From the Institute of Pharmacology and Toxicology[1] and the Unit of Physiology and Biophysics, WG Environmental Health[2], Department for Biochemical Sciences, University of Veterinary Medicine Vienna

Thermal drug storage conditions in veterinary vehicles – a one-year field study in Austria

A. HABERLEITNER[1], G. SCHAUBERGER[2], J. HORAK[2] and I. SCHMEROLD[1]*

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Summary

Concerns that storage temperatures of drugs transported in veterinary practice vehicles may deviate from the range recommended in the summary of product characteristics have been raised. This study determined the actual temperatures in veterinary practice vehicles through every season of one year to identify risk factors and to give recommendations to avoid inadequate drug storage. Temperature data loggers were placed at several locations generally used for drug storage in ten practice vehicles operating in central and eastern areas of Austria. The temperatures were recorded for up to twelve months and the data were compared with the recommended drug storage conditions. The temperature was frequently outside the specified ranges of 2 °C–8 °C and 2 °C–25 °C. In the cooling devices of five vehicles, 14.4%–19.8% of all measurements exceeded the 8 °C threshold and maximum and minimum temperatures of 26.2 °C and -12.9 °C were recorded in cooling boxes. In the cooling devices of four of these vehicles, only 51.9% to 68.6% of the measurements fell between 2 °C and 8 °C. Nevertheless, in two of the cooling boxes the temperature remained within the appropriate range over 73.7%

Zusammenfassung

Thermische Bedingungen der Arzneimittellagerung in tierärztlichen Praxisfahrzeugen – eine Feldstudie über ein Jahr in Österreich

Einleitung

Immer wieder werden Befürchtungen darüber geäußert, dass die Lagerungstemperaturen in tierärztlichen Praxisfahrzeugen mitgeführter Arzneimittel von den in den Fachinformationen vorgeschriebenen Temperaturbereichen abweichen könnten. Zwar existieren internationale Leitlinien hinsichtlich „good distribution practices“ für Arzneimittel, doch beziehen sich diese nicht auf tierärztliche Praxisfahrzeuge. In Österreich enthält die Apothekenbetriebsordnung 2005 den allgemein formulierten Passus, dass die vorgesehenen Lagerbedingungen von Arzneimitteln ohne Unterbrechung einzuhalten sind, was den Transport von Arzneimitteln sinnentsprechend einschließt. Das Ziel der vorliegenden Studie war es, die tatsächlichen Lagertemperaturen in tierärztlichen Praxisfahrzeugen zu messen, Risikofaktoren zu identifizieren und Empfehlungen für eine adäquate Arzneimittellagerung in der „tierärztlichen Autoapotheke“ zu formulieren.

Material und Methoden

Temperaturdaten-Logger wurden in zehn, in Mittel- und Ostösterreich operierenden Praxisfahrzeugen an typischen, der Arzneimittellagerung dienenden Stellen platziert, die Temperaturen kontinuierlich bis zu zwölf Monate aufgezeichnet und die Messdaten mit der Außentemperatur und den gemäß Fachinformation vorgeschriebenen Lagerbedingungen verglichen.

Ergebnisse

Die Analysen zeigten häufige Temperaturüber- und -unterschreitungen der überprüften Bereiche 2 °C–8 °C bzw. 2 °C–25 °C. In fünf Fahrzeugen, die mit einer Kühleinrichtung ausgestattet waren, lagen 14,4 %–19,8 % aller gemessenen Temperaturen über der 8 °C-Grenze. Die Maximal- und Minimalwerte dieser Kühleinrichtungen betrugen 26,2 °C und -12,9 °C; in den Kühleinrichtungen von vier dieser Fahrzeuge lagen nur 51,9 % bis 68,6 % der Jahresmesswerte zwischen 2 °C und 8 °C. Einzig in zwei Fahrzeugkühleinrichtungen wurde der korrekte Temperaturbereich mit 73,7 % und 93,9 % des Messzeitraumes aufrecht erhalten. In acht Fahrzeugen schwankten an ungekühlten Lagerungsstellen (z. B. Schubladen, offene Lagerung im Auto) die oberen Temperaturen zwischen 31,8 °C und 44,1 °C.

and 93.9% of the observation period, indicating that it is possible to maintain appropriate temperatures. For the uncooled storage sites in eight vehicles, maximum temperatures of 31.8 °C to 44.1 °C were recorded. Medicines transported in practice vehicles are frequently exposed to temperatures that do not comply with recommended storage conditions. There is an evident need to develop standard operating procedures for drug transportation in veterinary mobile pharmacies.

Schlussfolgerungen

In tierärztlichen Fahrzeugen mitgeführte Medikamente sind Temperaturen ausgesetzt, welche die Qualität und Wirksamkeit von Arzneimitteln beeinträchtigen können. Dies macht die Notwendigkeit deutlich, Leitlinien („Standard Operating Procedures") für den Arzneimitteltransport im Praxisfahrzeug zu formulieren. Als geeignete Maßnahmen für den Arzneimitteltransport stellten sich ein striktes „Rein-Raus-Management" heraus, bei welchem i) mobile Kühlboxen oder passiv gekühlte Isolierboxen während längerer Standzeiten des Fahrzeuges in größere Kühleinrichtungen transferiert werden oder ii) die Dauerlagerung in Fahrzeugen, in welchen kompressorgekühlte Transportbehältnisse ohne (oder mit nur sehr kurzfristiger) Unterbrechung mit Strom versorgt sind.

Introduction

Many veterinary practitioners transport drugs in their cars during their daily work at farms or elsewhere where they look after animals. The drug arsenal normally carried in these vehicles includes all classes of medicines: antibacterial drugs, parasiticides, drugs with hormonal action, anti-inflammatory drugs, analgesics and vaccines. Presumably, most of the products are intended for the treatment of food-producing species.

