The value of single-dose extended therapy with EXCEDE® Sterile Suspension

Timothy Baker, BS; Gloria Basse, MBA; David Galligan, VMD, MBA; Christopher Hollenbeak, PhD; Michael Layfield, BS; Roger Saltman, DVM, MBA; Sonja Sorensen, MPH

Key Points

• Compliance in U.S. dairies is one of the least considered aspects of successful antibiotic therapy.
• The impact and cost of non-compliance encompasses management, economic, and animal health factors.
• Economic modeling now enables analysis of the financial impact of antibiotic treatment compliance.
• Proven effectiveness for bovine respiratory disease (BRD) organisms shows a single dose of EXCEDE® (ceftiofur crystalline free acid) Sterile Suspension provides extended therapy in cattle, now available for lactating dairy cattle.
• EXCEDE administered as a single treatment according to label instructions requires no milk discard.

Introduction

In well-controlled clinical trials, ideal (100%) compliance with antibiotic regimens is inherent in clinical study protocols. In daily practice, however, compliance is often overlooked as being an essential aspect of successful antibiotic therapy. Strong and consistent evidence links treatment failure with non-compliance in human medicine, but few studies of compliance exist in the veterinary literature. The impact of non-compliance includes treatment failure, suboptimal therapy, additional expense, and increased risk of side effects. Economic modeling now allows dairy producers to analyze the costs and benefits of improved compliance.

What is Compliance?

The simplest definition of compliance is administering medication as directed — the prescribed dose at the prescribed time(s) for the prescribed duration. Full compliance encompasses numerous factors related to the patient, the product, and the person administering treatment. For example, compliance in dairies includes keeping accurate records and observing milk discard and pre-slaughter withdrawals as well as administering drugs correctly. Numerous other management, economic, and animal health factors also influence compliance in dairy operations.
Mapping the flow of treatment events and their consequences (Figure 1) serves as the foundation for assessing the economic impact of antibiotic treatment. The cost of antibiotic therapy is driven by the cost of initial treatment, subsequent therapy, and losses due to treatment failure, such as mortality or culling, discarded milk, decreased milk production, weight loss, and impaired reproductive health. In the flow of treatment events, the consequences of poor compliance include decreased symptom resolution and increased downstream costs. While full compliance increases the probability of complete symptom resolution, it also increases initial drug costs. Economic modeling offers producers the opportunity to determine if this increase is offset by the cost and consequences of non-compliance (lack of symptom resolution).

**Figure 1. Treatment Events and Their Consequences**

**Flow of Treatment Events**

1. Start antibiotic treatment
2. Complete with treatment
   - With full compliance
   - With partial compliance
   - With non-compliance
3. Symptom resolved
4. Partially resolved
5. Do not return
6. Culling or death

**Consequences**

A more comprehensive approach for comparing the relative costs of these different treatment strategies utilizes the Compliance Model. As indicated in Table 1, this model includes assumptions about Maximum Symptom Resolution if treatments are given according to label ("full compliance") or if labels are not followed ("non-compliance") in dosage or duration of treatment.

Table 1. Key Variables for Economic Modeling

<table>
<thead>
<tr>
<th>Simple Treatment Comparison Model (Additional Variables)</th>
<th>Compliance Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Number of cattle in herd and infection rate</td>
<td>• Symptom resolution rates (&quot;Cure rates&quot;)</td>
</tr>
<tr>
<td>• Average weight, dosage and length of treatment</td>
<td>• Number of days of treatment typically completed</td>
</tr>
<tr>
<td>• Acquisition cost of medication</td>
<td>• Lost milk production</td>
</tr>
<tr>
<td>• Timeliness to administer medication, and administrator hourly wages</td>
<td>• Culling and death rates, retreatment rate</td>
</tr>
<tr>
<td>• Length of milk discard, average daily production, price of milk</td>
<td>• Replacement cost, salvage value, cost per day open</td>
</tr>
</tbody>
</table>

In human medicine, improved compliance has been associated with decreased costs. Shorter therapy regimens, convenient administration, and lack of side effects. These factors might also be expected to improve compliance in veterinary medicine. Assuring full compliance aligns with judicious use principles for antimicrobial therapy, and could help avoid suboptimal responses, as well as the time and expense of treating recurrent infections.

