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An innovative shock-absorbing blue silicone shell to reduce breakage of veterinary pharmaceutical glass vials

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Abstract

Although glass is an excellent material for manufacturing containers for pharmaceutical use, it remains fragile. This study aimed to support the qualities of glass by protecting the bottles with a shell made of polysiloxane elastomer, and to compare the relative resistance to breakage of this combination with that of a specifically designed plastic bottle.320 vials (250 and 500 ml) made of both glass and plastic, containing injectable veterinary drugs, were subjected to serial drop tests. A first group of containers (SCG: Silicone-Coated Glass) made of Type-1 glass were protected at the shoulder and bottom by a blue silicone soft shell, while those in the second group (LAS: Layered Anti-Shatter) were made of layered shatter-resistant plastic available on the market. Drop tests were carried out at three different angles (0°, 45°, 90°) from the vertical axis of the drop, from two drop heights (80 and 120 cm). All drop conditions (angle, height) and packaging (250 and 500 ml) combined, the risk of breakage of SCG vs LAS vials was RR=0.250 (shattered/intact ratio: 6/154 vs 24/136, 95% CI [0.105;0.595], P=0.002). Up to h=80 cm, no SCG (250 or 500 ml) was broken (0/80), compared to 9/71 for LAS (RR=0.053, 95% CI [0.003; 0.889], P=0.041). The 45° drop on the heel of the bottle produced the most damage for LAS containers (0/80 vs 23/57, RR=0.021; 95% CI [0.001; 0.344], P=0.007). In the event of an accidental fall, the contents of the glass bottle in a silicone shell are significantly better protected than in the multi-layer plastic bottle.

Keywords: Glass vial; Plastic vial; Breakage; Silicon elastomer; Pharmaceuticals

1 Introduction

Packaging can be defined as an economical means of providing presentation, protection, identification, information, packaging, convenience and compliance for products during storage, transport and display until they are used. It must be economical and provide protection against climatic conditions, as well as biological, physical and chemical hazards.

Packaging in the pharmaceutical industry makes use of two main materials for preserving the stability and quality of injectable pharmaceuticals: glass and plastic. Selecting the most suitable packaging is essential for ensuring the *safety* and *effectiveness* of drugs for use by veterinary professionals. Glass containers are extensively used for injectable pharmaceuticals since they offer important advantages over other materials. They are easy to sterilize with heat. Glass is chemically inert and does not react with the contents of the vial. Colored glass has the ability to block certain wavelengths, including UV radiation. Even when colored, glass remains transparent, so the contents, volume and possible abnormalities are visible. Finally, glass containers are airtight and waterproof, which makes them ideal for storing drugs. Although all types of glass can offer these benefits, not all glass vials are appropriate for pharmaceutical use. Though always made of silica, Type-1 glass (80% SiO_2, 10% B_2O_3, Al_2O_3, Na_2O) is by far the most appropriate

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material for pharmaceuticals. Boric oxide makes it hydrolytically resistant and chemically inert. It has a very low coefficient of expansion and fairly high resistance to thermal shock. Despite its hardness, glass is fragile, which can pose problems in veterinary medicine. Glass is quite heavy compared to other packaging materials (2.5-3.0 kg/dm^3). Glass manufacturing is relatively costly. When glass breaks, it becomes hazardous in two ways: the sharp edges of shards can damage skin, and broken bottles release their contents which can be dangerous for the environment, particularly with compounds like antimicrobial agents or hormones.

Veterinary drugs for livestock are concentrated formulations intended to reduce the volume injected, *e.g.* large 500 ml vials can contain 50g of tulathromycin (100mg/ml) or 100g of oxytetracycline (200mg/ml), while antibiotics can easily pollute both land and water [1, 2]. Studies have demonstrated that both oxytetracycline and macrolides have been detected in chlorine-treated water [3], and the European Commission has added three macrolide drugs to the watch list of water pollutants [4]. Although progress has been made in the chemical strengthening of glass by ion exchange over nearly five decades, further research is needed to develop a fundamental understanding to obtain more resistant glass products [5].