In practice, medicines have a limited shelf life, are temperature-sensitive and must be stored under specific thermal conditions that are detailed in the ‚Summary of Product Characteristics (SPC)'. Generally, the recommended storage temperatures define the cool (controlled room temperature) and cold storage conditions as the ranges from 2 °C to 25 °C and 2 °C to 8 °C, respectively (SUMMERHAYS, 2000; TAYLOR, 2001). Most vaccines and many liquid products must be prevented from freezing. The thermal storage conditions inside a vehicle may deviate from the recommended storage temperatures stated in the SPC. The quality of the medicines may be negatively affected when they are subjected to improper temperatures; thermal degradation and a loss of clinical efficacy may occur after drugs are exposed to extreme temperatures (JOHANSEN et al., 1993; GRANT et al., 1994; CHURCH et al., 1994; BALLEREAU et al., 1997). KÜPPER et al. (2006) recommended that temperature-sensitive drugs be replaced after experiencing any temperature beyond the limits provided by the manufacturers and that drugs be replaced at least once per year.

International guidelines and other documents regarding good distribution practices for medicinal products do not specifically take the requirements of drug transportation in veterinary practice vehicles (VPVs) into account (WORLD HEALTH ORGANISATION, 2003, 2010). Nevertheless, in Austria (APOTHEKENBETRIEBSORDNUNG, 2005) and other EU member states, such as Germany (TÄHAV, 2009), national legislation requires that the veterinary surgeon continuously maintain the required storage conditions for drugs, including during the storage and transportation of drugs in practice vehicles for visits. Although the transport of drugs is specifically regulated by law in Austria (ARZNEIMITTELBETRIEBSORDNUNG, 2009) the regulation pertains only to firms such as drug producers or distributors of medicinal products and explicitly not to veterinary dispensaries.

A specific ‚quality management system' to reduce the risk of violation of the appropriate drug storage conditions during visits depends solely on the awareness and ‚know-how' of the individual veterinary practitioner.

This one-year study assessed the thermal aspect of drug storage conditions during transport in Austrian VPVs and identified risk factors of improper drug storage. The results form the basis of suggestions for correct drug storage during transport.

Materials and Methods

Practice vehicles

The thermal conditions in ten veterinary vehicles in the Austrian federal states of Niederösterreich and Styria were monitored from November 2007 to December 2008. One vehicle participated in the study until May 2009. No modifications or adjustments to the vehicles were performed; all practitioners participated of their own free will. Data were not recorded for the periods when vehicles were not in use (e.g. holidays), leading to a low percentage of missing data. Table 1 summarizes the main characteristics of the vehicles. All cars are typical practice vehicles without any extra equipment.

The measuring period was shortened for car F because the study had to be terminated ahead of schedule for technical reasons. Car D was temporarily out of service but remained in the study.

Tab. 1: Characteristics of the veterinary practice vehicles

Vehicles	Type	AC	Uncooled storage bin	Cooled storage (el. power)	Parking facility	Period of investigations (month/year)
A	Audi A6 Avant	+	D	-	G	10/07–12/08
B	VW Transporter	-	D	cB (35–70 W)	CP	10/07–11/08
C	Opel Vivaro	+	uB	-	CP	10/07–11/08
D	Citroen Berlingo	-	D	cD (10–35 W)	G	07/08–06/09
E	Citroen Berlingo	-	D	cB (45 W)	G	10/07–11/08
F	VW Transporter	-	D	R (50 W)	O	10/07–03/08
G	VW Transporter	-	D	R (50 W)	G	11/07–1/08
H	Chrysler Voyager	+	D	cB (45 W)	G	11/07–12/08
J	Audi A6 Avant	+	uB	caB	G	11/07–07/09
K	VW Sharan	+	D	cB (48 W)	O	05/08–01/09

AC=air-conditioning; cB=compressor-cooled box; caB=box with cooling accumulators; uB=unconditioned box; CP=carport; D=drawer (unconditioned); cD=conditioned drawer; G=garage; O=outdoor; R=Refrigerator (compressor type) Car D: Equipped with a drug storage system (type AK-5; Indulab AG, Gams, Switzerland) including three actively cooled (compressor type) and two insulated, uncooled drawers.

Two temperature ranges were defined in this study: room temperature (RT) (2 °C ≤ T ≤ 25 °C) and cold (2 °C ≤ T ≤ 8 °C). Unregulated storage sites usually consisted of a wooden drawer system (8/10). Two vehicles were equipped with insulated storage boxes (Styrofoam) (C and J) and two with a refrigerator (compressor type), while one vehicle had a cooled drawer system (‚5-Schub-Kühlapotheke AK-5', compressor type; Indulab AG, 9473 Gams, Switzerland); four vehicles contained actively cooled/heated boxes (thermoelectric type) and one vehicle utilized insulated Styrofoam boxes filled with thermal packs. Two vehicles did not contain any specific equipment for storing drugs (Tab. 1).

Measurement of temperatures

The temperatures were measured with two types of calibrated data loggers (Testo GmbH, Vienna, Austria). The Testo 174 unit had one internal channel to measure the air temperature in direct proximity, while the Testo 175-T2 unit utilized an additional external sensor mounted at the end of an insulated cable. This sensor was affixed in an imitation drug bottle (100 ml) filled with a mixture of water and alcohol to prevent freezing. The 175-T2 loggers could simultaneously determine the temperature both of the air at the storage site and of the aqueous ‚drug bottle's' interior. The measurement range was -30 °C to 70 °C, the accuracy was ±0.5 °C and the resolution was 0.1 °C. The temperature was recorded every 15 min and the data were read from the loggers by a laptop through a USB-interface every three to four weeks. To program the data-loggers and read the data from the firmware, Comfort-Software Basic (Testo 2004 V 3.4.) was used.

Generally, temperature data loggers were placed at three sites where drugs are generally stored: the dashboard or somewhere near the driver (Testo 174), at an unregulated RT storage site (e.g., drawer of the storage system, Testo 175-T2) and in a cooled (2 °C to 8 °C) site, if present (Testo 175-T2). One Testo 174 was placed underneath the car, where the sensor was protected from solar radiation and well ventilated when the car was in motion to estimate the ambient air temperature.

In addition, ambient air temperature data were requested from four meteorological stations operated by the Austrian Weather Service: Wiener Neustadt-Flughafen (47°83'22''N 16°23'14''E), St. Pölten-Landhaus (48°19'97''N 15°63'11''E), Mürzzuschlag (47°60'22''N 15°67'27''E) and Schwechat (48°11'08''N 16°57'08''E). Hourly mean values were used for the analysis.

