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QUALITY OF VETERINARY MEDICINAL PRODUCTS IN CIRCULATION IN CAMERON AND SENEGAL

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Quality of veterinary medicinal products in circulation in Cameron and Senegal

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Summary

Two surveys were conducted in Cameroon and Senegal to contribute to the study on the quality of veterinary medicinal products (one survey in Cameroon in 2006 and the other in Senegal in 2007). The surveys covered trypanocides, endectocides, anthelminthics and antibiotics in circulation in the two countries.

Samples were purchased in the regions of Dakar, Kaolack and Thiès in Senegal (48 samples) and in all 10 provinces of Cameroon (55 samples). They were bought on both the legal and illegal markets.

The samples were analysed using the methods of inspection, control of galenic preparations and high-performance liquid chromatography (HPLC) in the Laboratory for the Control of Veterinary Medicinal Products in Sub-Saharan Africa, the OIE reference laboratory in Dakar.

The results revealed that 69% of veterinary medicinal products failed to comply with requirements in Cameroon and 67% in Senegal.

In Cameroon, the diminazene- and isometamidium-based group of trypanocides tops the non-conformity list, with 100% of the class failing to comply with requirements. In Senegal, however, the oxytetracycline-based group of antibiotics has the highest level of non-conformity (93% of the class).

Non-conformities were found in both the official sector and the unofficial market.

This points to an urgent need to establish a regulatory and legislative framework for the control of veterinary medicinal products in Sub-Saharan Africa and to endow it with the required resources for its effective application.

I. Introduction

The development of livestock production in sub-Saharan Africa is dependent on controlling the different animal diseases by means of a good animal health policy, based in part on the use of quality veterinary medicinal products. Regrettably, the data available on the quality of veterinary medicinal products consumed in the livestock sector is none too precise [1]. In Cameroon, the livestock sector accounts for around 165 billion CFA francs of gross domestic product (GDP), generating income for almost 30% of the rural population [2]. In Senegal, the livestock sector is a key part of the economy, promoting exports, creating jobs and satisfying the nutritional requirements of rural and urban populations [3]. The huge potential of these countries is being stymied by animal health constraints and one of the major inputs is veterinary medicinal products [4]. In Senegal, the turnover of the veterinary drug market is more than one billion CFA francs [5], a sum equivalent to 1.5 million euros, and in Cameroon the market is approaching 20 billion CFA francs (equivalent to 31 million euros), with a flourishing black market run primarily by non-professionals [6]. Although counterfeit and sub-standard human medicinal products have been reported in West and Central Africa [7] where there is a direct impact on human health, veterinary medicinal products have not been afforded the same attention, even though the scale of the problem is just as great, if not greater.

This paper reports on a pilot study conducted in Cameroon in 2006 and in Senegal in 2007 on the quality of veterinary medicinal products in circulation in these two countries.

II. Objectives of the study

The general objective of this study is to help to improve the quality of veterinary medicinal products sold in Cameroon and Senegal. More specifically, the study aims to:

- Analyse the quality of veterinary medicinal products (trypanocides, endectocides, anthelminthics and antibiotics) in circulation in Cameroon and Senegal.
- Study the proportion of non-conforming products in the various sales circuits and among the different classes of veterinary medicinal products.
- Inform the competent authorities and livestock-sector stakeholders about the non-conformity of veterinary medicinal products in Cameroon and Senegal so that corrective measures can be taken.

III. Equipment and methods

1. Sites and sampling period

In Cameroon the samples were taken between 2 August and 17 September 2005 in the 10 provinces making up the country, and in Senegal they were taken between 5 February and 30 April 2007 in the Dakar, Thies and Kaolack regions. The sampling points correspond to the different strata of the distribution network for veterinary medicinal products (the regulated market and the parallel market).

In Cameroon, samples were taken at six (6) sites on the official circuit and five (5) sites on the parallel market, whilst in Senegal, eight (8) sites were sampled for the official circuit and seven (7) for the parallel market.

2. Veterinary medicinal products

The study analysed 103 samples of veterinary medicinal products, including 48 in Cameroon and 55 in Senegal.

