to be cleaned in a specific way and replaced frequently with a new inhaler. Technosphere® insulin utilizes an improved inhaler, which provides for easier use. The package insert for TI provides clear instructions for its use.

Main points for patient counseling include:
- The cartridges must be refrigerated.
- The inhaler and the cartridge must be at room temperature for at least 10 minutes prior to its inhalation and administration.
- When the patient is using the inhaler, it must remain level and upright in the proper orientation; this is because the cartridge is punctured when it is placed into the base of the inhaler, and the powder becomes loose and can spill out if not kept parallel to the ground.
- This inhaler must be thrown away and exchanged for a new one every 15 days.
- Inside the packaging, there are two blister cards in a foil pack.
  - In each blister card, there are five strips, and each strip contains three cartridges.
  - A patient is to rip off one strip at a time when using this product.
  - When a strip is torn from the main blister card, the strip (of three cartridges) must be used within three days; after that it must be thrown away.
- The blue cartridges contain four units of insulin, and the green cartridges contain eight units of insulin.
  - Each dispensed package will only come in one strength (blue [four units] or green [eight units]).

**Literature Review**

**Trial 1**

Tack and colleagues performed a double-blind, placebo-controlled, randomized controlled trial as part of phase 2 clinical trials for the approval of TI. The trial was designed to test efficacy and evaluate dose-dependent response of four different doses of TI and compare them to placebo over the course of 11 weeks. The population used included 227 patients with type II DM and poor glycemic control with other medications. In addition to either TI or placebo, all patients were switched from their previous regimen to insulin glargine for basal maintenance dosing. The subjects were then randomized into five groups: TI cartridge doses of 14, 28, 42 or 56 unit equivalents (U*), respectively. Assuming administration by inhalation provides a bioavailability of 26 percent, the TI doses were assigned equivalents to usual subcutaneous regular human insulin of 3.6, 7.3, 10.9 and 14.6 U*, respectively. Patients to be given the higher doses started an initial dose of 3.6 U* and were titrated up by 3.6 U* per week until the assigned dose was reached. Efficacy endpoints included reduction in HbA1c, area under the glucose curve (AUC_glucose), and maximum concentration of plasma glucose reached after eating a meal (G_max). Each of these measures was compared to baseline and adjusted for baseline differences by comparing to placebo. Specific goals for significant HbA1c reduction were set for each dose prior to the beginning of the trial. To reach desired goal for HbA1c compared to baseline, a change of -0.4, -0.5, -0.5 and -0.6 (p-value<0.05) was required for 3.6, 7.3, 10.9 and 14.6 U* doses, respectively. When adjusted relative to placebo, HbA1c reduction should reach -0.4, -0.67, -0.7 and -0.78 (p-value<0.04) for above doses to be statistically significant. Secondary end-
Table 1: Summary of HbA1c Results from data by Tack and colleagues

<table>
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<tr>
<th>Dose (U*)</th>
<th>HbA1c change from baseline (Δ)</th>
<th>p-value</th>
<th>HbA1c change from placebo (Δ)</th>
<th>p-value</th>
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<td>3.6</td>
<td>-0.4±1.2</td>
<td>0.05</td>
<td>-0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>7.3</td>
<td>-0.5±1.2</td>
<td>0.004</td>
<td>-0.67</td>
<td>0.001</td>
</tr>
<tr>
<td>10.9</td>
<td>-0.5±0.9</td>
<td>0.002</td>
<td>-0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>14.6</td>
<td>-0.6±1.1</td>
<td>0.001</td>
<td>-0.78</td>
<td>---</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2±0.9</td>
<td>0.098</td>
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</tr>
</tbody>
</table>

points were to test safety by monitoring occurrence of adverse events.

