TriboFilm Research, Inc.

HOW LUBRICANT CHOICE AFFECTS DOSE ACCURACY IN INSULIN PUMPS

The development of fully automated, closed-loop glucose monitoring and insulin delivery systems can significantly improve patients' quality of life by closely mimicking a real pancreas. However, since the patient is not directly involved in administering the dose, these devices depend on one key factor - dosing accuracy. One wrong dose can be fatal. Here, Jackson Thornton, Associate Director of Research, and Vinay Sakhrani, Vice-President, Technology, both of TriboFilm Research, examine how lubricant selection in the insulin cartridge, which is typically an afterthought, can make the delivery device more accurate. They also look at how lubricant choice affects dosing accuracy using a "real-patient simulation" test method.

Insulin pump therapy is considered the gold standard of care for insulin-requiring diabetic patients. An insulin pump provides glucose control by subcutaneously delivering fast-acting insulin to the patient in a programmed sequence that mimics the pancreas. In addition to the clinical benefits of glucose control, insulin pumps can improve the quality of life for patients with diabetes by eliminating the need for multiple daily insulin injections.

The US FDA recently approved the first "artificial pancreas" for diabetes treatment, which wirelessly links an insulin pump to a glucose monitor using a closed-loop control system. To achieve closed-loop control, the insulin pump must accurately deliver the dose requested by the control unit on short timescales.

Accurate dose delivery becomes problematic when the device flow rate changes throughout the day – such as when mimicking a healthy pancreas that reacts rapidly and precisely to changing amounts of glucose in the blood stream. Rapid infusion start-up and precise delivery at low infusion rates are critical to ensure patient safety and maintain the integrity of the feedback control.

This publication examines how improving the frictional properties of pump components, particularly the lubricant in the insulin container closure system, impacts infusion pump response time and leads to superior pump operation.

The current insulin reservoir lubrication methods and testing standards used to evaluate pump operation are insufficient for the new artifical pancreas devices. Thus a next-generation lubricant coating and test set-up were used to evaluate the dose accuracy of a pump using a realistic insulin delivery profile.

"Lubrication is usually an afterthought when drug delivery systems are designed. However, the lubricant is an integral system component that facilitates the movement of the plunger through the barrel of an insulin reservoir."

Dr Jackson D Thornton
Associate Director of Research
T: +1 919-838-2844
E: thornton@tribofilmresearch.com

Mr Vinay G Sakhrani
Vice-President, Technology
T: +1 919-838-2844
E: vinay@tribofilmresearch.com

TriboFilm Research, Inc
625 Hutton Street, Suite 105
Raleigh
NC 27606
United States