Conversely, plastic for containers is something of a wonder material. It has proven so valuable to humans since the 1950s that the production of plastic and plastic products has grown exponentially. Plastic containers are shock-resistant, lightweight and truly inexpensive to manufacture. They can easily be molded and remolded, are collapsible and have excellent finishing. To some extent, plastic containers are chemically inert and corrosion-resistant. All these characteristics make plastic containers ideal for marketing and storing foodstuffs, including elaborate preparations that require heating and cooling. The materials used in the pharmaceutical industry are polypropylene (PP), polyethylene (PE) and polyethylene terephthalate (PET). Plastics serve extensively to make containers for administration sets, especially disposable ones. Only polypropylene containers can withstand sterilization by autoclaving. Most plastics selectively permit passage of chemical molecules and are permeable to gases. Although most plastic materials used in the medical field have relatively few additives, some may contain substantial amounts of plasticizers, fillers, antistatic agents, antioxidants and other ingredients added for special purposes. Since such ingredients are not usually chemically bound, they may migrate from the plastic into the product. Reactivity due to sorption (absorption and/or adsorption) has been observed most frequently with polyamide polymers (nylon), but additives leached from any of these plastic materials may interact with any drug in the medication. Though relatively sturdy and durable, plastics may break down into micro-plastics that can transport adsorbed pharmaceuticals over considerable distances after discharge [6].

Combining the stability of glass and the resistance to breakage of plastic is something the pharmaceutical industry has often tested. In most cases, primary glass packaging is reinforced by external protection, whose geometric attributes contribute to the absorption of mechanical energy. This principle is similar to that of the cardboard boxes designed for the transportation of eggs, making it possible to ship billions of eggs every day. The development of silicone rubber protection is far rarer. Silicone elastomers are easily molded and can be used to produce devices which adhere to the surface of glass containers by simple friction. This opens the way to developing rubber shock absorbers to protect glass bottles.

The purpose of this study was to compare the resistance to breakage of two types of primary pharmaceutical packaging: multi-layered plastic bottles and silicone elastomer-coated glass vials in different conditions of drop height and angle when a bottle strikes a hard surface.

2 Material and methods

2.1 Selection of the containers

Test batches of 250 or 500 ml containers were prepared for this trial, using two types of vials (figures 1 & 2): 1) 160 glass bottles protected on the shoulder and bottom by a two-part soft shell (SCG) made of a recently developed blue silicone (figure 1) (VIRBAC, Carros, France) and provided by the manufacturer, and 2) 160 layered shatter-resistant bottles (CLAS®, CEVA, Libourne, France; figure 2) purchased from a specialized wholesaler in France (LAS). Both types of vials were filled with the same volume of two different solutions of similar density.

Figure 1 CLAS (Ceva Layered Anti Shatter) vial (CEVA, Libourne, France)

Figure 2 Type-1 glass container protected by a two-piece silicone rubber shell (VIRBAC, Carros, France)

2.2 Number of containers

A preliminary study (not published) with batches of 4 vials revealed that specific experimental conditions (drop height and angle) potentially resulted in greater damage than others. Batch size was increased to a minimum of 10 bottles, with up to 20 for higher-risk situations. Consequently, the required number of vials was calculated as:

$$N = 2_{packaging} \times 2_{volume} \times 2_{height} \times \left[10_{angle\_1} + 20_{angle\_2} + 10_{angle\_3}\right]$$

Three hundred and twenty (320) vials were tested: 80 SCG (250 ml), 80 SCG (500 ml), 80 LAS (250 ml) and 80 LAS (500 ml).

2.2.1 Experimental apparatus

An experimental condition refers to a combination of drop height and drop angle (where the vial strikes the surface). All experimental conditions are summarized in Figure 3. With the exception of negligible forces, the way the bottles fall is governed solely by the Earth's gravity, since they all strike the ground at identical speed (v), proportional only to the drop height according to the formula: $v = \sqrt{2gh}$, where $g = 9.81\ \mathrm{m.s^{-2}}$, h drop height (m). At the instant of impact, however, each bottle must dissipate kinetic energy (E_c) proportional to its mass (m), such that $E_c = \frac{1}{2}mv^2$.