**Quantifying the Value of Compliance**

Two economic models, developed by scientists at United BioSource Corp. and the University of Pennsylvania, and available from Pfizer, now enable financial analysis of increased compliance with antibiotic therapy. Economic modeling facilitates analyses of complex interactions based on selected variables and their associated costs. Developed from the perspective of a dairy producer, the new models analyze the year-long financial impact of treatment for BRD by comparing NANCELL (ceftiofur sodium) Sterile Powder, EXCEDE® RTU (ceftiofur hydrochloride) Sterile Suspension, Polyflex® (ampicillin trihydrate for injectable suspension, veterinary), Liquamycin® LA 200® (oxytetracycline), or penicillin G procaine regimens for lactating cows. The computerized spreadsheet allows users to customize the major variables affecting compliance. The year-long perspective captures one milk-production cycle.

The Simple Treatment Comparison Model considers the cost of labeled drug use, assuming equal efficacy and perfect compliance for all of the drugs. The Compliance Model estimates the economic impact of partial/non-compliance with labeled antibiotic treatment. Key variables for the two models are listed in Table 1.

The Simple Treatment Comparison Model is straightforward, comparing different economic outcomes from different treatment regimens. The time necessary to identify and restrain a cow for treatment, give the injection, and record the treatment is included in this comparison. A default value of 5.63 minutes to give an injection is included in this model.1 This example assumes a 500 cow herd of 1,350 lbs avg body weight animals with a 5% infection rate over a milking cycle. Other assumptions include: 1. Herd average of 80 lbs of milk/cow/day 2. Labor cost of $10/hr. 3. 30% of these infected animals require a veterinarian visit that costs $75 per visit 4. Label milk discarded times (when used according to the label).

Using this Simple Treatment Comparison Model, a single-dose regimen of EXCEDE can be compared to the use of penicillin G procaine or EXCEDE® RTU at appropriate (based on label) dosage and duration of treatment (Table 2).

The magnitude of these relative costs are graphically compared in Figure 2. A more comprehensive approach for comparing the relative costs of these different treatment strategies utilizes the Compliance Model. As indicated in Table 1, this model includes assumptions about Maximum Symptom Resolution if treatments are given according to label ("full compliance") or if labels are not followed ("non-compliance") in dosage or duration of treatment.

Table 2. Simple Treatment Comparison Model (25 Treated Cows)

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>EXCEDE®</th>
<th>Penicillin G Procaine®</th>
<th>EXCEDE® RTU®</th>
<th>Extra Cost of Penicillin G Procaine Compared to EXCEDE</th>
<th>Extra Cost of EXCEDE® RTU Compared to EXCEDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administration</td>
<td>$23</td>
<td>$37</td>
<td>$37</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Veterinary services</td>
<td>$563</td>
<td>$563</td>
<td>$563</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$1,330</td>
<td>$2,182</td>
<td>$1,476</td>
<td>$852</td>
<td>$146</td>
</tr>
</tbody>
</table>

* Costs rounded to nearest whole dollar. 1 Assumes 1 dose, 1.5 ml/100 lbs, zero milk discard.
2 Assumes 3 daily doses, dose estimated from common farm practice, 72 hr milk discard.
3 Assumes 3 daily doses, 1.5 ml/100 lbs, zero milk discard.