The veterinary medicinal products sampled were based on albendazole, levamisole, ivermectin, diminazene, isometamidium and oxytetracycline. A breakdown of samples taken by product group and by sales sector is found in tables 1 and 2.

3. Sampling protocol

The majority of the medicinal products were bought from vendors in cash. Each sample contains at least 20 therapeutic units for solid forms (powders, granules, boluses, pills) and five flasks for liquid forms. The samples taken were each sealed in a plastic pack, then labelled (sample number) by batch with the site and sampling date. They were identified on a form drawn up for this purpose, and then sent together to the veterinary medicinal product control laboratory (LACOMEV). They were stored in the sample bank at the laboratory before being analysed prior to the expiration date for samples with packaging. They were analysed from February to December 2006 for Cameroon and from May to June 2007 for Senegal.

4. Laboratory analysis

The analyses were carried out at LACOMEV in Dakar, a reference laboratory of the World Organisation for Animal Health (OIE).

Physical and chemical analysis equipment

The glassware used was the same as that used in quality control laboratories and the apparatus was that of a well-equipped analytical laboratory.

Pharmaceutical quality control of samples

The control consisted of galenic tests, organoleptic tests and high performance liquid chromatography (HPLC).

Galenic and organoleptic tests

The sample packaging and presentation were inspected, comparing them with an original supplied and certified as conforming by the manufacturing laboratories; these samples are available at LACOMEV.

In the case of solid forms (pills, boluses and granules), the uniformity of the mass was studied according to the European Pharmacopeia method [**8**].

The pills or boluses were subjected to a disintegration test according to the European Pharmacopeia method [**8**]. They were considered to conform when the disintegration time was less than or equal to 30 minutes.

The limpidity of ready-to-use injectable solutions was studied with the bare eye. Injectable solutions conform if they are free from particles under suitable conditions of visibility [**9**].

HPLC test

The HPLC analysis methods used were based on the manufacturer's dossiers and the Moroccan national laboratory for the control of veterinary medicinal products (LCNMV). These methods were transferred, validated and subjected to quality assurance procedures under LACOMEV conditions.

HPLC identification was used to compare the retention time of the active ingredient in the finished product with that of the reference substance.

HPLC dosage: for each molecule, the extraction solvents and chromatographic conditions are described in ***table 3.***

The content of the active ingredient was calculated on the basis of the sample peak surface areas at a known dilution factor, compared with that of the reference substance in a solution with a known concentration.

Two tests were performed on each sample. The result was accepted only where the difference in content between the two tests was $\leq$ 3%. Products were labelled as non-conforming when the average content of the active ingredient for the two tests differed by 10% (more or less) from the nominal content.

Data processing

The analysis results and the date from the sample records were processed using EXCEL spreadsheet and ACCESS database software. The analysis results are expressed as a percentage of the size of the samples analysed.

IV. Results

In Cameroon, galenic tests identified 19 non-conforming samples and the analytical test identified 22. The total number of non-conforming samples from galenic and/or HPLC testing was 33 out of 48 analysed, representing 69% pharmaceutical non-conformity.

In Senegal, 24 samples failed to conform in galenic tests and the analytical tests revealed 29; the total number of non-conforming samples in galenic and/or HPLC testing was 37 out of 55 analysed, representing 67% pharmaceutical non-conformity.

The non-conformities included faulty packaging, limpidity defects (Figure 1) and disintegration defects (Figure 2). HPLC identification and dosage revealed products with no active ingredient (Figures 3 and 4), under-dosed products and over-dosed products.

The levels of non-conformity by country are shown in table 4.

The non-conformities were noted for all therapeutic classes studied and are found in the different distribution sectors (tables 5 and 6).

V. Discussion

1. Scope of the study

This study covers the quality of veterinary medicinal products in Senegal, more specifically in the regions of Dakar, Kaolack and Thies, and in the 10 provinces making up Cameroon. The samples were purchased on both legal and illegal markets. They were bought discreetly in order to avoid attracting the attention of nearby people, which might have resulted in the buyers being denied access to the veterinary medicinal products. This situation did not make it easy to set up a truly random sampling plan for these investigations.

