Date of Approval: January 28, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-616

Cefenil® RTU

ceftiofur hydrochloride sterile suspension

Swine and Cattle

Swine: Cefenil® RTU is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis*.

Cattle: Cefenil® RTU is indicated for treatment of the following bacterial diseases: Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida and Histophilus somni*, acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

Sponsored by:

Norbrook Laboratories, Ltd.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-616

B. Sponsor

Norbrook Laboratories, Ltd.
Station Works, Newry
BT35 6JP, Northern Ireland

Drug Labeler Code: 055529

US Agent Name and Address:
Bill Zollers, Ph.D.
Norbrook, Inc.
9401 Indian Creek Parkway, Suite 680
Overland Park, KS 66210

C. Proprietary Name

Cefenil® RTU

D. Drug Product Established Name

Ceftiofur hydrochloride sterile suspension

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Sterile suspension

G. Amount of Active Ingredient

50 mg/mL

H. How Supplied

100 and 250 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 h intervals for a total of three consecutive days.

Cattle: For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 h intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer intramuscularly or subcutaneously 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW every other day on Days 1 and 3 (48 h interval). Do not inject more than 15 mL per injection site. Selection of dosage level (0.5 to 1.0 mg/lb) and regimen/duration (daily or every other day for BRD only) should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response. For acute post-partum metritis: administer by intramuscular or subcutaneous administration at the dosage of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 h intervals for five consecutive days. Do not inject more than 15 mL per injection site.

K. Route of Administration

Injection

L. Species/Class

Swine and cattle

M. Indication(s)

Swine: Cefenil® RTU is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis*.

Cattle: Cefenil® RTU is indicated for treatment of the following bacterial diseases:

- Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*.
- Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

N. Reference Listed New Animal Drug

Excenel® RTU; ceftiofur hydrochloride sterile suspension; NADA 140-890; Zoetis Inc.

II. BIOEQUIVALENCE

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug (RLNAD)). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

For this ANADA, three *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD (ceftiofur hydrochloride sterile suspension) 50 mg/mL. One study was conducted using the intramuscular (IM) route of administration in pigs and in cattle, and one was conducted using the subcutaneous (SC) route of administration in cattle. The IM administration blood-level bioequivalence study in pigs was conducted in 20 healthy male Landrace cross pigs at a dose of 5.0 mg/kg. The IM administration blood-level bioequivalence study in cattle was conducted in 16 healthy male beef cattle at a dose of 2.2 mg/kg. The SQ administration blood-level bioequivalence study in cattle was conducted in 16 healthy male beef cattle at a dose of 2.2 mg/kg. Bioequivalence in all studies was demonstrated between RLNAD ceftiofur hydrochloride sterile suspension and the generic ceftiofur hydrochloride sterile suspension, by demonstrating that the confidence limits for the difference between the pivotal parameters C_{MAX} and AUC are contained within the equivalence limits of 80.00% and 125.00%. No adverse reactions were noted in any of the *in vivo* blood-level studies. The study information is summarized below.

A. IM Administration in Pigs:

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the 50 mg/mL generic and RLNAD formulations of ceftiofur hydrochloride sterile suspension when injected intramuscularly to pigs.

Study Title: A Cross-Over Pharmacokinetic Study to Determine the Plasma Levels of Ceftiofur (Measured as Ceftiofur Free Acid Equivalents) in Pigs Following the Intramuscular Administration of Ceftiofur Hydrochloride Injection (Norbrook Laboratories Limited, Product Code: P-CEFT-020) and Excenel® RTU Sterile Suspension (Pfizer Inc., NADA 140-890) (Study No. 003/15)

Study Dates: January 27, 2015 to May 06, 2015

Study Location:
In-life phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of generic sponsor's generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) and the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension) in a randomized, two-period, two-sequence, single-dose crossover study in pigs using OECD Principles on Good Laboratory Practices standards.

Study Animals: 20 Landrace cross-bred pigs weighing between 48.3 and 64.0 kgs at the time of first administration.