Table 1 outlines HbA1c results related to Tl efficacy for the trial, with statistically significant values in bold. Based on this data, all doses of Tl demonstrated a significant reduction in HbA1c compared to placebo. Other measurements of Tl efficacy found statistically significant results when comparing Tl to placebo at 10.9 and 14.6 U* doses for AUC_glucose and 7.3, 10.9 and 14.6 U* doses for C_max measurements. The data shows with sufficient confidence that the reduction in HbA1c is linked to increased dose of Tl, and AUC_glucose also decreases at higher doses. No statistically significant differences were found between Tl and placebo groups regarding adverse reactions, and Tl doses were well tolerated.

Tack and colleagues performed a strong clinical study by standardizing titration of Tl doses, thoroughly documenting criteria and data, and accounting for baseline differences (although minimal) in their statistical analysis. The necessary sample size (260) to achieve 80 percent power was calculated before the trial was performed, but only 227 patients could be gathered, and only 205 completed the entire trial, so there is a risk of type II error. The authors indicated the forced titration design did not optimize treatment of patients, and the study was of short duration. Additionally, it should be noted that this trial employed the MedTone® inhaler, not the DreamBoat® inhaler that MannKind is now marketing with Tl.

**Trial 2**

Rosenstock and colleagues performed a randomized, multicenter, open-label, parallel-group study, funded by MannKind, assessing the efficacy and safety of prandial Tl compared with twice daily bipart insulin. The efficacy endpoint was a change in HbA1c, and the main safety endpoints were hypoglycemia and cough. There were 677 patients included in the study (462 completed the study and 448 were analyzed in per-protocol population) aged 18 to 80 years with type II DM and HbA1c greater than 7 percent and less than 11 percent. Patients must have been nonsmokers for at least six months before the study, have forced expiratory volume in one second (FEV1) of 70 percent, have total lung capacity of 80 percent or higher, have a body mass index (BMI) ≤40kg/m², and need less than 1.4 IU insulin per kg. Patients excluded from the study were those who had clinically significant diabetes complications, hepatic/renal disease, severe/several allergies, chronic pulmonary disease, present drug or alcohol abuse, major psychiatric disorders, myocardial infarction/stroke in the last three months or unstable diabetes (two or more episodes of severe hypoglycemia or any emergency room visit for diabetes in the last six months). The data was collected over a period of 19 months.

Randomization was completed by an independent system (ClinPhone, East Windsor, NJ, USA) to place the patients into two groups in a 1:1 ratio, where one group would receive prandial Tl powder plus bedtime insulin glargine by subcutaneous injection and the other would receive twice daily premixed bipart insulin by subcutaneous injection. No blinding was used for this study because of the multi-continental study design and the drug administration times.

A 90 percent power was provided for the sample size of 677 patients for the comparison of HbA1c. The study used analysis of covariance (ANCOVA) to analyze the change in HbA1c, FPG, PPG, weight and pulmonary function tests from baseline after 52 weeks. The study utilized a paired t-test for within-treatment comparisons, odds ratio for at least one hypoglycemic event, Poisson regression model for rates of hypoglycemic events, ANCOVA for between-treatment differences and logistic regression analysis to show the treatment difference in responder rates. A short form-36 quality of life (SF-36 QoL) and insulin treatment questionnaires were also used to assess progress.

Data gathered from the trial with upper 95 percent confidence intervals (CI) less than 0.4 showed Tl and insulin...
The definition of "usual care" was determined by doctor discretion (n = 743) or usual antidiabetic (n = 824) treatment groups. Mean FPG for TI plus insulin glargine versus biaSPART insulin at 52 weeks was 7.8 mmol/L (2.0 mmol/L change from baseline; SD 0.3, 95% CI -2.5 to -1.5) and 8.7 mmol/L (1.0 mmol/L change from baseline; SD 0.2, 95% CI -1.5 to -0.5), respectively. The between-group difference was -1.0 mmol/L (SD 0.3, 95% CI -1.6 to -0.3, p=0.0029). Postprandial glucose AUC for zero to 360 minutes was similar between both treatment groups: 59.8 mmol/h per L for TI and insulin glargine and 56.7 mmol/h per L for biaSPART insulin. However, the mean one hour PPG levels were lower with TI and insulin glargine versus biaSPART insulin (9.5 mmol/L; SD 0.3 and 11.6 mmol/L; SD 3.9, p=0.0001). After two hours, glucose excursions were higher with TI and insulin glargine versus biaSPART insulin, and glucose levels remained below baseline with biaSPART insulin after 200 minutes. Adverse events occurred in 272 patients (84%) on TI and insulin glargine and in 296 patients (89%) on biaSPART insulin. Hypoglycemia was the most common adverse event occurring in 99 patients (31%) on TI and insulin glargine and 163 patients (49%) on biaSPART insulin. Cough was reported frequently with 103 patients (32%) on TI and insulin glargine and 14 patients (4%) on biaSPART insulin. Most of the coughs from patients on TI and insulin glargine occurred within 10 minutes of inhalation. There were no significant differences between the two groups with pulmonary function.