As it is rare to find a street vendor selling the required quantities of veterinary medicinal products for testing, the batch numbers often vary. The real-life situation therefore forced us to adapt the laboratory test methods.

Analytical tests were performed to check the identity and dosage of the active ingredient(s), which enabled us to judge the minimum characteristics required for the efficacy and safety of the products. The excipients, deterioration products and substitution products were not included in this study.

Despite the methodological weaknesses of this study, it nevertheless gives an indication of the pharmaceutical quality of the veterinary medicinal products in circulation in the study areas over a given period.

2. Non-conformities in both types of market

The non-conforming veterinary medicinal products identified by this study were found in both the official and parallel markets.

In Cameroon, 18 samples of veterinary medicinal products out of the 28 that we took from the official market (64%) did not conform, whilst 15 out of 20 (75%) in the parallel market did not conform. In Senegal, out of 29 veterinary medicinal products sampled in the official market, 20 did not conform (69%), compared with 17 out of 26 (65%) in the parallel market.

According to these results, in Cameroon there are more poor-quality veterinary medicinal products in the parallel market than in the official circuit. These findings corroborate those for Benin, Togo, Mali,

Mauritania and Chad [**10, 11, 12, 13**] where there are proportionally more non-conformities in the parallel market.

The relatively high incidence of non-conformities in the parallel or illegal market is due partly to poor storage conditions for veterinary medicinal products, which tend to be generally exposed to high temperatures and to the sun (***Figure 5***) and partly to the dubious sources of supply in this market.

The opposite was observed in Senegal where more non-conformities were found in the official circuit.

In Senegal we find this situation unacceptable for a so-called legal sector in a country where there is a marketing authorisation (MA) procedure subject to quality control. This is proof of the pressing need to introduce systematic controls on the supply, distribution and sales circuits for veterinary medicinal products in Cameroon, Senegal and other sub-Saharan African countries, backed by a team of specially trained inspectors.

In these distribution circuits for veterinary medicinal products, the full range of anomalies was found to varying degrees in all the therapeutic classes inspected.

3. Least-conforming therapeutic classes

In Cameroon, trypanocides (diminazene and isometamidium) are the leading source of non-conformity with a rate of 100% for the samples in this class, followed by antibiotics (oxytetracycline) and anthelminthics, with 71% and 52% non-conformity in their class respectively. This order gives a true reflection of the situation in the veterinary drug market in Cameroon. Similar findings were made for Benin-Togo, Mali, Mauritania and Chad.

However, in Senegal, oxytetracycline is the class with the highest level of non-conformity (93%), followed by diminazene (70%) and antiparasitic agents, anthelminthics and endectocides (53%). This order more or less matches the breakdown of Senegal's veterinary drug market by therapeutic class.

It is the responsibility of the African countries concerned to arm themselves with the regulatory and technical means to ensure that these products are properly managed, especially trypanocides.

4. Types of non-conformity and their impact

The non-conforming veterinary medicinal products identified in these studies display galenic defects (especially disintegration and limpidity). Some products are under-dosed and some are over-dosed, whilst others fail to contain the stated ingredient.

The impact of such quality defects in veterinary medicinal products can be very serious: lack of efficacy and more damaging residues for consumers [**14**].

This study found cases of boluses that failed to disintegrate. Even if the drug contains the correct active ingredient, its efficacy can be dangerously reduced (modification of bio-availability) if it does not dissolve as it should [**15**].

The risk of pathogens developing resistance to the medicinal molecules described is usually the result of under-dosage [**16, 17**]

The administration of over-dosed products can result in the unsuspected accumulation in the animal organism of an excess of the active ingredient, resulting in longer waiting periods for these products.

Products that fail to contain the active ingredient stated on the label may contain substances that are not recommended or are toxic for the animal concerned. Similar cases have been observed in human drugs in Nigeria where hundreds of children died after consuming paracetamol syrup containing the antifreeze diethylene-glycol, instead of the pharmaceutical excipient propylene-glycol.

