Abstract
The potency and purity of compounded preparations of ketoprofen, amikacin, and boldenone were highly variable compared with Food and Drug Administration (FDA)-approved preparations of these drugs. These differences in concentration and purity could have important consequences for the efficacy and safety of the drug.

1. Introduction
Veterinarians must, on occasion and by necessity, use products that are compounded to meet a specific medical need. However, the American Veterinary Medical Association (AVMA) guidelines for pharmaceutical compounding state that compounded products “may be used only when a need has been established and Food and Drug Administration (FDA)-approved products are not available or clinically effective” [1]. Although FDA-approved products are extensively tested for efficacy, quality, purity, strength, bioavailability, and stability, the testing that compounded formulations are subjected to is extremely variable. Studies investigating the differences between FDA-approved formulations and compounded preparations of drugs for horses have been limited. Recently, a study comparing the bioavailability and efficacy of an FDA-approved omeprazole paste and a compounded omeprazole suspension found that the paste was more bioavailable than the suspension and significantly more effective in promoting healing of gastric ulcers [2]. While the omeprazole study tested the bioequivalence of the different omeprazole preparations, the present study investigates the pharmaceutical equivalence. If drug products contain the same active ingredients and are identical in concentration, dosage form, purity, and route of administration, they are considered pharmaceutically equivalent [2]. Thus, the purpose of this study was to investigate the potency and purity of compounded preparations of ketoprofen, amikacin, and boldenone and to compare the pharmaceutical equivalence of the compounded preparations with FDA-approved drug preparations for these three drugs.

2. Materials and Methods

Boldenone and Ketoprofen Sampling Procedure for Purity and Potency
All products had implied starting concentrations of 100 mg/ml for ketoprofen and 50 mg/ml for boldenone, with one exception for boldenone (25 mg/ml). Using a 50-µl Hamilton gas-tight syringe, 50 µl of each preparation was transferred to a 50-ml, class A volumetric flask. A small amount of methanol was then added, and each sample was vortexed vigorously. The solutions were increased to their final volume of 50 ml with methanol and transferred to pre-labeled amber vials. The process was repeated for a duplicate sampling of each preparation. The duplicate aliquots of each preparation were analyzed using high-pressure liquid chromatography (HPLC) with ultraviolet (UV) detection through an Agilent 1100 Binary LC with photodiode array detector.

Amikacin Sampling Procedure for Purity and Potency
All products had theoretical starting concentrations of 250 mg/ml for amikacin, with one exception of 50 mg/ml. Using a 50-µl Hamilton gas-tight syringe, 50 µl of each preparation was transferred to a 50-ml, class A volumetric flask. A small amount of water was then added, and each sample was vortexed vigorously. The solutions were increased to their final volume of 50 ml with water and transferred to pre-labeled amber vials. The process was repeated for a duplicate sampling of each preparation. The duplicate aliquots of each preparation were analyzed using HPLC with mass spectrometry (MS) detection.
through a Agilent 1100 Binary LC with Thermo Finnigan TSQ Quantum detector.

Microbiology
Boldenone was tested for sterility by streaking 0.1 ml of each product on trypticase soy agar (TSA) and blood agar plates. The TSA plates were incubated at 30ºC and the blood agar at 37ºC. All plates were evaluated for signs of growth after 1 and 2 days of incubation.

3. Results
Ketoprofen
The two FDA-approved preparations of ketoprofen varied less than 5% from the expected concentration of 100 mg/ml, and less than 0.1% of the preparation was comprised of impurities (Table 1). Although most of the compounded drugs were within 10% of the expected concentration of 100 mg/ml (95.1 - 107.4 mg/ml), one compounded drug was approximately one-half the expected strength, with a concentration of 50.4 mg/ml (Fig. 1). Total percent impurities was less than 2% for all the compounded drugs (0.02 - 0.58%).

All ketoprofen products were prepared in 10% alcohol solution; therefore, none were evaluated for bacterial contamination.

Table 1. Concentration and Purity of Preparations of Ketoprofen, Amikacin, and Boldenone

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Ketoprofen (100 mg/ml)</th>
<th>Amikacin (250 mg/ml)</th>
<th>Boldenone (50 mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration (mg/ml)</td>
<td>Total impurities</td>
<td>Concentration (mg/ml)</td>
</tr>
<tr>
<td>Fort Dodge 1</td>
<td>103.6</td>
<td>0.04</td>
<td>48.7*</td>
</tr>
<tr>
<td>Fort Dodge 2</td>
<td>103.3</td>
<td>0.09</td>
<td>270.9</td>
</tr>
<tr>
<td>Compounder A</td>
<td>105.2</td>
<td>0.04</td>
<td>164.7</td>
</tr>
<tr>
<td>Compounder B</td>
<td>105.3</td>
<td>0.09</td>
<td>146.4</td>
</tr>
<tr>
<td>Compounder C</td>
<td>50.4</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Compounder D</td>
<td>100.3</td>
<td>0.09</td>
<td>-</td>
</tr>
<tr>
<td>Compounder E</td>
<td>100.7</td>
<td>0.07</td>
<td>165.9</td>
</tr>
<tr>
<td>Compounder F</td>
<td>95.1</td>
<td>0.12</td>
<td>180.9</td>
</tr>
<tr>
<td>Compounder G</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Compounder H</td>
<td>-</td>
<td>-</td>
<td>190.8</td>
</tr>
<tr>
<td>Compounder I</td>
<td>107.4</td>
<td>0.21</td>
<td>-</td>
</tr>
<tr>
<td>Compounder J</td>
<td>100.5</td>
<td>0.58</td>
<td>-</td>
</tr>
<tr>
<td>Compounder K</td>
<td>-</td>
<td>-</td>
<td>281.4</td>
</tr>
<tr>
<td>Compounder L</td>
<td>98.6</td>
<td>0.10</td>
<td>351.0</td>
</tr>
<tr>
<td>Compounder M</td>
<td>101.6</td>
<td>0.07</td>
<td>-</td>
</tr>
</tbody>
</table>