tribofilmresearch.com

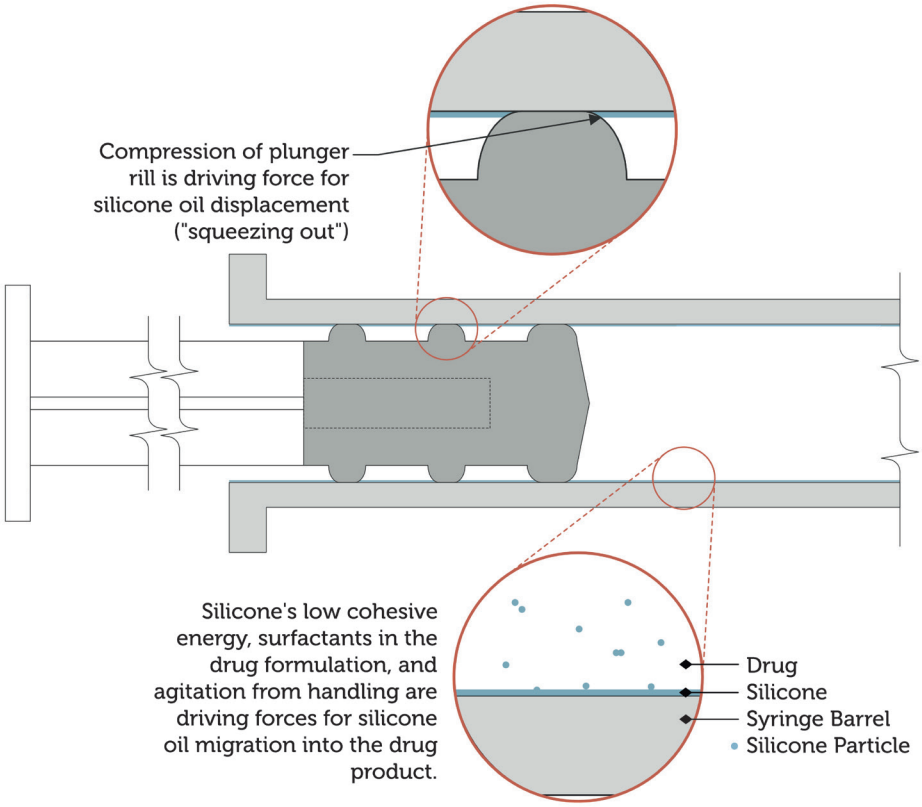

Figure 1: Silicone oil, the most commonly used pharmaceutical container lubricant, can easily be displaced by the plunger, leading to stick-slip.

LUBRICATION IN INSULIN INFUSION PUMPS

Most insulin infusion pumps use a container closure system, which consists of a 3 mL plastic or glass cartridge that is filled with insulin and sealed using an elastomer plunger. The pump drive mechanism pushes the plunger to deliver insulin to the patient through a subcutaneous cannula. Insulin is delivered in small, discrete pulses, where the volume of each pulse and the time between pulses dictates the time-averaged insulin infusion rate. The container closure system must be lubricated to ensure proper movement of the plunger through the cartridge.

Lubrication is usually an afterthought when drug delivery systems are designed. However, the lubricant is an integral system component that facilitates the movement of the plunger through the barrel of an insulin reservoir. Silicone oil, the most commonly used lubricant, can easily be displaced under the compressive loads exerted by the slow-moving plunger. The displacement of silicone oil leads to "stick-slip" plunger movement, dosage inaccuracies due to plunger compression and sub-visible lubricant particles in the drug medium (see Figure 1).

TriboFilm Research has developed a unique atmospheric gas plasma technology that immobilises a lubricant onto the surface of a drug container. This immobilisation prevents the lubricant layer from being displaced by the plunger seals and maintains a stable, low-friction surface for the plunger to glide along while maintaining the container closure integrity.

TriboFilm's technology – originally developed under a grant from the US National Institues of Health for prefilled syringes – has shown huge improvements over traditional silicone oil lubricants for syringe force profiles as well as a reduction in sub-visible lubricant particles in the drug medium. Given the success of this lubricant coating in prefilled syringes, an insulin pump manufacturer asked if the coating could improve pump performance.

COMPARING LUBRICATION SYSTEMS

The aim of this article is to highlight the effects of lubrication in pump applications and demonstrate how plunger forces affect pump response time and dose accuracy. The customer's infusion pump was mimicked using commercially available 1 mL long cyclic olefin polymer (COP) syringes with butyl rubber plungers. A Zwick universal testing machine was used as the pump drive mechanism, which also measured the force required to advance the syringe plunger.

A comparison of lubrication systems was performed between silicone oil, the industry standard syringe and cartridge lubricant; and TriboGlide DS®, a silicone-free immobilised lubricant. The syringes were filled with purified water to represent insulin, and attached to a time-stamped microbalance using an infusion tube and cannula. Water was dispensed through the tubing and into a beaker on the microbalance with a thin film of paraffin oil on top to prevent evaporation of the water. Weight readings were recorded every 10 seconds so that pulse-to-pulse variability could be analysed. A schematic of this test set-up is shown in Figure 2.