Experimental Design: A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of a generic ceftiofur hydrochloride sterile suspension following an IM dose of 5.0 mg/kg to an equivalent dose of the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension).

Drug Administration: A 5.0 mg/kg dose of test or reference sterile suspension was administered intramuscularly to each test animal in a two-sequence cross-over study.

Measurements and Observations: The plasma concentrations of ceftiofur were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health, adverse events, and injection site reactions.

Statistical Method: The study was conducted as a two-period, two-sequence, single-dose crossover study with a 14-day washout time between periods. Twenty Landrace cross-bred pigs were administered either the test article or the reference article in each period. Primary variables evaluated were area under the curve from time 0 to the first observed concentration below limit of quantitation (AUC) and maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) was also evaluated.

Prior to analysis, AUC and C_{MAX} were transformed using the natural logarithmic transformation. Ninety percent confidence intervals about the difference of the means for the logarithmically transformed variables (test − reference) were estimated. The endpoints for the confidence interval were back-transformed to geometric means. For the two products to be considered bioequivalent, the back-transformed confidence bounds for both AUC and C_{MAX} must fall between 0.80 and 1.25.

Results: As seen in Table II.1 below, the bioequivalence criterion is met for both AUC and C_{MAX} and it can be concluded that bioequivalence has been established between Norbrook Laboratories Ltd.'s formulation of ceftiofur hydrochloride sterile suspension (test) and Zoetis Inc. Excenel® RTU sterile suspension (reference).

Table II.1. Bioequivalence Evaluation

Parameter	Test	Reference	Ratio*	Ratio Lower Bound	Ratio Upper Bound
AUC (ppm*h)	227.72†	235.85†	0.97	0.92	1.02
C_{MAX} (ppm)	16.84†	18.19†	0.93	0.84	1.02
T_{MAX} (h)	1.51‡	1.71‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
* Ratio = Test/Reference
NE = not estimated

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 50 mg/mL generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) (test) and the RLNAD 50 mg/mL Excenel® RTU (ceftiofur hydrochloride sterile suspension) (reference) has been established in the *in vivo* bioequivalence study.

B. IM Administration in Cattle:

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the 50 mg/mL generic and RLNAD formulations of ceftiofur hydrochloride sterile suspension when injected intramuscularly to cattle.

Study Title: A Pharmacokinetic Study to Determine the Plasma Levels of Ceftiofur (Measured as Ceftiofur Free Acid Equivalents) in Cattle Following the Intramuscular Administration of a Formulation of Ceftiofur Hydrochloride Injection (Norbrook Laboratories Limited, Product Code P-CEFT-020) and Excenel RTU (Pfizer Limited, NADA 140-890) (Study No. 046/14)

Study Dates: November 24, 2014 to May 14, 2015

Study Location:
In-life phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of generic sponsor's generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) and the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension) in a randomized, two-period, two-sequence, single-dose crossover study in cattle using OECD Principles on Good Laboratory Practices standards.

Study Animals: 16 male beef cattle weighing between 283 and 351 kgs at the time of first adminstration.

Experimental Design: A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of a generic ceftiofur hydrochloride sterile suspension following an IM dose of 2.2 mg/kg to an equivalent dose of the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension).

Drug Administration: A 2.2 mg/kg dose of test or reference sterile suspension was administered intramuscularly to each test animal in a two-sequence cross-over study.

Measurement and Observations: The plasma concentrations of ceftiofur were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health, adverse events, and injection site reactions.

Statistical Method: The study was conducted as a two-period, two-sequence, single-dose crossover study with a 7-day washout time between periods. Sixteen cattle representative of US beef breeds were administered either the test article or the reference article in each period. Primary variables evaluated were area under the curve from time 0 to the first observed concentration below limit of quantitation (AUC) and maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) was also evaluated.