Whenever drugs were relocated from the car into a refrigerator of the veterinary´s dispensary for temporary storage, the related temperature data loggers remained with the drugs.

Results

The temperature at the selected sites was evaluated against the two ranges defined for this study: cooled (2 °C–8 °C) and uncooled (unconditioned) conditions (RT; 2 °C–25 °C). The lower threshold of both ranges was 2 °C, chosen to assess temperatures close to freezing; this temperature is also the specified lower temperature limit of many veterinary medicinal products. In this paper the focus is directed on critical results with informative value for practitioners.

General meteorological conditions for 2007 and 2008

In Niederösterreich and Styria, the meteorological conditions in 2007 and 2008 included 72 and 66 summer days (maximum >25 °C) and 17 and eleven hot days (maximum >30 °C), as well as 53 days of frost (minimum <0 °C) (meteorological station St. Pölten-Landhaus). During this period, ten VPVs were available for the majority of the investigation. Additional measurements were performed in February and May 2009 using car D.

Influence of the ambient temperature on drug storage sites

The impact of the ambient temperature can be demonstrated by data from vehicle D obtained during February and May 2009. This car was equipped with a commercial, actively cooled drawer system using a compressor-type cooling device (Tab. 1). The temperature profiles of one representative cooled drawer and other unconditioned drug storage sites are displayed in Fig. 1a and 1b. When out of operation, vehicle D was parked in a garage with the cooling device connected to the public power supply.

February

During the chosen week in February, the temperature ranged between -2.2 °C and 9.0 °C. The temperature at the car's dashboard oscillated between 2.9 °C and 24.5 °C based on whether the car was parked or in use with the heating turned on.

The temperature inside the unconditioned drawer ranged between 4.0 °C and 10.2 °C, roughly following the fluctuations of the temperatures inside the car but with some delay and a diminished amplitude. The cooled drawer usually (for 89.6% of the time) maintained temperatures between 4.8 °C and 8.0 °C, with only 10.4% of the measurements transiently (total 17.5 hours) and slightly increased (maximum 8.4 °C) (Fig. 1a).

May

During a single week in May the outdoor ambient temperatures fluctuated between 9.2 °C and 35.5 °C while the temperature near the driver roughly followed the outside temperature; the maximum temperature occurred (35.9 °C) around noon, revealing the effect of the solar radiation on that day (28 May); the minimum temperature (13.4 °C) was reached in the evening of 29 May.

The temperatures in the uncooled drawer oscillated between 17.6 °C and 28.5 °C. Due to the thermal insulation (polystyrene foam insulation covered with plastic plates), the fluctuation pattern was muted and delayed for approximately two hours relative to the ambient temperature. The temperature in the drawers exceeded the upper range of 25 °C on five of the eight days. In the cooled compartment, the temperature usually remained between 2 °C and 8 °C. The temperature of the liquid in the ‚injection bottle' and the surrounding air diverged by up to 1–2 °C due to the slightly different positions of the bottled and air sensors attached to the logger relative to the air flow and to the thermal inertia of the liquid in the bottle (Fig. 1b, enlarged image).

Garage vs. outdoor parking under winter conditions

Six of the ten VPVs were routinely parked outdoors, while two of the remaining four occupied a carport or a garage. Fig. 2a and b display the measured temperatures of two identical vehicles (VW Transporter, white) that belonged to the same practice and were parked either in the open air (vehicle F, Fig. 2a) or in a garage (vehicle G, Fib. 2b) during February 2008.

In both VPVs, the drugs were stored in an unconditioned wooden drawer system. For the vehicle parked outdoors (F), a distinct linear relationship between ambient temperature and temperature in the drawer was found. The ambient temperature had a minimum of -10.6 °C and a maximum of 18.1 °C that were closely followed by the temperature in the drawer.

The temperatures in vehicle G's unconditioned drawer were significantly less related to the ambient temperature (regularly parked in a garage). The meteorological station at St. Pölten-Landhaus recorded ambient temperatures between -10.6 °C and 18.1 °C in February 2008, while the temperature in the drawer oscillated between 6.8 °C and 17.1 °C.

Vehicles B and C were usually parked under a carport and their minimum temperatures were below 0 °C in the uncooled storage sites during December 2007 and January 2008.

Thermal conditions at unconditioned and conditioned sites

Fig. 3 and 4 reveal the cumulative frequency distribution of the recorded temperatures during the entire observation period for unconditioned (Fig. 3) and conditioned (Fig. 4) storage sites in eight VPVs. The deviation from the optimum ranges can be estimated by the intersection of the cumulative frequency line and the threshold lines (2 °C, 8 °C, 25 °C).

Unconditioned sites

Unconditioned sites are sites for storing medicines that do not explicitly need cool storage conditions.

As shown in Fig. 3 and Tab. 2, most of the measured temperatures fell between 2 °C and 25 °C; only in vehicles H, D, C, and B did a small percentage of the measurements fall below the 2 °C threshold. The highest percentage of temperatures above 25 °C was found in vehicle G (19.9%), while the lowest was observed in vehicle J (0.2%). Vehicle J had the best fit for the RT storage conditions, spending 96.1% of the