Table 3. Compliance Model (25 Treated Cows)

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<thead>
<tr>
<th>Cost Component</th>
<th>EXCEDE®</th>
<th>Penicillin G Procaine®</th>
<th>EXCEDE® RTU®</th>
<th>Extra Cost of Penicillin G Procaine Compared to EXCEDE</th>
<th>Extra Cost of EXCEDE® RTU Compared to EXCEDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial drug administration</td>
<td>$744</td>
<td>$109</td>
<td>$844</td>
<td>$-635</td>
<td>$99</td>
</tr>
<tr>
<td>Initial drug administration</td>
<td>$23</td>
<td>$70</td>
<td>$70</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Milk discarded</td>
<td>$0</td>
<td>$1,440</td>
<td>$0</td>
<td>$1,440</td>
<td>$0</td>
</tr>
<tr>
<td>Veterinary services</td>
<td>$563</td>
<td>$563</td>
<td>$563</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$3,279</td>
<td>$4,073</td>
<td>$3,417</td>
<td>$795</td>
<td>$137</td>
</tr>
</tbody>
</table>

* Costs rounded to nearest whole dollar. 1 Assumes 1 dose, 1.5 ml/100 lbs, zero milk discard.
2 Assumes 3 daily doses, dose estimated from common farm practice, 72 hr milk discard.
3 Assumes 3 daily doses, 1.5 ml/100 lbs, zero milk discard.
This analysis shows that the expected total costs were: EXCEDE = $3,279 ($131/cow), penicillin G procaine = $4,073 ($163/cow), and EXCENEL RTU = $3,417 ($137/cow). Initial drug acquisition and administration and milk discard (no milk discard) comprise about 23 to 27% of the total costs while costs due to retreatment, milk production loss from cows not curering, decreased reproductive success, and dead and culled animals that occur when Symptom Resolution Rates (“Cure rates”) decrease. If penicillin G procaine or EXCENEL RTU are administered for 2 days rather than the recommended full 3-day course of treatment, symptom resolution rates drop from 85% to 63% (Adjusted Resolution Rates). Although drug acquisition and administration and first treatment milk discard costs decrease, the extra costs of retreatment and treatment failures can be significant. In this example, compared to the “full compliance” course of treatment, non-compliant treatment (2 days of treatment versus 3 days of treatment for the daily dose therapies) created total costs of $7,486 for penicillin G procaine and $6,490 for EXCENEL RTU (Table 4). Even more important economically, comparing these non-compliance treatments with the “full compliance” course of treatment achieved with a single dose of EXCEDE, the use of EXCEDE decreases the cost of treatment by $4,206 compared to penicillin G procaine and $3,210 compared to EXCENEL RTU.

Quantifying the Cost of Non-compliance
The cost of non-compliance is the extra cost in retreatment (with concurrent administration and milk discard costs), increase in milk production loss from cows not curering, decreased reproductive success, and dead and culled animals that occur when Symptom Resolution Rates (“Cure rates”) decrease. If penicillin G procaine or EXCENEL RTU are administered for 2 days rather than the recommended full 3-day course of treatment, symptom resolution rates drop from 85% to 63% (Adjusted Resolution Rates). Although drug acquisition and administration and first treatment milk discard costs decrease, the extra costs of retreatment and treatment failures can be significant. In this example, compared to the “full compliance” course of treatment, non-compliant treatment (2 days of treatment versus 3 days of treatment for the daily dose therapies) created total costs of $7,486 for penicillin G procaine and $6,490 for EXCENEL RTU (Table 4). Even more important economically, comparing these non-compliance treatments with the “full compliance” course of treatment achieved with a single dose of EXCEDE, the use of EXCEDE decreases the cost of treatment by $4,206 compared to penicillin G procaine and $3,210 compared to EXCENEL RTU.

Conclusions
Proven effectiveness for BRD organisms shows a single dose of EXCEDE provides extended therapy in lactating dairy cattle with no milk discard. Dairy producers can now estimate the economic impact of partial/non-compliance with labeled antibiotic treatment using computerized models. These models allow dairy producers to evaluate the economic implications of improved compliance by selecting variables that reflect their own operations.

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug. Though safe in cattle when properly given, inadvertent intra-arterial injection in the ear is possible and is fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days.

As with all drugs, NAXCEL should not be used in animals found to be hypersensitive to the product. NAXCEL has a pre-slaughter withdrawal time of 4 days in cattle.