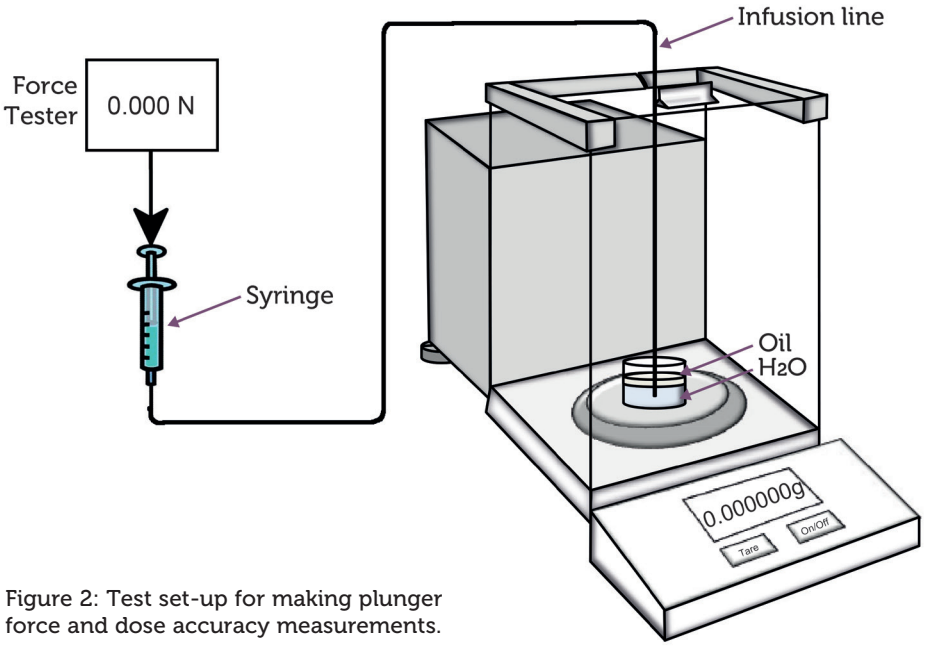

Figure 2: Test set-up for making plunger force and dose accuracy measurements.

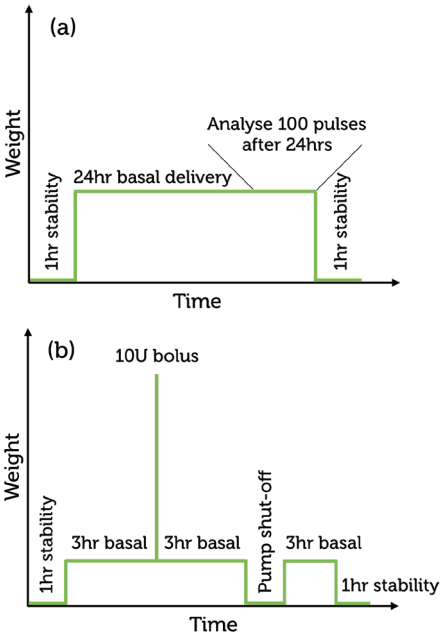

Figure 3: (a) Dispensing profile for the international standard EN 60601-2-24, which uses a 24-hour stabilisation period at the basal dose, followed by analysis of 100 pulses; (b) modified dispensing profile used in TriboFilm's study to simulate a realistic dosage scenario for a diabetic patient.

MEASUREMENT OF DOSE ACCURACY

Currently, insulin pump manufacturers specify ±5% delivery accuracy using methods established in the international standard EN 60601-2-24. The standard calls for a 24-hour stabilisation period followed by the measurement and averaging of 100 consecutive pulse deliveries as shown in Figure 3a. Averaging over many pulses after a 24-hour stability period provides limited information about the initial pump start-up, accuracy of the individual pulses and quick response to changing dose requirements, all of which have become increasingly important as the industry moves toward an artificial pancreas. Thus, the EN 60601-2-24 standard may provide misleading results for an insulin infusion pump.

Tests were performed using the EN 60601-2-24 standard (data not shown), and as expected, both the silicone oil and TriboGlide-DS® coated syringes passed. This data can be found on our website at tribofilmresearch.com/doseaccuracy. However, an insulin pump will also deliver several bolus doses throughout the day based on the needs of the user, along with extended periods of basal delivery and complete pump shut-off in emergencies – and thus it never experiences a 24-hour stabilisation phase.

"An understanding of how plunger forces affect infusion pump dosing accuracy provides tremendous benefit for improving device function."

To improve on the testing method and provide more suitable data for artificial pancreas devices, the standard testing sequence was modified to simulate a realistic dose scenario for a diabetic patient as shown in Figure 3b.