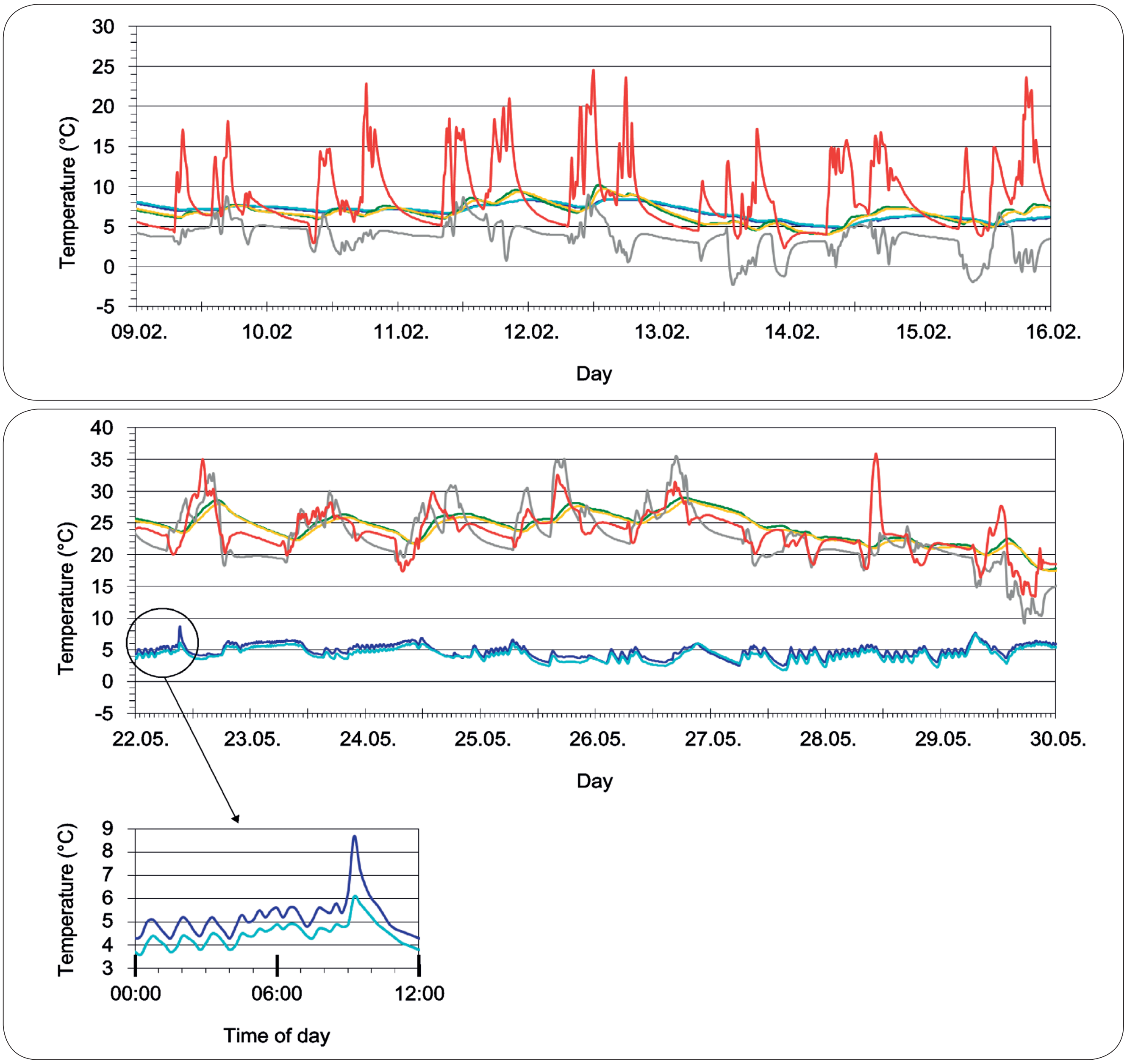

Fig. 1a and 1b: The temperatures over time at different sites for vehicle D equipped with a compressor cooled drawer-system (Indulab AG, Gams, Switzerland) from February 9-15, 2009 (Fig. 1a) and May 22-29, 2009 (Fig. 1b). The magnified extract in Fig. 1b illustrates the temperature differences between the liquid in the bottle and the surrounding air. The regular fluctuations mirror the periodic cooling activity of the compressor. Abscissa: time of day. Dark blue: air-conditioned drawer; green: unregulated drawer; light blue: bottle in the air-conditioned drawer; yellow: bottle in the air-conditioned drawer; red: driver´s cabin; grey: ambient temperature (recorded using a data logger mounted underneath the car).

time between 2 °C and 25 °C and exceeding the upper threshold for only 0.2% of the time. In the unconditioned storage sites, the minimum temperature fell below 0 °C in four of the eight vehicles. In eight VPVs, the maximum temperatures exceeded 25 °C and in seven of the eight unconditioned sites temperatures of over 30 °C were recorded (Tab. 2).

Table 2 summarizes the temperatures measured at the unconditioned sites in eight VPVs over the entire year. The lowest 5th percentiles were found for vehicle B (2.7 °C), which also gave the highest 95th percentiles (28.4 °C). Vehicle J displayed the highest frequency within the optimum range; the lowest frequency was found for vehicle E (72.2%) (Fig. 3).

Cooled sites

Temperatures below the 2 °C threshold occurred in the cooling devices of all cars (Fig. 4), dropping below 0° C in five cars (minimum of -12.9 °C in car H; Tab. 3). The 8° C threshold was exceeded in every car, most frequently in car E (45.0%). In five of the six cooling devices, the temperatures repeatedly exceeded 25 °C (maximum of 26.2 °C in car B).

The cooling device in vehicle J maintained the optimum temperature range (2 °C to 8 °C) for 93.9% of the time while the lowest value was 59.4% in car H (Tab. 3).