Rosenstock and colleagues conclude that TI plus insulin glargine is an effective alternative to conventional subcutaneous insulin therapy in patients with type II DM, and it may result in less weight gain and hypoglycemia.20

Trial 3

Raskin and colleagues performed a prospective, randomized, open-label study to determine the pulmonary safety of TI versus usual diabetes medications in patients with DM.21 The patients had either type I DM or type II DM and were stratified by DM type prior to randomization into prandial insulin TI (n=743) or usual antidiabetic (n=824) treatment groups. The definition of "usual care" was determined by doctor discretion and could include any range of oral antidiabetic medications with or without insulin, and patients in the TI group also remained on other diabetes medications as needed. The study also included a control group of 145 patients who did not have DM and were not receiving treatment in order to assess standard lung function. The primary objective of the study was to evaluate change in pulmonary function of each treatment group and determine if TI pulmonary safety was noninferior to usual care. To accomplish this, Raskin and colleagues measured lung function by the primary endpoint, FEV, and secondary endpoints forced vital capacity (FVC), total lung capacity (TLC) and lung diffusion capacity for carbon monoxide (DLCO) for each patient at zero, three, six, 12, 18 and 24 months. Any adverse reactions were also assessed. Baseline demographics and pulmonary function were determined to be similar between treatment groups of DM patients.

Calculations for statistical analysis were based on the null hypothesis that difference in FEV, change was not less than 0.050 L/year ± 0.100 L in TI groups compared to usual care groups.21 To achieve 80 percent power and alpha of 0.05, it was calculated a sample size of 50 patients for each treatment arm would be necessary. The number of patients enrolled well exceeded these requirements, so type II error in statistical analysis is unlikely. Of 2,053 patients originally enrolled in the study, 763 dropped out (mainly due to withdrawal of consent, not as a result of any major side effects), leaving 1,699 patients who were included in the analysis.

Pulmonary function declined marginally in all groups compared to baseline, and overall pulmonary safety of TI was determined to be noninferior to usual care over the course of two years.22 The primary endpoint met the noninferiority goal with a mean change (TI minus usual care) over two years in FEV,=0.037 L (95% CI 0.014 to 0.060). Secondary endpoint mean differences were FVC=0.034 L (95% CI 0.008 to 0.06), TLC=0.005 L (95% CI -0.042 to 0.031), and DLCO=0.269 mL/min/mmHg (95% CI -0.373 to 0.574). There was a greater initial decline (zero to three months) in lung function in the TI group compared to the usual care group, but when compared with data from three to 24 months, there was no statistically significant difference between the groups. Generally TI was well tolerated with no safety concerns. The most common treatment-related adverse effect in both groups was hypoglycemia. The second most common adverse effect, a mild, nonproductive cough that occurred within 10 minutes of inhalation, was more common in the TI group, but it did not affect overall lung function. It was reported by patients within the first month of therapy and declined over time. No lung malignancy was reported in either group. Raskin and colleagues concluded that any differences in the change in lung function between the TI and usual care groups was observed early and did not progress over two years, so this is unlikely to have clinical significance. Overall, the study was sufficient to indicate that TI does not pose any serious pulmonary safety concerns when used as intended.