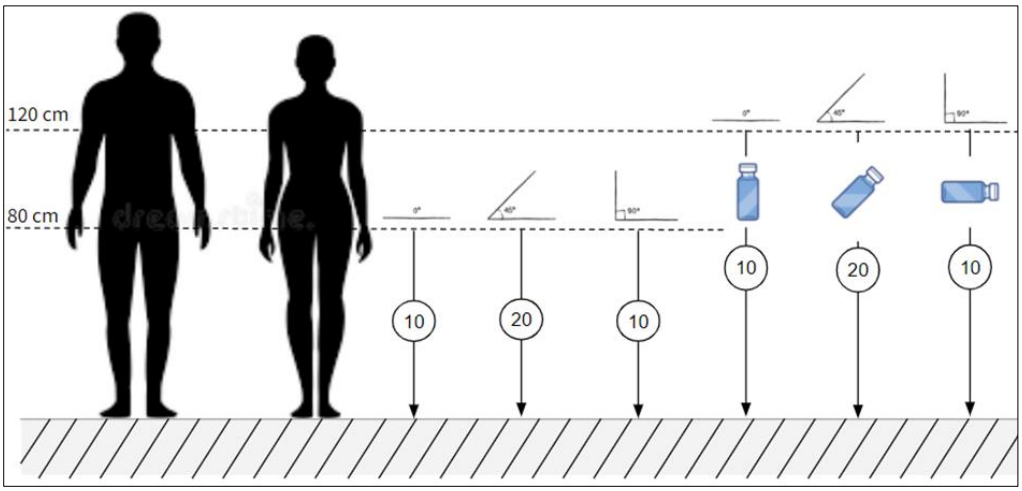

Figure 3 Summary of experimental conditions: circled numbers indicate the number of vials tested for each packaging type (SCG or LAS) and their volume (250 or 500 ml)

Two drop heights were tested (80 cm and 120 cm): 80 cm corresponds to a situation where someone drops a bottle while holding it at hip level and at arm's length, while 120 cm corresponds to someone withdrawing a volume of medication using a syringe while holding the bottle at chest level. Three angles were tested: impact on the bottom of the bottle by dropping it vertically (0°), on the body (90°), and on the heel holding the bottle tilted with its mouth facing upward (45°). The first two angles correspond to extreme situations while, in fact, a falling bottle usually strikes the ground at a random angle, with an expected value of approximately 45° (with the mouth of the bottle facing upward). The same six combined test conditions were repeated for both sizes of SCG and LAS vials.

2.3 Statistical analysis

Statistical analysis of the results was performed with an online calculator (MedCalc Software Ltd., Version 20.115, accessed 30 September 2022), Relative Risk Calculator (https://www.medcalc.org/calc/relative_risk.php). The risk of damaged vials in both branches is compared as the ratio of the probability of breakage in the SCG group with the likelihood of breakage in the LAS group, or Relative Risk (RR). Relative risk, the standard error of the log relative risk ($SE\{\ln(RR)\}$ and 95% confidence interval ($CI_{95\%}$) were calculated according to D. Altman, 1991 [7]. A standard normal deviate (z-value) was calculated as $\ln(RR)\,/SE\{\ln(RR)\}$, with the P-value as the surface area of the normal distribution falling outside $\pm z$. The significance level was set at 0.05.

3 Results

The outcomes of the trial are shown in Table 1 as 'damaged' vs 'intact' vials after the test. 30 vials of all kinds were broken in this study (9.37%, $CI_{95\%}$ [6.18; 12.57]). Drop tests damaged 24 LAS bottles (15.00%). In contrast, only 6 SCG vials did not pass the test (3.75%) (RR=0.250, $CI_{95\%}$ [0.105; 0.595], P=0.002). Finally, the relative risk of breakage of SCG vs LAS is reported in Table 2 for different conditions of drop height, vial format and angle of the vial.

Unfortunately, in comparison with the lesser height (80 cm), a drop from a height of 120 cm is likelier to result in serious damage to the packaging (9 vs 21 breakages out of 160 trials, RR=0.429 [0.203; 0.907], P=0.027], whatever the nature of the packaging, its size or drop angle. Unfortunately, for each type of bottle - SCG or LAS - it was not possible to determine whether drop height had a greater impact on 500 ml bottles than on those containing 250 ml. The small sample size of the experimental groups (10 or 20 vials) compromised this analysis. Nevertheless, the nature of the packaging significantly influenced the survival rate of the vials, regardless of drop height: 80 cm or 120 cm (P=0.041 and P=0.045, respectively).