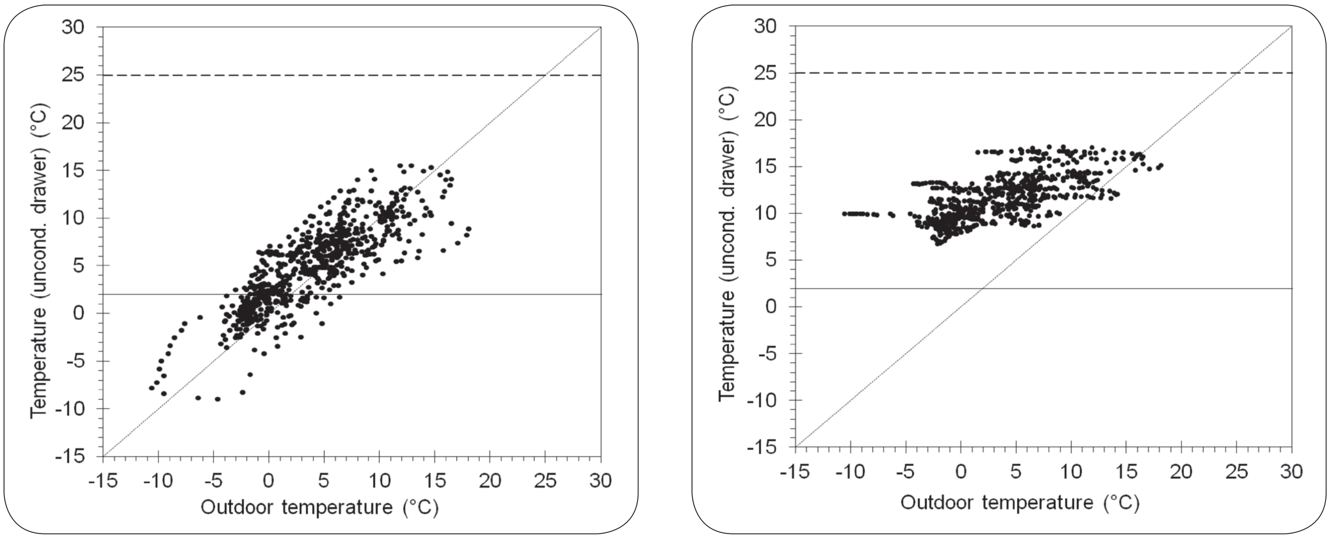

Fig. 2a and 2b: Scatter plot of the ambient temperature (data from the meteorological station at St. Pölten) vs. the temperature in an unregulated drawer in vehicles F and G recorded continuously from February 1-29, 2008. Vehicle F was parked outdoors (Fig. 2a), and vehicle G was kept in a garage (Fig. 2b) during storage. The closer the temperatures are to the line of identity, the stronger the thermal coupling between the indoor and the outdoor thermal situation.

The 5th percentile fell below zero in two of the six cooling devices with the highest frequency of temperatures below 2 °C in car H (24%); the lowest temperature was also found in this car (-12.9 °C). The highest 95th percentile was determined for car E (21.8 °C), in which the 8 °C threshold was exceeded with the highest frequency (54%).

In vehicle J, the drugs were stored solely inside insulated boxes. During off-duty periods, the boxes were transferred from the car into a practice-owned walk-in refrigerator adjusted to 5 °C. This drug storage management led to a 93.9% retention time within the optimal range. Vehicle J exceeded the 8 °C threshold only 2.2% of the time and the frequency of all temperatures measured below the 2 °C threshold was 0.2%.

A more detailed analysis

Vehicle D, equipped with a cooling unit, was chosen for a more detailed analysis of the thermal differences between the unconditioned and cooled storing sites. The unconditioned drawer was only passively protected by the drawer's insulation, revealing a correlation between the inside temperature and the ambient temperature between 8.2 °C and 31.8 °C that was close to the line of identity (Fig. 5a).

In a cooled drawer in the same vehicle, 73.7% of the temperature data fell between 2 °C and 8 °C (Fig. 5b) but significant deviations occurred: in zone α, the measured values mirrored the conditions in the uncooled drawer (closely following the identity line), while zones β and γ were located either below the 2 °C or above the 8 °C threshold line.

Discussion

The study was performed to investigate the thermal conditions that affect veterinary drugs during their transport in VPVs under actual conditions during all seasons of a year. The equipment in the ten vehicles and the management of drug transport remained unchanged during the study; the practitioners were not informed of the data recorded in their cars.

Ambient thermal situation and temperature inside the car

When the radiation balance is dominated by the incoming solar radiation, the temperature inside the car is stable within a range between 20 °C and 35 °C above the outside temperature (ROBERTS and ROBERTS, 1976; KING et al., 1981; SURPURE, 1982; JASCHA and KECK, 1984; GIBBS et al., 1995; GREGORY and CONSTANTINE, 1996; MCLAREN et al., 2005; GRUNDSTEIN et al., 2009), although MARTY et al., (2001) reported a temperature difference of nearly 60 °C. For rough estimation, the authors specified that the inside temperature may reach 30 °C for winter, 60 °C for spring and autumn, and 90 °C for summer conditions due to solar radiation. There are numerous reports of the dynamic temperature behaviour observed after parking a vehicle in the sun (ROBERTS and ROBERTS, 1976; JASCHA and KECK, 1984; GIBBS et al., 1995; GREGORY and CONSTANTINE, 1996; MCLAREN et al., 2005; GRUNDSTEIN et al., 2009). In most cases, a value close to the maximum temperature is reached within 20 min after stopping any ventilation. The most effective method for lowering the interior temperature is to increase ventilation by partly opening the windows (ROBERTS and ROBERTS 1976; KING et al., 1981; SURPURE 1982; JASCHA and KECK 1984). Protecting against incoming solar radiation by covering the window was investigated by JASCHA and KECK (1984) (paper fabrics and tin foil) and by DEVONSHIRE and SAYER (2005) (infrared reflecting foils). JASCHA and

Tab. 2: Descriptive statistics and relative retention times (%) for the uncooled drug storage (2 °C ≤ T ≤ 25 °C) during the entire measuring period of one year

	A	B	C	D	E	G	H	J
Statistics								
Maximum (°C)	44.1	36.4	31.3	31.8	33.0	31.9	31.8	26.7
95th Percentile (°C)	26.5	28.4	26.2	26.4	26.2	28.2	26.8	22.0
5th Percentile (°C)	9.5	2.7	3.7	4.1	6.3	6.8	5.7	7.2
Minimum (°C)	1.7	-3.7	-4.0	-8.2	1.4	2.2	-2.8	5.2
Missing data (%)	1.0	1.4	1.4	4.5	18.6	1.5	2.2	3.6
Relative retention time (%)								
T > 25 °C	10.8	14.7	7.8	10.8	9.1	19.9	10.7	0.2
2 °C ≤ T ≤ 25 °C	88.2	79.9	88	83.6	72.2	78.6	86.3	96.1
T < 2 °C	0.0	3.9	2.7	1.2	0.0	0.0	0.8	0.0

Vehicles F and K are not included due to their downtime.

KECK (1984) found a reduction of up to 11 °C, while DEVONSHIRE and SAYER (2005) found a better thermal comfort score compared to the unprotected windows. In reasonable accordance with these reports, the temperatures measured close to the driver´s seat (e.g. by the instrument panel) in eight of the ten cars without any thermal insulation were above 40 °C. A maximum temperature of 53.8 °C was recorded in car C during a sunny day in August 2008 (ambient temperature 33.1 °C). Vehicle E, which was regularly parked in a garage, gave the best correspondence with the RT range (83.7%). During the winter, the temperatures fell below 0 °C in every vehicle; the lowest value was -11.9 °C measured in vehicle K (data not shown in detail).