Some specialists [**18**] quite rightly believe that the circulation of counterfeit drugs in most sub-Saharan African countries inevitably leads to the persistence of animal diseases.

VI. Conclusion

The results obtained by these studies have no national statistical value; they highlight the existence of non-conforming veterinary medicinal products and relatively high levels of non-conformity, in a small geographical area over a limited period. They nevertheless show that all veterinary drug distribution sectors contain non-conforming products. This study's finding of rates of 67% and 69% non-conforming medicinal products, albeit from a relatively small sample, point to a dysfunction that needs to be urgently addressed. The quality problem with veterinary medicinal products in sub-Saharan Africa is of concern to all stakeholders in the sector, in that veterinary medicinal products should no longer be assessed from the 'patient' standpoint, but from that of the consumer. In other words they must be assessed in terms of public health.

Corrective measures must therefore be taken in the interests of consumer protection, continued animal welfare and the promotion of livestock production in sub-Saharan Africa. We believe that control mechanisms need to be reinforced at all levels and that illegal markets must be controlled, with adequate political support region-wide, following the example of the West African Economic and Monetary Union (WAEMU).

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Appendices

Table 1: Breakdown of samples by veterinary medicinal product group and by sales sector in Cameroon

Distribution circuit	Anthelminthics and endectocides	Trypanocides	Antibiotics	Total
Official circuit	13	07	08	28
Parallel circuit	10	04	06	20
Total	23	11	14	48

Table 2: Breakdown of samples by veterinary medicinal product group and by sales sector in Senegal

Distribution circuit	Anthelminthics and endectocides	Trypanocides	Antibiotics	Total
Official circuit	16	05	08	29
Parallel circuit	14	05	07	26
Total	30	10	15	55

Table 3: HPLC test procedures

Active ingredients	**Mobile Phase**	**Extraction solvents**	**Characteristics of the column**	**UV detection level**
Oxytetracycline	Mobile phase: solution A and acetonitrile (ACN) (90/10 V/V). Solution A: pH 3.3, dimethylformamide (DMF) (90/10 V/V). Preparation of solution pH 3.3: EDTA Sodium salt:……0.168 g Potassium nitrate:…….5.055 g Citric acid: ……3.132 g Sodium citrate:……..1.4 g Dissolve it in 1000 ml ultra pure water (UPW)	pH 3.3 and dimethylforma-mide (DMF)	C18, kromasil 5µm, 4.6 x 150 mm	360 nm
Albendazole	Mobile phase: buffer solution pH 5 and acetonitrile (50/50 V/V) buffer pH5: Weigh 6.8 g of sodium acetate and place it in 1000 ml UPW. Adjust with glacial acetic acid.	Dimethylforma-mide (DMF)	C18, kromasil 5µm, 4.6 x 150 mm	290 nm
Levamisole	Mobile phase: acetonitrile and buffer solution pH 8 (42/58 V/V) Buffer solution pH 8: Weigh 5g of ammonium carbonate and place it in 1000 ml UPW.	Acetonitrile (ACN)	C18, kromasil 5µm, 4.6 x 150 mm	220 nm
Ivermectine	Methanol, acetonitrile and UPW (37,8/57,2/50 V/V/V)	Methanol	C18, kromasil 5µm, 4.6 x 150 mm	254 nm
Diminazene diaceturate and antipyrine	Peak B5 and methanol (66/34 V/V).	UPW	C18, kromasil 5µm, 4.6 x 150 mm	230 nm
Isometamidium	Mobile phase: phosphate buffer pH 2.5, acetonitrile (77/23 V/V) Phosphate buffer pH 2.5: Weigh 2.7 g of potassium dihydrogenophosphate (KH2PO4). Dissolve in 1000 ml in a graduated flask. Adjust the pH using orthophosphoric acid.	Acetonitrile and ultra pure water (30/70 V/V)	C8, kromasil 5µm, 4.6 x 250 mm	220 nm

Figure 1:

Comparison between diminazene and isometamidium-based injectable preparations subjected to the limpidity test

Figure 1a:

Diminazene-based injectable preparations (poor limpidity on the left with residue present, and limpid solutions on the right)

Figure1b:

Isometamidium-based injectable preparations (poor limpidity on the left with residue present, and limpid solutions on the right)

Figure 2: Albendazole-based boluses after 30 minutes of the disintegration test

Figure 3:

Chromatographs comparing standard samples of diminazene and antipyrine with a sample purported to contain the same active ingredients

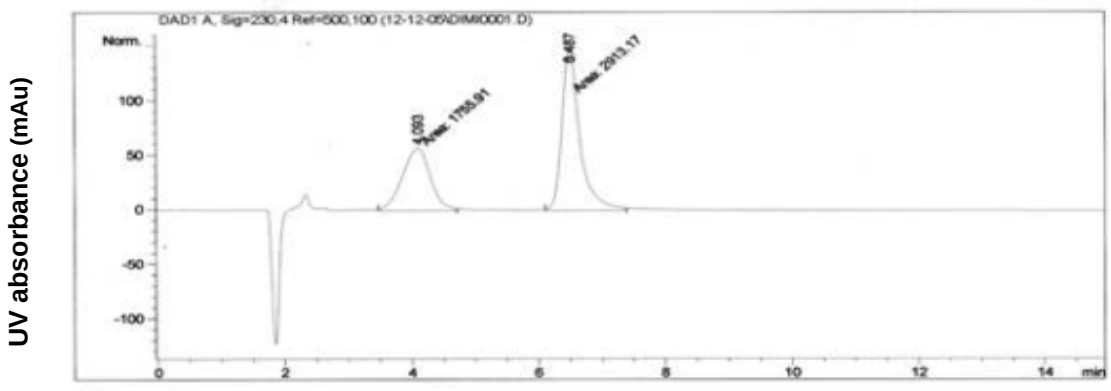

Figure 3 a: Chromatograph of diminazene and antipyrine standard samples

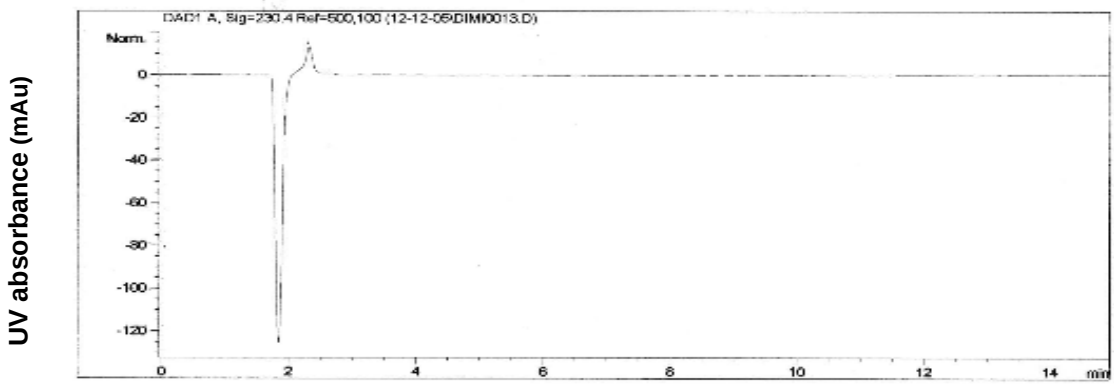

Figure 3b: Chromatograph of a sample purported to contain diminazene and antipyrine

Figure 4:

Chromatographs comparing standard samples of oxytetracycline
with a sample purported to contain the same active ingredient

