

How Long Should Insulin Be Used Once a Vial Is Started?

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Editor's comment: The commentary by Dr. Grajower has such important clinical relevance that responses were invited from the three pharmaceutical companies that supply insulin in the U.S. and the American Diabetes Association, and all of these combined in this commentary. The commenting letter and individual responses were authored separately and are completely independent of each other.

Diabetic patients treated with insulin, whether for type 1 or type 2 diabetes, are prone to often unexplained swings in their blood glucose. These swings can vary from dangerously low to persistently high levels. Most diabetic patients, and most physicians, will adjust insulin regimens so as to avoid hypoglycemia at the expense of hyperglycemia. Among the "textbook" reasons for variable glucose responses to any given insulin regimen are 1) site of administration, 2) exercise, 3) bottles not adequately mixed before drawing the insulin (for NPH, Lente, or Ultralente), and 4) duration of treatment with insulin (1).

A new insulin was marketed by Aventis Pharmaceuticals about 1 year ago, insulin glargine (Lantus). The manufacturer seemed to stress that patients not use a started bottle of this insulin for >28 days (2). Two patients of mine highlighted this point.

L.K. is a 76-year-old woman with

type 2 diabetes, diagnosed at 55 years of age, and treated with insulin since age 56. Her insulin regimen was changed to Lantus at night together with Novolog before meals. She monitors her blood glucose four times a day. She used a bottle of Lantus until it ran out; therefore, a bottle lasted for 2 months. Her recent HbA_{1c} was 7.6%. I retrospectively analyzed her home glucose readings by averaging her fasting blood glucose levels for the first 15 days of a new bottle and the last 15 days of that same bottle. The results were 137 ± 20 and 187 ± 13 mg/dl, respectively.

E.T. is a 77-year-old man with type 1 diabetes since 29 years of age. His regimen was changed from Humulin N plus Lispro to Lantus at bedtime and Lispro before meals. He checks his blood glucose levels four times a day. He observed on his own that the last 25% of his Lantus bottle didn't seem as potent as the first 75% and questioned me about this. I asked him how long a bottle of Lantus insulin lasts for him. He told me 40 days (consistent with his dose of 25 U/day). Simple math revealed that his last 25% was past the recommended 28 days.

I set out to review the available literature on insulin storage. Lilly recommends using an opened bottle of Humulin R for 4 weeks, Humalog for 4 weeks, and Humulin N for only 1 week, whether refrigerated or at room temperature. Humalog Mix 75/25, Humulin 70/

30, and Humulin N cartridges can be used for 7–10 days (3). Novo Nordisk states that vials or cartridges of Novolog can be used for 28 days at room temperature but says nothing about how long it will last if refrigerated (4). In a private communication with a staff pharmacist at Novo Nordisk, I received the following message: "If human insulin vials that are stored under refrigeration are used beyond 30 days, the stability of human insulin vials is dependent upon a number of factors in addition to temperature [sic]. These factors include the number of injections per day, volume of insulin remaining in the vial, exposure to light, agitation, and technique used for dose preparation. The impact of these factors is difficult to measure and the health professional should advise patients on an individual basis concerning long-term storage of opened insulin vials when refrigerated."

An exam review for pharmacists lists the expiration date for opened vials of Humalog as 4 weeks, but other vials of human insulin are listed as 30 days unrefrigerated and 3 months refrigerated. Cartridges of R and Lispro are listed as stable for 4 weeks and 70/30 or N for 1 week (5).

I dare say that most physicians are not aware of the potency of the various insulins once a cartridge or vial is opened. This is probably due to a combination of reasons: contradictory information in print (as illustrated above), lack of adequate dissemination of this information, and lack of real data on this subject.

Indeed, the comprehensive, well-written, and up-to-date American Association of Clinical Endocrinologists (AACE) Diabetes Guidelines do not refer to the issue of storage of an opened vial or cartridge at all, either as an issue for the physician to be aware of or as a point of discussion with patients as part of their self-management (6).

A search of the American Diabetes Association (ADA) website on the subject of storage revealed the following comment: "Although manufacturers recommend storing your insulin in the refrigerator, injecting cold insulin can sometimes make the injection more painful. To counter that, many providers recommend storing

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M.M.G. has received honoraria from Novo Nordisk, Aventis, and Eli Lilly.