Prior to analysis, AUC and C_{MAX} were transformed using the natural logarithmic transformation. Ninety percent confidence intervals about the difference of the means for the logarithmically transformed variables (test − reference) were estimated. The endpoints for the confidence interval were back-transformed to geometric means. For the two products to be considered bioequivalent, the back-transformed confidence bounds for both AUC and C_{MAX} must fall between 0.80 and 1.25.

Results: As seen in Table II.2 below, the bioequivalence criterion is met for both AUC and C_{MAX} and it can be concluded that bioequivalence has been established between Norbrook Laboratories Ltd.'s formulation of ceftiofur hydrochloride sterile suspension (test) and Zoetis Inc. Excenel® RTU sterile suspension (reference).

Table II.2. Bioequivalence Evaluation

Parameter	Test	Reference	Ratio*	Ratio Lower Bound	Ratio Upper Bound
AUC (ppm*h)	105.50†	108.47†	0.97	0.94	1.01
C_{MAX} (ppm)	9.94†	10.43†	0.95	0.90	1.01
T_{MAX} (h)	2.13‡	2.13‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
* Ratio = Test/Reference
NE = not estimated

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 50 mg/mL generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) (test) and the RLNAD 50 mg/mL Excenel® RTU (ceftiofur hydrochloride sterile suspension) (reference) has been established in the *in vivo* bioequivalence study.

C. SQ Administration in Cattle:

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the 50 mg/mL generic and RLNAD formulations of ceftiofur hydrochloride sterile suspension when injected subcutaneously to cattle.

Study Title: A Pharmacokinetic Study to Determine the Plasma Levels of Ceftiofur (Measured as Ceftiofur Free Acid Equivalents) in Cattle Following the Subcutaneous Administration of a Formulation of Ceftiofur Hydrochloride Injection (Norbrook Laboratories Limited, Product Code P-CEFT-020) and Excenel RTU (Pfizer Limited, NADA 140-890) (Study No. 001/15)

Study Dates: February 17, 2015 to October 06, 2015

Study Location:
In-life phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of generic sponsor's generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) and the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension) in a randomized, two-period, two-sequence, single-dose crossover study in cattle using OECD Principles on Good Laboratory Practices standards.

Study Animals: 16 male beef cattle weighing between 374 and 427 kgs at the time of first administration.

Experimental Design: A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of a generic ceftiofur hydrochloride sterile suspension following an SQ dose of 2.2 mg/kg to an equivalent dose of the RLNAD Excenel® RTU (ceftiofur hydrochloride sterile suspension).

Drug Administration: A 2.2 mg/kg dose of test or reference sterile suspension was administered subcutaneously to each test animal in a two-sequence cross-over study.

Measurements and Observations: The plasma concentrations of ceftiofur were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health, adverse events, and injection site reactions.

Statistical Method: The study was conducted as a two-period, two-sequence, single-dose crossover study with a 16-day washout time between periods. Sixteen cattle representative of US beef breeds were administered either the test article or the reference article in each period. Primary variables evaluated were area under the curve from time 0 to the first observed concentration below limit of quantitation (AUC) and maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) was also evaluated.

Prior to analysis, AUC and C_{MAX} were transformed using the natural logarithmic transformation. Ninety percent confidence intervals about the difference of the means for the logarithmically transformed variables (test — reference) were estimated. The endpoints for the confidence interval were back-transformed to geometric means. For the two products to be considered bioequivalent, the back-transformed confidence bounds for both AUC and C_{MAX} must fall between 0.80 and 1.25.

Results: As seen in Table II.3 below, the bioequivalence criterion is met for both AUC and C_{MAX} and it can be concluded that bioequivalence has been established between Norbrook Laboratories Ltd.'s formulation of ceftiofur hydrochloride sterile suspension (test) and Zoetis Inc. Excenel® RTU sterile suspension (reference).