Direct exposure to sunlight and storing completely unprotected drugs in VPVs must be strictly avoided. This is the most flawed method for transporting drugs in VPVs.

Garage vs. outdoor parking

It must be noted that only four of the ten VPVs were routinely parked in a garage or under a carport when the vehicles were inoperative. Fig. 2a and 2b illustrate that during winter conditions, when direct sunlight is less likely to increase the temperatures inside the cars, outdoor parking is unsafe because the temperatures fall below freezing (Fig. 2a and 2b). The temperatures in the unconditioned drawer of a car always parked outdoors paralleled the ambient air temperatures, falling below 0 °C with the ambient air. Because the regression line for the temperatures in the unconditioned drawers linearly follows the ambient temperature (in the absence of direct sunlight) when the outside temperatures exceed 25 °C or fall below the freezing point, the storage temperatures do not conform to the range recommended for most medicines.

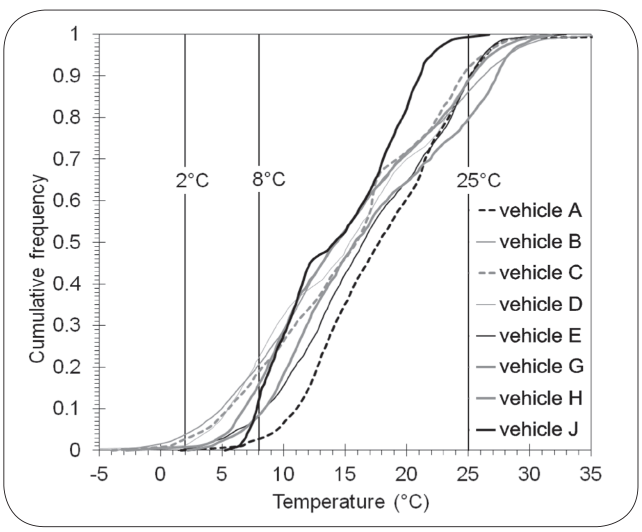

Fig. 3: Cumulative frequency of the temperatures at uncooled storage sites for eight vehicles, analysed continuously from November 2007 to December 2008.
Styrofoam boxes: C, J; drawers: A, B, D, E, F, D, H. For the details ofvehicles A-J, refer to Tab. 1. Vehicles F and K are not included due to their downtime.

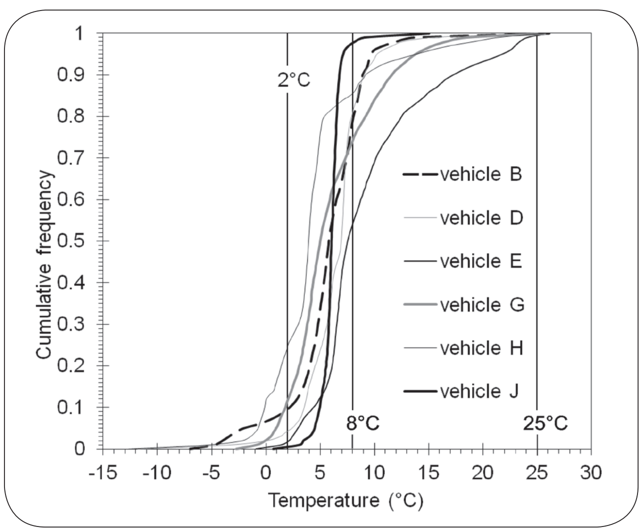

Fig. 4: Cumulative frequency of the temperatures inside the cooled storage sites for six vehicles, analysed continuously over twelve months. For the details regarding vehicles A-G, refer to Tab. 1. Vehicles F and K are not included due to their shortened measuring periods, while vehicles A and C were missing their cooling equipment.

Tab. 3: Descriptive statistics and relative retention times (%) for the cold drug storage (2° C ≤ T ≤ 8° C) during the entire measuring period of one year

	A	B	C	D	E	G	H	J
Statistics	-							
Maximum (°C)	-	26.2	-	25.1	25.9	25.7	26.0	15.1
95th Percentile (°C)	-	9.8	-	26.4	26.2	28.2	26.8	22.0
5th Percentile (°C)	-	-2.4	-	2.4	3.0	1.0	-0.7	4.5
Minimum (°C)	-	-7.0	-	-11.8	-0.9	-2.7	-12.9	0.7
Missing data (%)	-	1.4	-	4.4	1.3	1.5	2.2	3.6
Relative retention time (%)								
T > 8° C	-	19.8	-	17.8	45	25.5	14.4	2.2
2° C ≤ T ≤ 8° C	-	68.6	-	73.7	51.9	61.5	59.4	93.9
T < 2° C	-	10.2	-	4.1	1.8	11.5	24.0	0.2

-, no cooling device; vehicles F and K are not included due to their downtime.

Freezing is deleterious to the quality of drugs that must be stored at temperatures above 2 °C, such as many injectable formulations and vaccines. Using a cool box or a refrigerator is not sufficient protection because these devices prevent excessively high temperatures but not freezing. The lowest temperatures measured in an unconditioned drawer in car G while it was regularly parked in a garage was 6.8 °C, similar to the conditions inside the garage. However, the temperature reached 17.1 °C (maximum) during normal visits when the car was moved. Well functioning cooling devices remain indispensable under winter conditions to limit temperature increases above 8 °C but they do not prevent storage temperatures below 0 °C (Fig. 2a and Fig. 2b). Parking in a garage during the winter (while avoiding direct sunlight throughout the year) will significantly lower the probability of violating the 2 °C and 25 °C thresholds defined for many medicinal products. In contrast to garages, carports protect against direct sunlight but not against temperatures below freezing.

The reduced fluctuations of the temperatures inside drawers are due to thermal insulation by the construction material. The liquid-filled bottles exhibited an approximately three hour delay in adjusting to ambient temperatures before matching the conditions of the car's interior due to the thermal inertia of the contents (Fig. 1b).