Abbreviations: ADA, American Diabetes Association.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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the bottle of insulin you are using at room temperature. Most believe that insulin kept at room temperature will last a month or so" (7).

It seems to me that the ADA should be able to issue a more authoritative (i.e., evidence-based) statement than "most believe." And what does "a month or so" mean? Given the 10-day manufacturer recommendation for Humulin N or 70/30, does that fall within the month? Is my patient's 40 days on Lantus considered a month?

When addressing the issue of insulin storage in the ADA's Clinical Practice Recommendations 2002, it is stated that "The patient should always have available a spare bottle of each type of insulin used. Although an expiration date is stamped on each vial of insulin, a loss of potency may occur after the bottle has been in use for >1 month, especially if it was stored at room temperature" (8).

The importance of not using bottles past their expiration date after opening is critical to good patient care. It is also an important cost issue. Many patients will be forced to throw out unfinished bottles of insulin. If the patient pays out-of-pocket, this increased cost could certainly spur the patient to continue using the bottle anyway, especially if he/she doesn't monitor glucose levels on a regular basis and therefore doesn't even see the difference between using a fresh or expired bottle. Do patients covered by prescription plans get enough insulin bottles to abide by the manufacturers' recommendations or do they calculate the number of bottles required by how many units the patient takes on a daily basis? Why can't manufacturers make smaller bottles of insulin for those on smaller daily doses to reduce wastage?

I have written this article with the following goals: 1) to increase awareness among physicians that storage of opened bottles of insulin is an important variable in controlling diabetes, 2) to spur manufacturers to present to the medical community scientifically rigid data on the expiration of their various insulins once opened and whether refrigeration affects this stability, 3) to then take these data and incorporate them into all future recommendations for the treatment of diabetic patients, whether taught by a physician, diabetes educator, nurse, or patient-oriented organization, and 4) to encourage pharmaceutical companies to

manufacture smaller bottles of insulin to reduce the cost of wasted insulin.

RESPONSE FROM AVENTIS

We appreciate the opportunity to respond to Dr. Grajower's request for information regarding Lantus (insulin glargine [rDNA origin] injection) and the following associated topics: stability information and prefilled syringe stability. Lantus is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes or adult patients with type 2 diabetes who require basal (long-acting) insulin for the control of hyperglycemia.

Warnings

Hypoglycemia is the most common adverse effect of insulin, including Lantus. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal and human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need to change dosage. Concomitant oral antidiabetes treatment may need to be adjusted. Lantus must not be diluted or mixed with any other insulin or solution.

Stability information

The following information is stated in the Lantus package insert (2):

Storage. Unopened vial: Unopened Lantus vials should be stored in a refrigerator at 36–46°F (2–8°C). Lantus should not be stored in the freezer and should not be allowed to freeze. The vial should be discarded if the contents are frozen.

Open (in-use) vial. Opened vials, whether or not refrigerated, must be used within 28 days. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days in a place away from direct heat and light, as long as the temperature is not >86°F (30°C).

This letter briefly describes the analytical processes and testing procedures used to support the labeled stability. The stability of Lantus has not been evaluated in con-

tainers other than those described for commercial distribution, nor has it been evaluated under physical conditions other than those described herein. Stability under other circumstances cannot be inferred from these data.

Analytical procedures

Lantus stability testing assesses the following parameters (Aventis, data on file): 1) appearance, 2) particulate matter, 3) sterility and bacterial endotoxin content, 4) pH, 5) insulin glargine and noninsulin glargine protein content, 6) preservative (*m*-cresol) content and stability, and 7) active insulin glargine content (bioactivity). Unless otherwise stated, Lantus met or exceeded stability requirements in these studies (Aventis, data on file).

Stability testing

Photostability. Lantus was found to degrade after extended exposure to either room light or artificial sunlight (Aventis, data on file). Due to this finding, all other stability testing was conducted in an environment protected from light. When not in active use, Lantus should be protected from light. An in-use vial of Lantus is stable in room light for a period of 28 days. Lantus should be protected from direct sunlight.