TriboFilm Research developed a real-patient simulation standard to mimic how diabetic patients use their pumps. Like the international standard, this test method delivers a constant basal phase but in this test method the basal dose is broken up by a mealtime bolus and pump shut-off. These two additional features are used to evaluate how changes in the pump delivery rate affect the plunger force and dose accuracy. For the real-patient simulation, the pumping sequence had five distinct segments:

1 **Basal period 1:** Dispense 0.05 IU pulses every three minutes for three hours while the patient enjoys some afternoon shopping.
2 **Mealtime bolus:** Provide a 10 IU mealtime bolus prior to eating dinner with friends.
3 **Basal period 2:** Continue with the 0.05 IU basal dosing for three hours after dinner while getting ready for bed.
4 **Pump shut-off:** Stop the flow of insulin due to a hypoglycaemic event during sleep.
5 **Basal period 3:** Continue with the 0.05 IU basal dosing once blood glucose returns to an acceptable level.

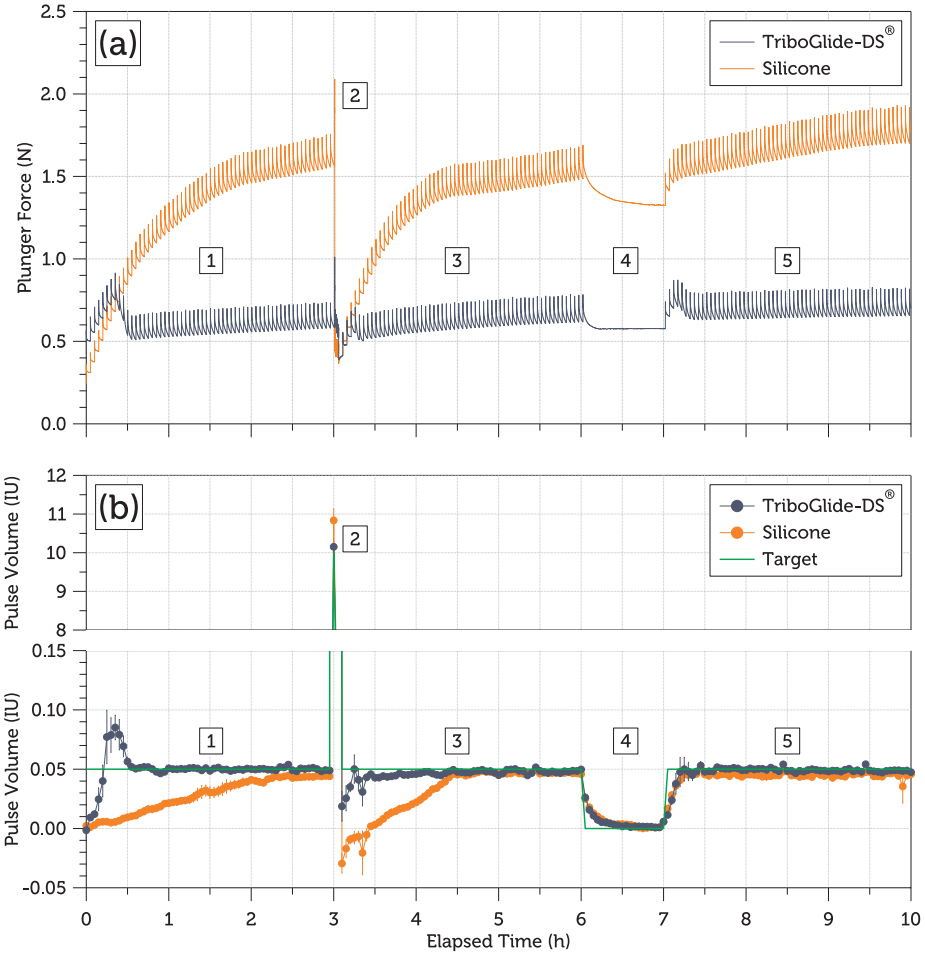

Figure 4: (a) Plunger force versus test time and (b) individual pulse volume versus test time for the realistic pump profile. The five different pump regions are labelled on the plot where [1, 3, and 5] correspond to basal delivery, [2] is a mealtime bolus and [4] is a pump shut-off.

RESULTS

The plunger force *versus* time and individual pulse volume *versus* time for the real-patient simulation is shown in Figure 4. Each plotted data series is the average of 10 measurements. The five segments listed above are readily distinguished in the figure, and observations of these regions are described in Table 1.