Table II.3. Bioequivalence Evaluation

Parameter	Test	Reference	Ratio*	Ratio Lower Bound	Ratio Upper Bound
AUC (ppm*h)	99.87†	101.09†	0.99	0.95	1.03
C_{MAX} (ppm)	8.35†	8.68†	0.96	0.89	1.03
T_{MAX} (h)	2.34‡	2.53‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
* Ratio = Test/Reference
NE = not estimated

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 50 mg/mL generic Cefenil® RTU (ceftiofur hydrochloride sterile suspension) (test) and the RLNAD 50 mg/mL Excenel® RTU (ceftiofur hydrochloride sterile suspension) (reference) has been established in the *in vivo* bioequivalence study.

III. EFFECTIVENESS

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY

Summary: The toxicological safety and the microbial food safety of the active ingredient in generic new animal drugs, such as Cefenil® RTU, are established during the approval of the reference listed new animal drug (RLNAD). Also, the codified tolerances established for the RLNAD apply to the generic new animal drug, once bioequivalence to the RLNAD is established. Therefore, for generic new animal drugs, such as Cefenil® RTU, Human Food Safety is assessed by a residue chemistry evaluation that establishes when residue concentrations in edible tissues and milk are less than the codified tolerance after administration of the drug (*i.e.*, safe for human consumption).

For the approval of Cefenil® RTU, the Agency reviewed five studies during the Human Food Safety evaluation. These studies demonstrated that ceftiofur residues are less than the codified tolerances in edible swine tissues at 4 days after the last treatment with Cefenil® RTU, in edible cattle tissues at 3 days after the last treatment with Cefenil® RTU, and in cow's milk at 0 days (12 hours) after the last treatment with Cefenil®. An analytical method for monitoring residues of ceftiofur in edible tissues and milk was developed during the approval of the RLNAD and is available.

The following are assigned to this product for cattle and swine:

A. Acceptable Daily Intake and Tolerances for Residues

The acceptable daily intake (ADI) for total residues of ceftiofur is 30 micrograms *per* kilogram of body weight *per* day. The tolerances established for the RLNAD apply to the generic product. A tolerance of 0.25 parts *per* million (ppm) is established for desfuroylceftiofur (the marker residue) in swine kidney (the target tissue), 3 ppm in swine liver, and 2 ppm in swine muscle, under 21 CFR §556.113. A tolerance of 0.4 ppm is established for desfuroylceftiofur (the marker residue) in bovine kidney (the target tissue), 2 ppm in bovine liver, 1 ppm in bovine muscle, and 0.1 ppm in bovine milk, under 21 CFR §556.113.

B. Withdrawal Periods and Milk Discard Time

The Agency evaluated five studies to assign the following withdrawal periods and a milk discard time to Cefenil® RTU:

- Withdrawal Periods
  - Swine: 4-day withdrawal period for swine treated with an intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb. body weight (3.0 to 5.0 mg/kg) for three consecutive days.
  - Cattle: 3-day withdrawal period for cattle treated with an intramuscular or subcutaneous injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).
- Milk Discard Time
  - Lactating Dairy Cows: 0-day milk discard time for lactating dairy cows treated with an intramuscular or subcutaneous injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).

The studies that supported the withdrawal periods and milk discard time for Cefenil® RTU are described below.

Study Title: A Tissue Residue Study to Determine Levels of Ceftiofur (Measured as Desfuroylceftiofur Acetamide Derivative) in pigs 1, 2, 3, 4 and 5 Days Following the Final Intramuscular Administration of Ceftiofur Hydrochloride Injection (Study No. 015/15)

Study Dates: September 25, 2015 to February 2, 2016

Study Location:
Animal phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of the study was to determine the concentration of ceftiofur and desfuroylceftiofur-related residues, as measured by the marker

residue desfuroylceftiofur acetamide (DCA), in kidney tissues from pigs treated with three daily intramuscular injections of Cefenil® RTU at a dose of 5.0 mg ceftiofur/kg of body weight. This study was conducted in accordance with the Good Laboratory Practices Regulations (GLPs; 21 CFR §58).

Study Animals: Twenty pigs, weighing 44.7 to 56.6 kg at the time of first administration.