In-use stability (open vial). The in-use stability of Lantus was assessed over a 4-week period with or without refrigerated storage (Aventis, data on file). During the study, 2 units of Lantus were removed each day and discarded. The samples were stored at either 41 or 77°F (5 or 25°C) for a period of 28 days. The remaining product after 4 weeks met all stability criteria. It is recommended that Lantus be discarded after 28 days following the first use, regardless of refrigeration.

Long-term storage stability (unopened vial). Lantus was found to meet stability criteria for at least 24 months when stored between 36 and 46°F (2 and 8°C) (Aventis, data on file). Accelerated stability testing at 77°F (25°C) revealed a slight loss in activity by 9 months. Testing at 95–102°F (35–39°C) for 1 month revealed an increase in impurities without loss of activity. Lantus should be stored in a refrigerator to maintain the labeled expiration date. In the absence of refrigeration, unopened vials of Lantus should be discarded after 28 days.

Adverse shipping condition stability.

The stability of Lantus was determined under conditions mimicking extreme temperature changes that may occur during shipment (Aventis, data on file). Two separate 28-day investigations of temperature fluctuations from 5 to 77°F (−15 to 25°C) and from 41 to 77°F (5 to 25°C) were conducted, with repeating cycles of 4 days at the lower temperature and then 3 days at 77°F (25°C). The content of Lantus did not change appreciably under either set of conditions and met stability criteria.

Summary

Unopened Lantus stored under refrigeration and without freezing will maintain stability to the expiration date stated on the packaging (Aventis, data on file). Should Lantus freeze, it should be discarded. If refrigeration is not available, unopened Lantus may be stored at controlled room temperature ($\leq 86^\circ\text{F}$, $\leq 30^\circ\text{C}$) for a maximum of 28 days. Lantus should be discarded 28 days after first use, regardless of refrigeration.

Prefilled syringe stability

The stability of Lantus when it is prefilled into syringes and stored up to 7 days was evaluated using four different types of syringes (Aventis, data on file). The following syringes were tested (200 syringes of each type): 1) BD Ultra-fine, U-100, 0.5 ml, 30 G \times 1/2 inch (Becton Dickinson [BD]); 2) BD Ultra-fine II (short needle), U-100, 0.5 ml, 30 G \times 5/16 inch (BD); 3) Walgreens super thin syringes, U-100, 0.5 ml, 29 G \times 1/2 inch (Walgreens); and 4) Reli-On insulin syringes, U-100, 0.5 ml, 30 G \times 5/16 inch (Wal-Mart).

The syringes were stored either at 41°F (5°C) or 77°F (25°C) for up to 7 days, after which the Lantus solution was tested for filtration time, byproducts, insulin glargine content, and *m*-cresol (preservative) content. The Lantus solution was visually inspected and pH measured every day (except days 4 and 5). Microbial contamination was not evaluated in this study.

Results

Visual appearance at 41°F (5°C). The Lantus solution became turbid more quickly in the Walgreens syringes compared with those of BD and Reli-On. By day 3, the Lantus solution was turbid in all four syringe types. After 2 days of stor-

age in the Walgreens syringes, the Lantus solution did not meet specification.

Visual appearance at 77°F (25°C). The Lantus solution became turbid in the Reli-On syringes by day 2, and turbidity occurred in the Walgreens and BD Ultra-fine II syringes by day 3. After 6 days of storage in the Walgreens syringes, the Lantus solution did not meet specification. A placebo solution stored in the Walgreens syringes at each temperature did not become turbid over 7 days.

Insulin glargine content, byproducts, filtration, and pH. For each syringe type, the Lantus solution complied with specifications.

***m*-Crescol content.** For each syringe type, the Lantus solution complied with specifications.

Summary

Aventis Pharmaceuticals does not recommend prefilling syringes with Lantus and storing for any period longer than needed for application. In addition BD states the following (9): “BD does not recommend that any of our syringes be prefilled more than a few minutes in advance of the injection. There are no conclusive studies to determine the safety or risks associated with this practice.”