The results in Figure 4 are attributed to the effects of plunger compression. Whenever an elastomeric sealing member is used to dispense fluid – such as the plunger in a syringe or cartridge – there is the potential for compression of the plunger, which can store unwanted stresses. A free lubricant, such as silicone oil, will be displaced from

Observation	Implications/Notes
1. **Basal period 1:** As the plunger transitions from static to dynamic friction conditions, the TriboGlide DS® syringes underdeliver the target volume for the first 15 minutes and then compensate by an equal overshoot for the next 15 minutes. At the 30-minute mark the cumulative amount delivered by TriboGlide DS® syringe is 95% of the target volume. Following this initial peak, the system delivers the target volume. The silicone oil-lubricated syringes underdeliver for over two hours while compressing the plunger and accumulating stress. After two hours, the plunger continues to move forwards in a stressed state. At the end of the first 30 minutes the silicone syringe only delivers 10% of the cumulative target dose.	Stress retained in the plunger causes severe deviation in the delivery targets for silicone oil-lubricated syringes. The displacement of the silicone oil due to plunger compression causes frictional forces to rise, leading to under-delivery of the target dose.
2. **Mealtime bolus:** A spike in force, followed by relief of the built-up stress in the plunger is observed during the mealtime bolus. The TriboGlide DS® lubricated syringes require 50% less force than silicone oil-lubricated syringes and the stress release is minimal because there was not much accumulated stress. With the silicone oil-lubricated syringes, all the plunger compression stress built up during the basal dose in step 1 is relieved causing an overshoot in bolus delivery by almost 1 IU. Following this bolus dose the plunger force returns to its pre-stressed state.	The lower force requirements for TriboGlide-DS® lubricated syringes can allow a smaller battery to be used for a pump, ultimately resulting in a smaller form factor. Additionally, the improved dose accuracy with TriboGlide DS® would improve patient safety.
3. **Basal period 2:** After the mealtime bolus, the basal phase continues where the TriboGlide DS® coated syringes remain at the steady state force observed before the bolus delivery, and the silicone oil-lubricated syringes require another two hours to return to equilibrium. The delivery accuracy results mimic the plunger forces.	Since all built-up stress in the silicone oil-lubricated syringe was released during the previous bolus, the plunger begins to compress again and accumulates stress which leads to severe under-delivery. This is attributed to slip-stick behaviour.
4. **Pump shut-off:** A pump shut-off occurs after the second basal period for one hour. Both lubrication systems significantly reduced fluid output within a few minutes when the pump sequence was halted. The plunger force for TriboGlide DS® returned to initial levels immediately. However, the silicone oil-lubricated syringes remained at a higher force level – retaining the stress in the plunger seals.	The retained stress in the silicone oil-lubricated syringe has the potential to deliver an unwanted bolus if the plunger decompresses due to an accidental mechanical shock to the pump. The potential for an unwanted bolus, especially during a hypoglycaemic event, is a liability for the device as it could be harmful to the patient and lead to a product recall.
5. **Basal period 3:** The third basal delivery continues for three hours after the pump shut-off with both syringe lubricant types remaining in the steady state of force that they were in prior to pump shut-off. The final basal dose is delivered at the 0.05 IU target very quickly for both syringe types.	While both systems show similar accuracy during this segment, the plunger in the silicone syringe advances at an elevated force level indicating that it is stressed.

Table 1: Observations of the five segments of the real patient simulation testing set-up.

Region	Target	Silicone Oil		TriboGlide-DS®	
	Net Volume (IU)	Net Volume (IU)	% of Target	Net Volume (IU)	% of Target
Basal 1	3	1.65	55%	**2.98**	99%
Bolus	10	10.84	108%	**10.15**	102%
Basal 2	2.95	1.82	62%	**2.69**	91%
Shutoff	0	0.11	N/A	**0.10**	N/A
Basal 3	3	2.65	88%	**2.88**	96%

Table 2: Total delivery volume dispensed versus target delivery volume for silicone oil and TriboGlide DS® lubricated syringes.

the plunger/barrel interface and the slowly advancing plunger will compress and plough through the silicone oil layer as it advances.

This is observed in the force curves where the silicone oil-lubricated syringes build up force for the first two hours while the plunger is compressing, and then plough along the barrel in the compressed state. This plunger compression and accumulation of stress leads to under-delivery of insulin for over two hours. In the case of the TriboGlide-DS® cross-linked lubricant, the coating is never completely displaced from the plunger/barrel interface and the plunger can glide on top of the lubricant layer. The TriboGlide-DS® coated syringes slightly underdeliver for the first 15 minutes as the plunger overcomes the static friction followed by compensating with an equal over-shoot for the next 15 minutes. Table 2 quantifies the delivery accuracy for both lubricant types in all five segments.