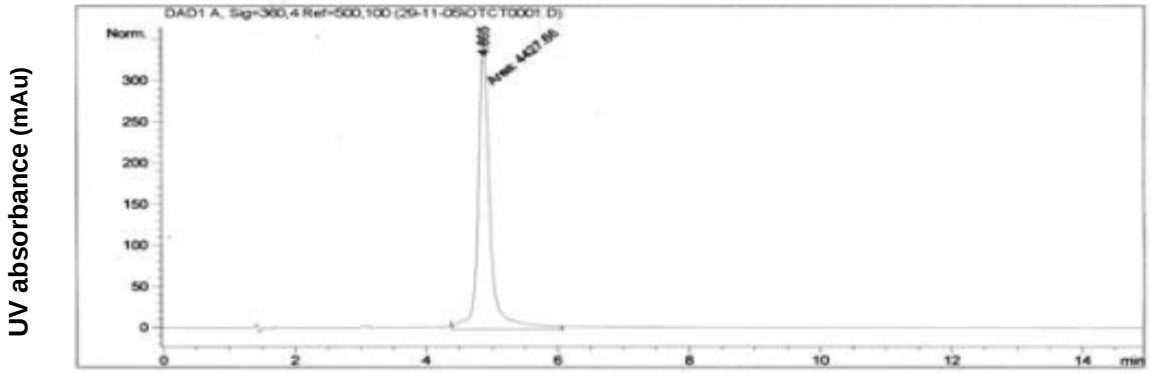

Figure 4 a: Chromatograph of an oxytetracycline standard sample

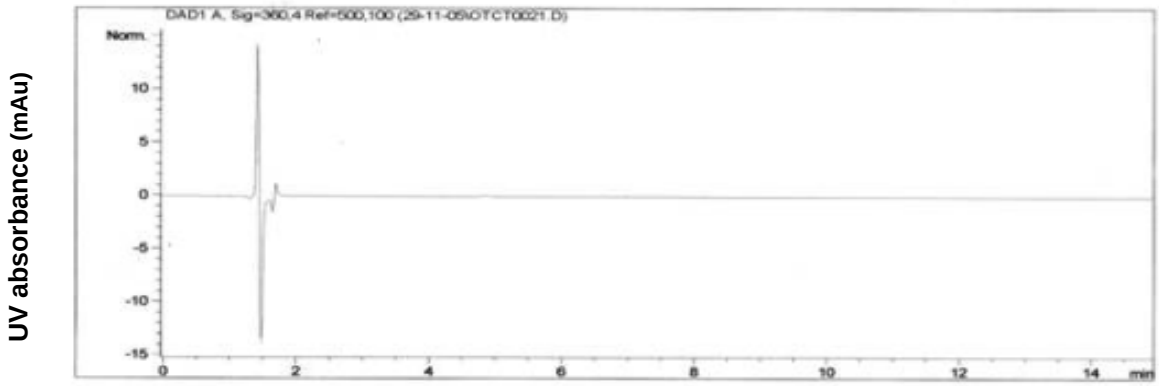

Figure 4b: Chromatograph of a sample purported to contain oxytetracycline

Table 4: Level of non-conformity by country studied

Country	Galenic test	HPLC test			Pharmaceutical non-conformity (galenic test and/or HPLC test)
	Packaging, disintegration and limpidity defects	Absence of active ingredient	Over-dosage	Under-dosage	
Cameroon	40% (19/48)	4% (2/48)	4% (2/48)	42% (20/48)	69% (33/48)
Senegal	43% (19/55)	2% (1/55)	33% (18/55)	20% (11/55)	67% (37/55)

Table 5: Proportion of non-conformities by distribution circuit in Cameroon

Distribution circuit	Anthelminthics and endectocides		Trypanocides		Antibiotics	
Formal circuit	13	6/13 (46%)	7	7/7 (100%)	8	6/8 (75%)
Illegal circuit	10	6/10 (60%)	4	4/4 (100%)	6	4/6 (67%)

Table 6: Proportion of non-conformities by distribution circuit in Senegal

Distribution circuit	Anthelminthics and endectocides		Trypanocides		Antibiotics	
Formal circuit	16	9/16 (56%)	5	3/5 (60%)	8	8/8 (100%)
Illegal circuit	14	7/14 (50%)	5	4/5 (80%)	7	6/7 (86%)

Figure 5:
Veterinary medicinal products displayed on the ground by a vendor at Touba-Toul market (Department of Thies, Senegal)