Conclusion

Technosphere® insulin has great potential to meet the need for medication that can imitate the fast-acting effects of endogenous insulin. Trials have proven it to be safe and efficacious as a rapid-acting insulin. The DreamBoat® inhaler is small, portable and easy to use. Although effective as a rapid-acting insulin, it is important to remember that TI therapy still requires administration of either inlineable or other antidiabetic therapy to maintain basal insulin levels, and therefore it may not completely eliminate the use of needles from a patient’s therapy. The true benefit of TI remains to be seen. Largely its success will depend upon patient preference and whether or not the advantages it offers can overcome the negative impression left by previous inhaled insulin.

References


*The authors have no conflict of interest or funding support to disclose.*
Assessment Questions

1. For what kinds of complications are DM patients at higher risk than patients without DM?
   A. Cardiovascular problems
   B. Blindness
   C. Kidney disease
   D. All of the above

2. What is the cause of type 1 DM?
   A. Insulin resistance
   B. The immune system destroys the beta cells in the pancreas
   C. Increased blood glucose levels during pregnancy
   D. Obesity

3. According to the study done by Cramer and Pugh, patients used what percent of their insulin prescriptions?
   A. 50 percent
   B. 67 percent
   C. 77 percent
   D. 80 percent

4. Which of the following were mentioned in this article as alternative methods of insulin administration under investigation?
   A. Oral
   B. Nasal
   C. Transdermal
   D. All of the above

5. What was the generic name of the inhaled insulin made by Pfizer?
   A. Insulin inhalation
   B. Technosphere® insulin
   C. Exubera®
   D. Afrezza®

6. Which of the following accurately describes the pharmacokinetics of Technosphere® insulin?
   A. Achieves 37 percent bioavailability
   B. Reaches peak insulin levels in 15 minutes
   C. Lower postprandial blood glucose (PPG) levels compared to subcutaneously injected insulin 30 to 120 minutes following a meal
   D. Two of the above
   E. All of the above

7. Which of the following accurately describes the pharmacodynamics of Technosphere® insulin?
   A. The neutral pH of the lungs slows absorption
   B. Absorbed through the lung tissue into systemic circulation
   C. Smoking decreases its absorption
   D. Two of the above
   E. All of the above

8. True or False: Technosphere® insulin's mechanism of action is identical to prandial subcutaneously injected insulin.
   A. True
   B. False

9. All of the following are advantages of inhaled insulin when compared to injectable insulin EXCEPT which one?
   A. Lower peak blood glucose
   B. Lower PPG levels 30 to 120 minutes following a meal
   C. Lower AUC glucose
   D. Lower FPG levels

10. How does the efficacy of Technosphere® insulin compare to bipart insulin?
    A. Significantly better efficacy
    B. Noninferior efficacy
    C. Poor efficacy
    D. Not enough information

11. What is the most common adverse reaction regarding Technosphere® insulin?
    A. Mild, nonproductive cough within 10 minutes of inhalation
    B. Decreased lung function
    C. Lung cancer
    D. None of the above

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Ohio Northern University
525 South Main Street
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### Ohio Northern University Continuing Education Registration & Evaluation Form

**Raabe College of Pharmacy Continuing Education Evaluation Form**

**Program Title:** FDA Approves New Inhaled Insulin: Afrezza® (Technosphere® Insulin)

**UAN:** 0048-0000-14-216-HO1-P

**CEUs:** 0.1 for pharmacists only

**All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.**

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**Name:**

**Address:**

**City:** [ ]

**State:** [ ]

**Zip:** [ ]

**Phone:** [ ]

**Email:** [ ]

**Pharmacy License #:** [ ]

**State:** [ ]

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**Comments/Suggestions for future programs:**

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**Thank you!**

**Answers to Assessment Questions—Please Circle Your Answer**

1. A B C D

2. A B C D

3. A B C D

4. A B C D

5. A B C D

6. A B C D

7. A B C D E

8. A B

9. A B C D E

10. A B C D

11. A B C D

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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