CONCLUSION

An understanding of how plunger forces affect infusion pump dosing accuracy provides tremendous benefit for improving device function. This study compared the force and dose accuracy of containers lubricated with traditional silicone oil and TriboGlide-DS®. Outcomes from the study include:

1. The TriboGlide-DS® lubrication system significantly reduced the plunger forces compared with traditional silicone oil. Lower forces require less battery power, which can reduce the size and weight of the overall device. Smaller form factor is a competitive advantage in the wearable insulin pump market.
2. A reduction in forces also allowed for significantly faster response time for the infusion pump to deliver the desired dose accurately. Faster response times will improve the feedback control for closed-loop artificial pancreas systems. Dose accuracy is crucial for the next generation of automated insulin delivery devices.
3. Higher plunger forces in silicone oil-lubricated syringes led to stress build-up and compression of the plunger for hours before equilibrium was achieved. If the pump were jarred accidentally, this stress could be released and dispense an unwanted and potentially harmful bolus to the patient. The lower forces and retained plunger stresses with TriboGlide-DS® reduce liability and recall risk resulting from unwanted boluses being administered to patients in a completely automated delivery system.
4. A modification of the standard dose accuracy test method was developed to show how realistic changes in the dosing rate throughout the day would affect the accuracy of a pump. We believe that the current standard does not require the precision and accuracy that will be needed as insulin delivery moves to a closed-loop automated system.

This research shows how the TriboGlide-DS® lubrication system provides a means to continue the trend of developing smaller, smarter and safer infusion pumps. However, this research is only the first step. We look forward to collaborating with the industry on the following issues:

- Working together to develop a new international standard that reflects the realistic usage of closed-loop insulin devices with integrated monitoring and delivery. In this article, we propose one possible starting point for work on this standard. More work will be required to define a comprehensive standard for a fully automated smart pancreas device.
- Replicating these tests on custom insulin delivery devices and improve dose accuracy and device performance even further.

Our primary research mission is to improve patient safety and disease management through innovation. If your product can benefit from improved dose accuracy, we look forward to validating these test results on your specific device.

ABOUT THE COMPANY

TriboFilm Research, Inc, based in Raleigh NC, US, is a one-of-a-kind entrepreneurial research incubator that develops advanced technologies for pharmaceutical packaging applications. With extensive knowledge and experience in surface engineering, TriboFilm has focused its research efforts on one critical aspect of parenteral packaging: device lubrication.

With research grants from the US National Institutes of Health, TriboFilm has developed two advanced lubrication technologies: TriboLink-Si™ and TriboGlide-DS®. TriboFilm has established worldwide patent protection on both lubrication technologies, and licenses these patents to medical device and pharmaceutical companies in targeted fields of use. Our research facility contains state-of-the-art equipment for product development, performance testing and small-scale manufacturing. TriboFilm has all the tools, experience and expertise necessary to create turnkey solutions to even the most demanding of customer challenges.

ABOUT THE AUTHOR

Dr Jackson Thornton is the Associate Director of Research at TriboFilm Research. With a PhD in Materials Science from North Carolina State University, Dr Thornton's expertise in plasma chemistry, surface modification and materials testing is applied to help the largest pharmaceutical companies in the world, as well as start-up biotech and medical device makers. He helps them reduce friction, stiction and sub-visible particles, which in turn reduces product recall risk and improves patient safety.

Vinay Sakhrani is Vice-President of Technology at TriboFilm Research. Since founding TriboFilm in 1997 with National Medal of Technology Laureate and IBM Inventor, Dr Jerry Cuomo, he has advised companies ranging from big pharmaceuticals to start-up device makers.

How accurate is your device?

TRIBO TESTING SERVICES

To schedule a free consultation please contact

Vinay Sakhrani
VP OF TECHNOLOGY
vinay@tribofilmresearch.com
Mobile: +1(919) 345-8744

TriboFilm Research, Inc.

Inventors of patented lubricants: TriboGlide-DS® and TriboLink-Si®
We help medical device designers make their products smaller, slicker and more accurate.
Read what our clients have to say at www.tribofilmresearch.com