In the LAS group, the vertical (0°) drop angle had an influence on the risk of breakage. While LAS vials appeared to withstand both bottom (0°) and lateral (90°) drops quite well, 23 of the 24 vials broken during the test had been dropped from a 45° angle. In contrast, SCG vials seem likelier to break when they hit the ground horizontally (90°), while none broke when dropped from a 45° angle.

Table 1 Ratio of damaged over intact vials for 320 vials, per format (250 or 500 ml) and per test conditions: drop height (cm) and drop angle (°)

Format (ml)	**Container type and volume (ml)**							
	Silicone-Coated Glass				**Layered Anti-Shatter**			
	250		**500**		**250**		**500**	
	height (cm)		***height (cm)***		***height (cm)***		***height (cm)***	
Angle	80	120	80	120	80	120	80	120
0°	0/10	0/10	0/10	0/10	0/10	1/9	0/10	0/10
45°	0/20	0/20	0/20	0/20	3/17	5/15	6/14	9/11
90°	0/10	0/10	0/10	6/4	0/10	0/10	0/10	0/10
Total per height	0/40	0/40	0/40	6/34	3/37	6/34	6/34	9/31
Total per format	0/80		6/74		9/71		15/65	
Total per type	6/154				24/136			

Table 2 Relative Risk of damage (*RR*) for different test conditions; 95% Confidence Interval in brackets and *P* value

Condition	**Container type**			
	Silicone-Coated Glass (damaged/intact)	**Layered Anti-Shatter (damaged/intact)**	***RR [CI$_{95\%}$]***	***P***
All vials	6/154	24/136	0.250 [0.105;0.595]	0.002
250 ml vials	0/80	9/71	0.526 [0.003;0.889]	0.041
500 ml vials	6/74	15/65	0.400 [0.166;0.977]	0.045
0° (all vials)	0/40	1/39	0.333 [0.014;7.946]	0.497
45° (all vials)	0/80	23/57	0.021 [0.001;0.344]	0.007
45° (500 ml vials)	0/40	15/25	0.032 [0.002;0.521]	0.016
45° (250 ml vials)	0/40	8/32	0.059 [0.004;0.986]	0.049
90° (all vials)	6/34	0/40	13.000 [0.757;233.337]	0.077
90° (500 ml vials)	6/14	0/20	13.000 [0.781;216.400]	0.074
80 cm (all vials)	0/80	9/71	0.053 [0.003;0.889]	0.041
120 cm (all vials)	6/74	15/65	0.400 [0.164;0.979]	0.045

4 Discussion

This study shows that the breakage of vials of parenteral pharmaceutical specialties remains a challenge even under controlled conditions that are not very severe in comparison with the conditions observed on farms. Assuming that every drop test is a Bernoulli trial with law $B(n,p)$, where n is the number of vials at risk and p the probability of breakage, then it is reasonable to expect that the number of broken vials X falls between two values, k_{inf} and k_{sup}, such that

$$P(\mathrm{X} < k_{\mathrm{inf}}) < {}^{\alpha}/_{2} \quad \text{and} \quad P(\mathrm{X} > k_{\mathrm{sup}}) < {}^{\alpha}/_{2}$$

Where P is the probability of this event and α is the risk level; k_{inf} and k_{sup} are determined with the binomial distribution formula as

$$\sum_{k=0}^{k_{inf}} \binom{n}{k_{inf}} p^{k_{inf}}(1-p)^{n-k_{inf}} < {}^{\alpha}/_{2} \text{ and } 1 - \sum_{k=0}^{k_{sup}} \binom{n}{k_{sup}} p^{k_{sup}}(1-p)^{n-k_{sup}} < {}^{\alpha}/_{2}$$

The CLAS vials (CEVA Layered Anti-Shatter) are multi-layered plastic polymer containers for storing pharmaceuticals [8]. These bottles are not as resistant as they may look. For a batch of 160 bottles (250 and 500 ml), we can expect breakage of between k_{inf} =13 and k_{sup}=36 in at least 99% of cases (α<0.01). In particular, it is quite fragile in a collision involving the heel of the bottle. Although this type of packaging offers good protection compared to unprotected glass, users should remember that it is far from guaranteed. SCG containers, however, seem markedly more resistant to shock. For a batch of 160 vials (two sizes), the expected breakage rate ranges from 1 to 13 (α<0.01). Nonetheless, the bottle's unprotected body remains exposed to direct shock, making this the weak point of the device.