Thermal conditions at unconditioned and conditioned storage sites

Fig. 3 and 4 provide an overview of the thermal conditions in the unconditioned and conditioned sites over the course of the year. At the unconditioned sites frequently used for storing drugs at RT, significant violations of the threshold limits at both 2 °C and 25 °C occurred. The highest temperatures (up to 44.1 °C) were recorded in the VPV G, which also had 5% of all

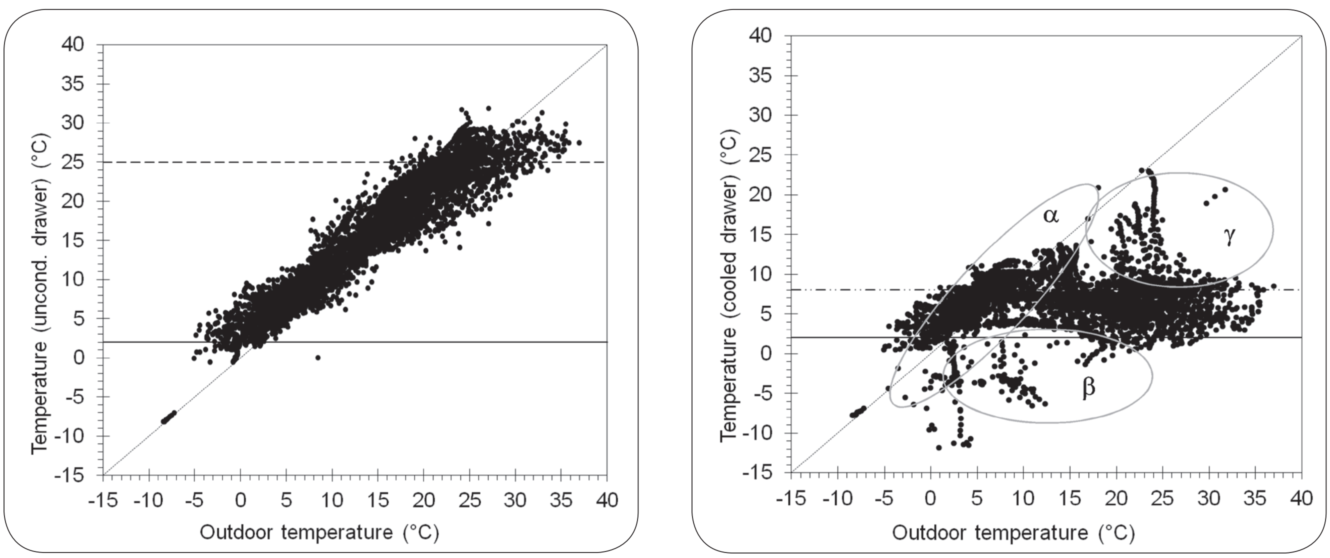

Fig. 5a and 5b: Scatter plot of the ambient temperature vs. the temperatures in an uncooled drawer (5a) and a cooled drawer (5b) continuously recorded in vehicle D from July 01, 2008 until May 31, 2009. The ambient temperatures were recorded by data loggers affixed to the bottom of the vehicles.

measured temperatures above 28.4 °C. In this vehicle, 19.9% of all measured values exceeded 25 °C. Although 72.2%–96.1% of the temperatures measured in all vehicles lay within the RT range, any thermosensitive medicinal product requiring storage between 2 °C and 25 °C would have been temporarily exposed to potentially detrimental conditions.

It can be argued that under practical conditions drugs are inevitably exposed to incorrect temperatures during the time between their delivery to the veterinary dispensary and their transport to a farm. Currently, however, practitioners have no information on tolerable deviations from the recommended storage temperatures given in the SPC that are not harmful.

Maximum temperatures between 15.1 °C and 26.2 °C were recorded in cooling devices and the lowest temperatures oscillated between 0.7 °C and -12.9 °C. Car E, which most frequently violated the cool storage conditions (Tab. 3), was equipped with an old cooling device that was not routinely connected to the public power supply during prolonged periods of parking (e.g. overnight).

For an example of the temperature data loggers' usefulness, the temperature profiles in an unconditioned and a conditioned drug storage drawer were evaluated in more detail in vehicle D, which was regularly parked in a garage. As depicted in Fig. 5a, the temperature in the unconditioned drawer roughly followed the outside temperature, measured by the data logger under the car, and oscillated between -8.2 °C and 31.8 °C over the course of the year. The temperature pattern in the conditioned drawer was quite different, although most of the measurements (73.7%) fell within the 2 °C to 8 °C limits, indicating that the cooling device had sufficient capacity to function appropriately in ambient temperatures above 35 °C. However, there are zones of deviant temperature. Zone α mirrors the identity line and the pattern of temperature in the drawer may reveal periods of inactivity of the cooling system with violation of the 8 °C threshold. Area β had several periods of below 0 °C despite concurrently moderate ambient temperatures (4.1 °C), indicating a possible malfunction in the cooling device or an incorrectly set thermostat. Zone γ also indicates a temporarily incorrect thermostat adjustment, prolonged opening of the drawer or filling of the drawers with warm items; these actions exceeded the device's capacity.

The lowest temperature (-12.9 °C) in car H's cooling box was measured when the outside temperature was 9.5 °C (March 2008). This may have been caused by an incorrect temperature setting; the cooling box was capable of providing a deep freeze.

Continuous monitoring of a cooling device's performance is essential. The use of data loggers allows direct monitoring of the actual temperature and continuous temperature recording for a subsequent computer-assisted evaluation of the thermal profile. In this study, the techniques proved very dependable. The thermal conditions must be constantly monitored to control and document correct storage conditions.

National legislation explicitly requires veterinary surgeons to maintain the correct storage conditions of drugs continuously. Nevertheless, the thermal conditions to which drugs are exposed in VPVs do not have to be documented. Drug storage in veterinary dispensaries is routinely controlled by the authorities (APOTHEKENBETRIEBSORDNUNG, 2005; TÄHAV 2009) but the storage temperatures in VPVs are often uncertain. Consequently, the frequency at which medicines of diminished quality are administered to animals is not known.