As with all drugs, EXCENEL RTU should not be used in animals found to be hypersensitive to the product. EXCENEL RTU has a pre-slaughter withdrawal time of 3 days in cattle.

References

Table 4. Cost of Non-compliance Using Compliance Model (25 Treated Cows)

<table>
<thead>
<tr>
<th>Cost Component*</th>
<th>EXCEDE</th>
<th>Penicillin G Procaine full compliance</th>
<th>1 day less than</th>
<th>Extra Cost Compared to EXCEDE</th>
<th>EXCENEL RTU full compliance</th>
<th>1 day less than</th>
<th>Extra Cost Compared to EXCEDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial drug acquisition</td>
<td>$744</td>
<td>$199</td>
<td>$73</td>
<td>$-671</td>
<td>$844</td>
<td>$562</td>
<td>$-182</td>
</tr>
<tr>
<td>Initial drug administration</td>
<td>$23</td>
<td>$47</td>
<td>$70</td>
<td>$-23</td>
<td>$70</td>
<td>$47</td>
<td>$23</td>
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<tr>
<td>Retreatment costs</td>
<td>$58</td>
<td>$13</td>
<td>$123</td>
<td>$-56</td>
<td>$69</td>
<td>$112</td>
<td>$54</td>
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<tr>
<td>Milk production lost to sickness (if milk discard)</td>
<td>$172</td>
<td>$25</td>
<td>$72</td>
<td>$-100</td>
<td>$152</td>
<td>$111</td>
<td>$100</td>
</tr>
<tr>
<td>Milk discard costs</td>
<td>$0</td>
<td>$1.57</td>
<td>$1.71</td>
<td>$0</td>
<td>$1.71</td>
<td>$0</td>
<td>$1.71</td>
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<tr>
<td>Reproduction costs</td>
<td>$9</td>
<td>$1.57</td>
<td>$1.71</td>
<td>$0</td>
<td>$1.71</td>
<td>$0</td>
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<tr>
<td>Replacement of culled cows</td>
<td>$1,164</td>
<td>$1,164</td>
<td>$3.38</td>
<td>$2,218</td>
<td>$1,164</td>
<td>$3.38</td>
<td>$2,218</td>
</tr>
<tr>
<td>Replacement of dead cows</td>
<td>$518</td>
<td>$518</td>
<td>$986</td>
<td>$1,503</td>
<td>$518</td>
<td>$1,503</td>
<td>$986</td>
</tr>
<tr>
<td>Veterinary services</td>
<td>$563</td>
<td>$563</td>
<td>$563</td>
<td>$0</td>
<td>$563</td>
<td>$0</td>
<td>$563</td>
</tr>
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<td>$3,417</td>
<td>$6,490</td>
<td>$3,210</td>
</tr>
</tbody>
</table>

* Costs rounded to nearest whole dollar.
EXCELEN RTU

CLINICAL PHARMACOLOGY

Ceftiofur hydrochloride is a broad-spectrum cephalosporin antibiotic active against gram-negative and gram-positive bacteria. It is known as a potent inhibitor of bacterial cell wall synthesis. The drug is rapidly absorbed after intramuscular or subcutaneous administration in cattle and is distributed throughout the body. It has a high protein binding capacity and is extensively metabolized in the body. The primary metabolite is desfuroylceftiofur. The mean plasma half-life of ceftiofur is about 11 hours in cattle.

Ceftiofur is metabolized primarily in the liver and excreted in the urine as desfuroylceftiofur. The elimination rate constants for both ceftiofur hydrochloride and ceftiofur sodium are similar. The pharmacokinetic parameters for ceftiofur are given in the Table 1.

The drug is ineffective against Pseudomonas aeruginosa and is highly active against many gram-negative bacteria, including Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae. It is also very active against many gram-positive bacteria, including Staphylococcus aureus and Streptococcus suis. The MIC of ceftiofur against E. coli is 0.03 mg/L. The MIC of ceftiofur against S. aureus is 0.5 mg/L.