Glass containers first appeared in Antiquity and their pharmaceutical use is attested by Pliny the Elder (AD 23/24-79), who recommended them in particular for storing wild boar urine (*urina apri in vitreo servata*) used for treating ear infections [9]. Later, the glass vial known as the Holy Ampulla (*Sainte Ampoule* in French), which held the oil (chrism) used for anointing French kings from 1131 until 1774, reputedly had a miraculous origin dating back to the baptism of Clovis I, King of the Franks, in AD 508 [10]. Modern-day connoisseurs are capable of tasting and fairly appraising French wine bottled as far back as the end of the 18th century [11]. It is estimated that approximately 98% of parenteral preparations (23 billion) were packaged in glass containers in 2012, most of them made of Type-1 borosilicate glass [12]. Unfortunately, glass is and remains fragile, likely to break at the slightest negligence. This is a major drawback since, not only do glass vials break or shatter, but minor cracks may develop into large penetrative fractures. Although such fissures may escape detection, they are deemed to be critical defects likely to result in potential hazards for patients [13]. Other frequent problems found with glass containers include chipping, abrasion and particle generation due to stress encountered during manufacturing (*e.g.*, filling, crimping and capping), transport or administrative procedures [14]. Ultimately, although breakage is the most spectacular result of an accidental fall, it is not the only one. Other kinds of damage, such as cracking and chipping, were not investigated in this study.

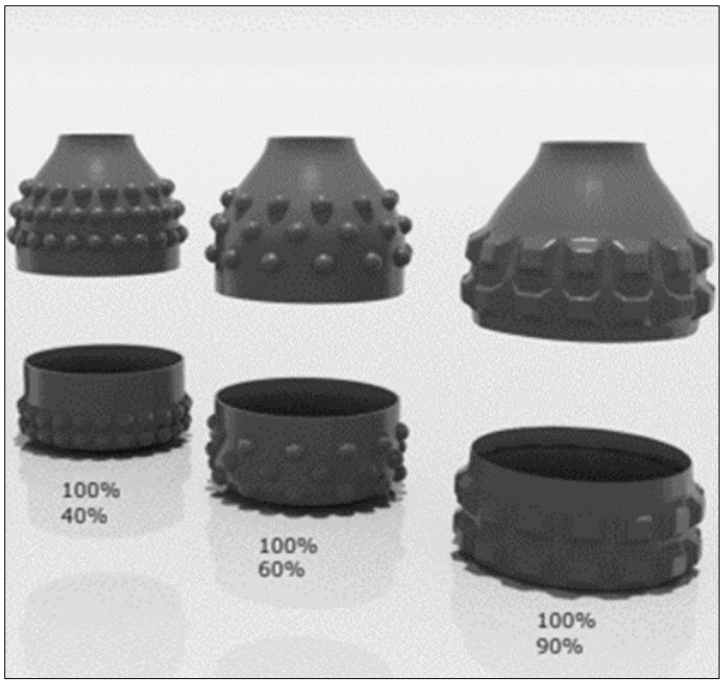

Figure 4 (a: left; b: middle; c: right) Three different shell designs tested prior to the onset of the study, all made of silicone elastomer. The numbers refer to the percentage of vials that remained intact in comparison with the goal (100% survival) for a drop test from a height of 120 cm and impact on the body of the vial (90°)