Detailed thermal stability data for veterinary medicinal products are usually not available and the SPC describes only the shelf life and storage conditions. Medicines, including vaccines, stored and transported aboard VPVs are exposed to temperatures that must be assumed to exert deleterious effects on quality, safety and clinical efficacy. The decline in drug quality increases with the storage time as well as with the number, duration and magnitude of temperature deviations from the recommended range. It is possible to transport medicines correctly, even those that must be kept refrigerated. An approach identified in this study included the following: i) the maintenance of either a strict in-out-system while the drugs are transported, using electric cooling boxes with a sufficient capacity or Styrofoam boxes containing thermal packs, and storage overnight in a practice-owned refrigerator (vehicle J) or ii) the permanent storage of drugs aboard the car in drawers or containers that are permanently cooled with a compressor-type device (vehicle D). According to this study, compressor-cooled boxes or drawer devices are best able to maintain temperatures between 2 °C and 8 °C in conventional types of VPVs.

The following deficiencies were among those observed in drug transportation: using damaged Styrofoam boxes with insufficient insulation properties; using thermal packs with an inadequate capacity; storing drugs in the wrong temperature compartment; power failures; incorrect operation and negligent monitoring of the cooling devices; and VPV parking without protection from the sun coupled with an unawareness of the temperature inside the vehicle.

The findings reveal the need for a transparent quality management system/standard operating procedure for appropriate (temperature-controlled) drug storage and transportation in mobile veterinary dispensaries. Each vehicle has individual properties; as a first step to reduce the risk of damaging thermolabile drugs, veterinary surgeons (if they do not already practise such a management system) are advised to monitor the thermal drug storage conditions inside their own vehicles continuously and to obtain practical experience.

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References

BALLEREAU, F., PRAZUCK, T., SCHRIVE, I., LAFLEURIEL, M.T., ROZEC, D., FISCH, A., LAFAIX, C. (1997): Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina FASO. Am J Trop Med Hyg **57**, 31–36.

CHURCH, W.H., HU, S.S., HENRY, A.J. (1994): Thermal degradation of injectable epinephrine. Am J Emerg Med **12**, 306–309.

DEVONSHIRE, J.M., SAYER, J.R. (2005): Radiant heat and thermal comfort in vehicles. Human Factors **47**, 827–839.

GIBBS, L.I., LAWRENCE, D.W., KOHN, M.A. (1995): Heat exposure in an enclosed automobile. J La State Med Soc **147**, 545–546.

GRANT, T.A., CARROLL, R.G., CHURCH, W.H., HENRY, A., PRASAD, N., ABDEL-RAHMAN, A.A., ALLISON JR, E.J. (1994): Environmental temperature variations cause degradations in epinephrine concentration and biological activity. Am J Emerg Med **12**, 319–322.

GREGORY, N.G., CONSTANTINE, E. (1996): Hyperthermia in dogs left in cars. Vet Rec **139**, 349–350.

GRUNDSTEIN, A., MEENTEMEYER, V., DOWD, J. (2009): Maximum vehicle cabin temperatures under different meteorological conditions. Int J Biometeorol **53**, 255–261.

JASCHA, I., KECK, G. (1984): Klima im Personenkraftwagen – ein Beitrag zum Tierschutz. Wien Tierärztl Monat **71**, 227–237.

JOHANSEN, R.B., SCHAFER, N.C., BROWN, P.I. (1993): Effect of extreme temperatures on drugs for prehospital ACLS. Am J Emerg Med **11**, 450–452.

KING, K., NEGUS, K., VANCE, J.C. (1981): Heat stress in motor vehicles: A problem in infancy. Pediatrics **68**, 579–582.

KÜPPER, T.E.A.H., SCHRAUT, B., RIEKE, B., HEMMERLING, A.V., SCHÖFFL, V., STEFFGEN, J. (2006): Drugs and drug administration in extreme environments. J Travel Med **13**, 35–47.

MARTY, W., SIGRIST, T., WYLER, D. (2001): Temperature variations in automobiles in various weather conditions: An experimental contribution to the determination of time of death. Am J Forensic Med Pathol **22**, 215–219.

MCLAREN, C., NULL, J., QUINN, J. (2005): Heat stress from enclosed vehicles: Moderate ambient temperatures cause significant temperature rise in enclosed vehicles. Pediatrics **116**, e109–e112.

ROBERTS, K.B., ROBERTS, E.C. (1976): The automobile and heat stress. Pediatrics **58**, 101–104.

SUMMERHAYS, G.E.S. (2000): Monitoring of temperature in cars with regard to the pharmaceutical precautions of medicine storage. Equine Vet Educ **12**, 307–311.

SURPURE, J.S. (1982): Heat-related illness and the automobile. Ann Emerg Med **11**, 63–265.

TAYLOR, J. (2001): Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products. The P J **267**, 128–131.

WORLD HEALTH ORGANISATION (2003): Guide to good storage practices for pharmaceuticals. In WHO Technical Report Series, No. 908, Annex 9. World Health Organisation.

WORLD HEALTH ORGANISATION (2010): WHO good distribution practices for pharmaceutical products. Annex 5. In WHO Technical Report Series, No. 957.

Legal Regulations

EU Commission Guideline (1994) Guidelines on Good Distribution Practice on Medicinal Products for Human Use (94/C 63/03). http://ec.europa.eu/health/files/eudralex/vol-4/gdpguidelines1.pdf (accessed 24.02.2014)

Verordnung der Bundesministerin für Gesundheit und Frauen über den Betrieb von Apotheken und ärztlichen und tierärztlichen Hausapotheken (Apothekenbetriebsordnung 2005). BGBl. II Nr. 65, 08.03.2005, as last amended by BGBl. II Nr. 83. 14.04.2014.

Verordnung des Bundesministers für Gesundheit, Familie und Jugend betreffend Betriebe, die Arzneimittel oder Wirkstoffe herstellen, kontrollieren oder in Verkehr bringen und über die Vermittlung von Arzneimitteln (Arzneimittelbetriebsordnung, 2009 – AMBO 2009). BGBl. II Nr. 324, S. 1, 17.09.2008; as last amended by BGBl. II Nr. 179, 24.06.2013.

Verordnung über tierärztliche Hausapotheken (TÄHAV) in der Fassung der Bekanntmachung vom 8. Juli 2009, BGBl. I Nr. 39 S. 1760.

***Corresponding author's address:**
Ivo Schmerold,
University of Veterinary Medicine Vienna,
Veterinärplatz 1, 1210 Vienna, Austria
e-mail: ivo.schmerold@vetmeduni.ac.at