* Expected concentration is 50 mg/ml.  § Expected concentration is 25 mg/ml.
Amikacin

The two FDA-approved preparations of amikacin varied less than 10% from the expected concentration of 50 and 250 mg/ml, and less than 0.5% of the preparations were comprised of impurities (Table 1). In contrast, compounded amikacin concentrations were widely variable (146.4 - 351.0 mg/ml), and none of the compounded drugs were within 10% of the expected concentration of 250 mg/ml as expressed on the label (Fig. 2). Most of the compounded preparations had much less drug, between 59% and 76% of the stated concentration, whereas two compounded preparations had much more drug than was expected at 112% and 140% of the stated concentration. All compounded drugs had a higher percentage of total impurities than the FDA-approved preparations (0.60 - 1.71%); two compounded drugs were above 1%, but none exceeded 2% total impurities.

No amikacin products were evaluated for bacterial contaminants.

Figure 2. Comparison of concentration in FDA-approved product and compounded preparations of amikacin. - To view this image in full size go to the IVIS website at www.ivis.org . -

Boldenone

The FDA-approved preparation of boldenone and two of the compounded preparations were within 10% of the expected concentration of 50 mg/ml (Table 1). A compounded preparation at a concentration of 25 mg/ml was also within 10% of the expected concentration. Although two compounded drugs were outside of the 10% expected concentration range, both were within 15%. The FDA-approved boldenone preparation had the lowest percent of total impurities, and all but one of the compounded drugs were less than 1% (Fig. 3). However, one compounded boldenone had nearly 2% of the preparation comprised of a single impurity, and the total percentage of impurities of approximately 5%.

None of the boldenone products developed any bacterial growth, indicating that all were free from bacterial contamination.

Figure 3. Comparison of percent total impurities in FDA-approved product and compounded preparations of boldenone. - To view this image in full size go to the IVIS website at www.ivis.org . -

Comparison of Compounded and FDA-Approved Preparations

The mean and SD of the percent expected concentration for the FDA-approved products tested (n = 5) was 102.8 ± 4.0%. The percent expected concentration for the compounded preparations (n = 22) was much more variable, with a mean and SD of 92.5 ± 20.5%. The FDA-approved products had a mean and SD for percent total impurities of 0.17 ± 0.18%. The compounded preparations were more variable with percent total impurities of 0.66 ± 1.01%.

4. Discussion

This study tested the potency and purity of compounded preparations of ketoprofen, amikacin, and boldenone and found them to be much more variable than FDA-approved preparations of these three drugs. The U.S. Pharmacopeia (USP) states that the total percentage of impurities should not exceed 2%, and no single impurity should exceed 0.1% [3]. The FDA states that the concentration of drug should not vary more than 10% from the expected concentration [4]. Several of the compounded products far exceed these guidelines, indicating that pharmaceutical equivalence between FDA-approved products and compounded preparations for ketoprofen, amikacin, and boldenone does not exist.

Although this study does not test bioequivalence, deviation from expected concentration and high levels of impurities could have significant consequences on the efficacy and safety of the drug once administered. For example, one compounded ketoprofen preparation had approximately one-half the expected concentration. Thus, a veterinary practitioner administering what he/she thought was a high dose of ketoprofen of 3.3 mg/kg would actually be outside of the dosage range for ketoprofen (2.2 - 3.3 mg/kg) at 1.65 mg/kg [5]. At a dose outside of the therapeutic range, the anti-inflammatory and analgesic effects of ketoprofen may be decreased, or the duration of the effects may be shortened. Similar efficacy issues may exist with compounded preparations of amikacin that are approximately 50 - 75% of the expected concentration, because the antibacterial activity of amikacin could be decreased or the duration of activity could be shortened with administration of these preparations. In contrast, compounded amikacin preparations that are approximately 150% of the expected concentration could result in nephrotoxicity, especially in neonates and geriatric horses already at a greater risk [5]. For compounded amikacin, the potential exists for severe toxicity; this necessitates amikacin measurement in plasma or serum, followed by appropriate dosage adjustments, if required.
Compounded preparations of boldenone with high levels of impurities also have toxicity potential. One veterinarian noted that horses receiving compounded preparations of boldenone developed allergic reactions at the injection site [a]. While the reason for these reactions is unclear and the reactions were controlled with other medication, the reactions may have been avoided if impurities were eliminated from compounded preparations.

It is inconceivable to think that there will ever be FDA-approved drugs labeled for every therapeutic need. Therefore, pharmaceutical compounding of veterinary products will remain an integral tool for equine practitioners. The present study determined many of the compounded preparations fumigating, boldenone, and ketoprofen were not pharmaceutically equivalent to FDA-approved preparations of these drugs. The wide variability in purity and potency found in the compounded preparations of ketoprofen, amikacin, and boldenone could significantly affect the efficacy and toxicity of these products. To insure effective therapeutics, veterinarians should be vigilant and thorough when selecting a compounder. Compounded medications should be prepared in a state-licensed facility, with strict quality control measures, by an experienced pharmacist who adheres to USP guidelines for good compounding practices.

However, whenever possible, FDA-approved products are preferable because manufacturers of approved drugs have to use Good Manufacturing Practices (GMPs). These products deliver the drug exactly as the label specifies with excellent quality to perform optimally.

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Footnote

References


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