The notion of protecting glass vials is not new and has already been applied with some degree of success to many materials, including straw, paper, cardboard and expanded polystyrene foam. For pharmaceutical-grade vials, where the risk of breakage is coupled with the risk of contamination of users and environmental pollution, glass bottles must

be protected during transportation and administration, and even beyond, until their destruction. Silicone or poly(organo)siloxane are synthetic polymers with a silicone-oxygen backbone similar to that in silicon dioxide (silica), but with organic groups attached to the silicon atoms by C-Si bonds. Their physical form and uses depend not only on the structure of the polymer, whether it is a short or long-chain molecule, a three-dimensional network or a cross-linked species similar to a silicate, but also on the organic groups attached to the Si-O framework. Thus, it is possible to make silicone elastomers (rubber), whose structure is somewhat similar to natural rubber. They behave like elastomers: amorphous solids, which, as their name implies, are elastic. They have coiled chains which can be stretched out, but spring back to their original shape when the stretching force is released. Protecting glass vials with a two-piece silicone elastomer shell that exactly fits the bottle's shape, at the shoulder and heel, is very effective for preventing glass breakage, as is the geometry of the shell. In a preliminary drop test carried out from a height of 120 cm with bottles held at a 90° angle, the results differed according to the shape and position of the elastomer bumpers. An initial test was carried out with a shell with rows of little bumps close to each other (Figure 4a). The survival rate for this test was 40%. A new geometry, again with bumps relatively far apart (Figure 4b), was tested and provided a 50% improvement in breakage resistance. In order to optimize these results, a new design with a pattern truncated pyramids (Figure 4c) was developed and tested, achieving a further 50% improvement in resistance to breakage compared to the previous one. Consequently, this was the pattern selected.

In addition to the geometry, the material's hardness also has a role in a glass vial's resistance to breakage. Tests were carried out on the shell textured with small truncated pyramids of the same material, but with two different degrees of hardness. On the one hand, shells with so-called "full" truncated pyramids made of soft material, *i.e.,* low on the Shore Hardness Scale and, on the other hand, shells with so-called "hollow" truncated pyramids with slightly harder material (higher on the Shore Hardness Scale). The drop height for this test was 120 cm and the bottle was horizontal. The results show that the use of a shell with "full" pyramids and softer material resulted in higher resistance to breakage (+33%) compared to the other design.

When it comes to recycling pharmaceutical vials, glass offers many advantages. Ideally, glass bottles can be collected, subjected to industrial cleaning, reconditioned and refilled, as has been done in the beverage industry for decades. At the energy cost of melting the glass (1500°C), new bottles can be made from waste material.

Similarly, discarded plastic items can be collected and recycled into new containers. In response to the explosion in consumption of disposable plastic materials during the Covid-19 crisis, recent studies have expounded on the importance and benefits of recycling medical-grade plastic (carbon dioxide or dioxin emissions) [15, 16]. The processability of different products (PE, PP, PET) may vary significantly, however. Several studies have reported that recycled plastic loses some of its mechanical properties compared to virgin plastic: tensile strength, elongation at break and impact strength, in particular. These property changes may result from thermal-mechanical degradation of the polymer during reprocessing, degradation over time, due mainly to photo-oxidation processes and/or contamination of the plastic waste, e.g., in cases with complex product designs involving several immiscible polymers or other materials. Plastic from household waste is a heterogeneous contaminated resource, leading to recycled plastic of lesser quality, limiting the potential for closed-loop recycling [17]. It can be expected that recycling medical plastic will result in a similar situation due to obvious problems in safely sorting or cleaning this material.

Polysiloxanes are remarkably degradable in soils and sediments, especially in the presence of clay-like materials that act as catalysts. It is also possible to synthesize polysiloxanes into environmentally friendly carbon dioxide [18]. Thus, the type-1 glass vial and silicone elastomer combination offers an environmentally sound solution for primary packaging of pharmaceuticals, especially those dedicated to the health of farm animals.

5 Conclusion

In the pharmaceutical industry, glass is often preferred to plastic for the primary packaging industry because of its good safety profile since glass is deemed inert. Moreover, glass is deemed environmentally friendly since it can be endlessly recycled. Yet, since glass is breakable, it must be protected from mechanical shock. An *ad hoc* silicone rubber protective shell offers very high shock absorption properties with an overall eco-friendly approach. This shell does not interfere with the use of the pharmaceutical contents, while preventing breakage and environmental pollution. Since it is made of an inert mono-material and can easily be removed, such shells can be recycled or discarded. Using a silicone elastomer shell to protect glass vials for parenteral injections makes them far more shock-resistant than plastic vials.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

All the authors are employees of VIRBAC Santé Animale (Carros, France) or its affiliates. Virbac produces and markets veterinary drugs under commercial license, including products protected by the device presented in this paper.

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