EXCELEN RTU Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic. It is indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with Fusobacterium necrophorum and Bacteroides melaninogenicus, two of the bacterial species most commonly associated with foot rot.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) please call 1-800-366-5288.

In the event of an adverse reaction please call 1-800-366-5288.
**CONTAMINANTS**

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals being treated with any other product containing ceftiofur crystalline free acid or any other product containing a drug whose active ingredient is a β-lactam antibiotic.

**WARNINGS**

Keep out of reach of children. Use of this product is intended for use in animals only. Animals treated with this product may be at a higher risk of developing hypersensitivity reactions than those treated with other β-lactam antibiotics.饲养人员在接触产品之后应彻底洗手。Please read the complete package insert for full details of the warnings and cautions.

**INDICATIONS**

EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystaline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against Gram-negative bacteria, including β-lactamase-producing strains. Like other cephalosporin, ceftiofur is a β-lactam antibiotic. EXCEDE Sterile Suspension is indicated for the treatment of the bacterial component of bovine respiratory disease (BRD) under field conditions. This product is also indicated for the treatment of salmonellosis and E. coli infections in cattle at a dosage of 3.0 mg CE/kg body weight (1.5 mL sterile suspension per 100 lb body weight). EXCEDE Sterile Suspension is contraindicated for intramuscular or intravenous use and should be given only as a subcutaneous injection at the base of the ear (head of the ear) in beef and non-lactating dairy cattle.

**DOSAGE**

**ADMINISTRATION FOR THE BASE OF THE EAR**

To administer a single subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to cattle at a dosage of 3.0 mg CE/kg body weight (1.5 mL sterile suspension per 100 lb body weight). EXCEDE Sterile Suspension is contraindicated for intramuscular or intravenous use and should be given only as a subcutaneous injection at the base of the ear (head of the ear) in beef and non-lactating dairy cattle which are at high risk of developing respiratory disease (BRD). Cattle are from multiple farm origins.

**ADMINISTRATION**

Cattle were from multiple farm origins that may have included feedlots or dairy herds. Blood samples and postmortem examinations were reviewed for signs of beta lactam susceptibility or resistance. The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

**ADVERSE EFFECTS**

A study was designed and conducted to specifically address exposure of cattle when EXCEDE Sterile Suspension was administered as a single 6 mg CE/kg bolus dose of ceftiofur crystalline free acid (3.0 mg per pound). Ceftiofur residues in milk were determined by a liquid-liquid extraction procedure followed by liquid chromatography-mass spectrometry. The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

**ANIMAL SAFETY**

**The local tissue reaction of the base of the ear**

When administered correctly, a subcutaneous bolus of EXCEDE Sterile Suspension at 6.6 mg CE/kg body weight was well tolerated by cattle. These deaths resulted from inadvertent intra-arterial injection. The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

**THE GLOBAL TISSUE REACTION OF THE BASE OF THE EAR**

When administered correctly, a subcutaneous bolus of EXCEDE Sterile Suspension at 6.6 mg CE/kg body weight was well tolerated by cattle. These deaths resulted from inadvertent intra-arterial injection. The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

**ABSORPTION**

The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

**CLINICAL EFFECTIVENESS**

A dose confirmation study for the treatment of BRD evaluated the systemic safety of ceftiofur crystalline free acid (3.0 mg CE/kg) for the treatment of the bacterial component of BRD under field conditions. All animals were administered in the middle third of their ear with cottonseed oil based suspension. Ceftiofur was well tolerated by cattle. The systemic safety of ceftiofur crystalline free acid was determined in various species including cattle, sheep, swine, and dogs. The main route of elimination of ceftiofur from the body is via the kidneys. The mean plasma t½ of ceftiofur was approximately 2.0 hours. A single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle of the ear adjacent to the pinna was achieved in 97.4% of cattle using cottonseed oil based suspension. Most animals will respond to treatment within five to six days. If a more rapid response is desired, a second treatment may be administered.

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