RESPONSE FROM ELI LILLY

We appreciate the opportunity to respond to Dr. Grajower's letter concerning in-use dating of insulin products manufactured by Eli Lilly. There are many issues affecting recommendations for storing insulin, and the labeling is controlled by global regulatory agencies, including the U.S. Food and Drug Administration. Considering the large number of factors that go into these recommendations, it is not surprising that there may be confusion about insulin potency during use.

When unopened vials, cartridges, or prefilled insulin pens are stored at the recommended temperatures (between 36 and 46°F [2 and 8°C]), insulin may be used until the expiration date printed on the insulin container or carton. At expiry, regulatory requirements state that the insulin product must retain at least 95% of its labeled potency.

However, once an insulin product is in use, the recommended durations of in-use differ depending on the particular formulation of insulin (regular, NPH, Humalog, etc.), its primary container (vial

or cartridge), the ambient storage conditions (room temperature or refrigerated), and regulatory requirements.

Two main factors influence recommended in-use durations: sterility of the product and potency. Eli Lilly establishes guidelines for storage based on recommendations by the Committee for Proprietary Medicinal Products (CPMP), with particular reference to guidance on sterile products for human use, which includes insulin products (10). Insulin products are sterile until the first dose is withdrawn by syringe or expelled from a cartridge. After first use, the contents of the vial or cartridge are technically no longer sterile, despite the presence of antimicrobial preservative agents, such as metacresol and phenol or methylparaben, in concentrations adequate to kill or retard the growth of small microbial challenges. Sterile products should be used in as short a time as possible to minimize concerns about microbiological contamination once the container has been opened or punctured. The CPMP has proposed a maximum-use period of 28 days for sterile products containing preservatives, including insulin products.

The chemical potency of insulin is measured by high-performance liquid chromatography and is unrelated to the above discussions of in-use dating relative to preservative effectiveness. At the time of manufacture, insulins available in the U.S. have a label potency of 100 units/ml. However, regulatory limits allow for $\pm 5\%$ variation around that standard. Internal standards for insulins manufactured by Eli Lilly are within $\pm 3.0\%$ at the time of release. At room temperature, the degradation of insulin is an approximately linear function. At elevated temperatures, insulin loses chemical potency, which is accelerated as the temperature increases. For example, at room temperature (77°F), insulin will lose $<1.0\%$ of its potency over 30 days, or $<0.03\%$ potency lost per day. In contrast, insulin stored in a refrigerator will lose $<0.1\%$ of its potency over 30 days (Lilly Research Laboratories, data on file). For this reason, and to maintain consistent temperature exposure, we recommend that any unused insulin be refrigerated. Importantly, the relatively small amount of degradation products that develop during storage, such as B-3 and A21-desamido insulin, remain partially biologically active. Although refrigeration should be

used when possible, the loss of the biological potency of insulin is so slow that if one carefully protects insulin supplies from extreme temperature, any losses of potency should have minimal, if any, effect on the control of diabetes. Ultimately, although “main peak” chemical potency as measured by high-performance liquid chromatography may decrease over time, the effect on insulin biological potency may be minimal.

Patients should not use insulins that have changed in appearance due to heat exposure or freezing. Freezing will cause modified insulins (i.e., those containing a precipitate such as NPH insulin, Ultralente insulin, or Lente insulin) to resuspend improperly after thawing, reducing the accuracy of dosing.

The in-use dating differences between vials and cartridges are primarily due to the reduced volumes, increased agitation, and potentially variable temperature exposures of a cartridge or prefilled pen during use. Therefore, the in-use dating recommendation for pens and cartridges is for somewhat shorter times than that for vials, reflecting the reduced volumes and the environment to which these products might be exposed. These recommendations may be found in the “Information for Patients” document included in insulin products.

In conclusion, the recommended in-use period for insulin is based primarily on a number of factors and regulatory requirements, particularly relating to sterility of the product. Chemical and biological potency are not the determining factors in storage recommendations for insulins.

RESPONSE FROM NOVO NORDISK

Thank you for sharing this letter regarding insulin storage guidelines. Novo Nordisk shares the commitment of health care professionals that insulin storage and handling should be appropriate to maintain consistent and predictable glycemic effects. We agree that storage and handling guidelines are essential for the patient to use insulin safely and effectively on a daily basis, in a variety of situations. We offer the following information regarding proper use of insulin formulations manufactured by Novo Nordisk.

General guidelines of insulin storage and handling

In general, insulin formulations should be inspected for physical changes, such as clumping, frosting, precipitation, or discoloration, that may be accompanied by a loss of potency. Insulin formulations should be optimally stored at refrigerated temperatures (36–46°F, 2–8°C) before use (1). Insulin formulations should never be allowed to freeze.

Extreme temperatures or excess agitation should be avoided during storage to prevent loss of potency of the formulation. Regardless of the temperatures experienced during storage, insulin formulations should never be used after the expiration date printed on the label and carton.

When a formulation is in use, insulin should be kept unrefrigerated to minimize local injection site irritation, which may occur after injection of cold insulin solutions (2). Unrefrigerated insulin formulations that are in use should be kept as cool as possible and away from excess heat or sunlight (11).

Storage guidelines: vials of Novolin R, Novolin N, Novolin 70/30, Novolin Lente, or Velosulin BR

The U.S. Pharmacopoeia Dispensing Information provides the following recommendations for storage of insulin vials: “An insulin bottle in use may be kept at room temperature for up to 1 month. Insulin that has been kept at room temperature for longer than 1 month should be thrown away” (11).

The ADA reminds health care professionals that even though each insulin vial is stamped with an expiration date, a slight loss of potency may occur after the vial has been in use for >30 days, especially if stored at room temperature (12). If human insulin vials are stored under refrigeration while in use and are used beyond 30 days, the stability of these vials may be affected by a number of factors. Such factors include the number of injections per day, volume of insulin remaining in the vial, exposure to light, agitation, and technique used for dose preparation. The impact of such factors is difficult to measure, and the health care professional should advise patients on an individual basis concerning long-term storage of opened insulin vials when refrigerated.

Storage of NovoLog (insulin aspart [rDNA origin] injection)

Unused vials of NovoLog should be stored under refrigeration between 36 and 46°F (2 and 8°C). The formulation must not be frozen. Do not use NovoLog if it has been frozen or exposed to temperatures in excess of 98.6°F (37°C). After a vial of NovoLog has been punctured, it may be kept at temperatures <86°F (30°C) for up to 28 days but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated.

NovoLog in the reservoir of an external insulin delivery pump for use during continuous subcutaneous insulin infusion should be discarded after no more than 48 h of use or after exposure to temperatures that exceed 98.6°F (37°C).

Novo Nordisk prefilled delivery systems and insulin cartridges

Prefilled pen and cartridge forms of insulin formulations (which contain 3 ml insulin rather than 10-ml vials) can be used to minimize waste of unused insulin. Since a prefilled pen or cartridge contains 300 units versus the 1,000 units of a vial, it takes the patient less time to exhaust that insulin when compared with the contents of a 10-ml vial. This smaller amount of insulin can mean that it is more likely that insulin will be used within the recommended in-use time period. Insulin pen devices are already the predominant form of insulin use outside of the U.S. Novo Nordisk offers the prefilled insulin delivery systems NovoLog FlexPen insulin aspart injection (rDNA origin), NovoLog Mix 70/30 FlexPen 70% insulin aspart (rDNA origin) protamine suspension and 30% insulin aspart (rDNA origin) injection, and Novolin InnoLet human insulin (rDNA origin). PenFill cartridges are used in insulin delivery devices such as NovoPen 3, InDuo, and Innovo. Prefilled pens and reusable devices with the cartridge inside are stored at room temperature during use and thereby offer improved convenience and portability. The in-use times recommended for prefilled pen and cartridge products are based on simulated in-use conditions and room temperature storage.

NovoLog FlexPen or NovoLog Mix 70/30 FlexPen prefilled syringes

NovoLog FlexPen is a 3-ml prefilled syringe that contains insulin aspart [rDNA origin] (100 units/ml). NovoLog Mix

70/30 FlexPen is a prefilled syringe that contains 3 ml of a mixture of 70% insulin aspart protamine crystals and 30% soluble insulin aspart (rDNA origin). FlexPen syringes that are not currently in use should be stored under refrigeration (36–46°F [2–8°C]), but not in the freezer compartment. An in-use FlexPen device should be stored at temperatures <86°F (30°C) for 14 days for NovoLog Mix 70/30 FlexPen and 28 days for NovoLog FlexPen.

Storage of Novolin InnoLet human insulin (rDNA origin)

Novolin InnoLet is a 3-ml prefilled insulin doser that contains Novolin R, N, or 70/30 insulin. InnoLet dosers that are not currently in use should be stored in a cold (36–46°F [2–8°C]) place, preferably in a refrigerator, but not in (or near) the freezer compartment. An in-use InnoLet doser should be stored at temperatures <86°F (30°C) for 28 days for Novolin R InnoLet, 14 days for Novolin N InnoLet, and 10 days for Novolin 70/30 InnoLet.

Storage of Novo Nordisk reusable insulin delivery devices and PenFill cartridges

NovoPen 3, InDuo, and Innovo insulin delivery devices should be stored at room temperature. Unused Novolin PenFill cartridges should be kept in a cold place, preferably in a refrigerator, but not in the freezer compartment. Unused NovoLog and NovoLog Mix 70/30 PenFill cartridges should be kept refrigerated. Do not allow the PenFill cartridges to freeze. Keep unused PenFill cartridges in the carton so that they will stay clean and protected from light.

Novolin, NovoLog, and NovoLog Mix 70/30 PenFill cartridges currently in use should not be refrigerated after insertion into NovoPen 3, InDuo, or Innovo insulin delivery devices. In-use NovoLog and NovoLog Mix 70/30 PenFill cartridges should be protected from extreme temperatures and should be stored at temperatures <86°F (30°C) for 28 days for NovoLog PenFill and 14 days for NovoLog Mix 70/30 PenFill.

In-use Novolin PenFill cartridges should be protected from extreme temperatures and sunlight. Unrefrigerated in-use Novolin PenFill cartridges can be used 28 days for Novolin R PenFill, 14 days for Novolin N PenFill, and 10 days for Novolin 70/30 PenFill. Unrefrigerated

PenFill cartridges should be discarded if not used within the time periods listed above. Storage at extreme temperatures should be avoided because the physical properties of the insulin may be altered.

Expiration dates for refrigerated unopened product and in-use times for opened room temperature product are based on data generated by Novo Nordisk and approved by regulatory authorities, such as the Food and Drug Administration, to ensure that the potency of a properly handled product is maintained while the product is in use. These times differ by brand and type of insulin, as well as by product presentation (i.e., vial versus cartridge), to ensure the longest in-use time without sacrificing potency. Proper storage and handling of insulin products is essential and must be considered as part of routine daily care by both the physician and patient when using insulin.

Novo Nordisk offers the aforementioned storage and handling guidelines for insulin vials, PenFill cartridges, and a variety of insulin pens and dosers to enable patients and health care professionals to use insulin safely and effectively. If you require any further information, please contact Novo Nordisk Pharmaceuticals at (800) 727-6500.

RESPONSE FROM THE ADA

Thank you for asking the ADA to respond to Dr. Grajower's letter. He raises several very important points regarding the storage of insulins and its possible effects on blood glucose control. His specific comments regarding the various insulins and what their manufacturers state regarding storage and product expirations will need to be addressed by the manufacturers themselves. If their guidelines were only evidence based, then they would have that data. I will comment on the general topic of insulin use as regards the guidelines that come from our 2003 Clinical Practice Recommendations. In general, patients are instructed that once opened, an insulin vial need not be refrigerated and can be kept at room temperature for ~1 month. Extremes of temperature should be avoided because these can lead to significant changes in insulin action. How long an insulin can be stored while unopened is based on the expiration date.

Dr. Grajower raises an excellent point in stating that changes in insulin action can lead to significant changes in blood glucose control. In our 2003 guidelines,

we state that "The person with diabetes should always try to relate any unexplained increase in blood glucose to possible reductions in insulin potency. If uncertain about the potency of a vial of insulin, the individual should replace the vial in question with another of the same type" (12). We agree that patients and providers need to consider changes in insulin activity as another important factor in evaluating changes in glucose control. Thank you for allowing us to respond.

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