Experimental Design: Pigs were assigned randomly to one of five groups (Table V.1) such that each group contained two males and two females (n = 4 *per* group).

Drug Administration: Pigs were treated once daily for three consecutive days with an intramuscular injection of 5.0 mg ceftiofur/kg of body weight in the following sequence of injection sites: right rump, left rump, and, finally, right neck.

Measurements and Observations: At the assigned time (Table V.1), pigs were slaughtered, and kidney samples were collected. The kidney samples were assayed for concentrations of ceftiofur and desfuroylceftiofur-related residues, measured as DCA, by a validated HPLC-UV procedure. The method's limit of quantification (LOQ) was 0.075 ppm. Kidney concentrations of DCA less than the method LOQ were excluded from the analyses.

Statistical Method: The residue data from Study 015/15 were analyzed using a statistical algorithm that calculated the upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence.

Results: Mean (± standard deviation) concentrations of DCA in kidney samples are presented in Table V.1.

Table V.1. Mean (± standard deviation) concentrations of ceftiofur residues (measured as desfuroylceftiofur acetamide (DCA)) in kidney tissues from pigs intramuscularly injected once daily for three consecutive days with 5.0 mg ceftiofur/kg of body weight.

Treatment Group	Slaughter Time (Days After Last Treatment)	Kidney DCA Concentration (ppm)
A	1	1.19 ± 0.20
B	2	0.41 ± 0.09
C	3	0.16 ± 0.07
D	4	0.08[1]
E	5	BLOQ[2]

[1]Only one sample had DCA concentrations greater than the limit of quantification.
[2] BLOQ, Below the limit of quantification (0.075 ppm)

The upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence was less than the codified kidney tolerance in swine at 4 days after the last injection.

Conclusion: The data from Study 015/15 support assigning a 4-day withdrawal period to Cefenil® RTU for pigs treated with an intramuscular injection of

1.36 to 2.27 mg ceftiofur equivalents/lb. body weight (3.0 to 5.0 mg/kg) for three consecutive days.

Study Title: A Tissue Residue Study to Determine the Levels of Ceftiofur (Measured as Desfuroylceftiofur Acetamide Derivative) in cattle 1, 2, 3, 4 and 5 Days Following the Final Intramuscular Administration of Ceftiofur Hydrochloride Injection (Study No. 026/15)

Study Dates: October 28, 2015 to March 1, 2016

Study Location:
Animal phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of the study was to determine the concentration of ceftiofur and desfuroylceftiofur-related residues, as measured by the marker residue DCA, in kidney samples from cattle treated with five daily intramuscular injections of Cefenil® RTU at a dose of 2.2 mg ceftiofur/kg of body weight. This study was conducted in accordance with GLPs (21 CFR §58).

Study Animals: Twenty cattle, weighing 354 to 446 kg at the time of adminstration.

Experimental Design: Cattle were assigned randomly to one of five groups (Table V.2) such that each group contained two males and two females (n = 4 *per* group).

Drug Administration: Cattle were treated once daily for five consecutive days with an intramuscular injection of 2.2 mg ceftiofur/kg of body weight in the following sequence of injection sites: right rump, left rump, right hind leg, left neck, and finally, right neck.
Measurements and Observations: At the assigned time (Table V.2), cattle were slaughtered, and kidney samples were collected. The kidney samples were assayed for concentrations of ceftiofur and desfuroylceftiofur-related residues, measured as DCA, by a validated HPLC-UV procedure. The method's LOQ was 0.075 ppm. Kidney concentrations of DCA less than the method LOQ were excluded from the analyses.

Statistical Method: The residue data from Study 026/15 were analyzed using a statistical algorithm that calculated the upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence.

Results: Mean (± standard deviation) concentrations of DCA in kidney samples are presented in Table V.2.

Table V.2. Mean (± standard deviation) concentrations of ceftiofur residues (measured as desfuroylceftiofur acetamide (DCA)) in kidney tissues from cattle intramuscularly injected once daily for five consecutive days with 2.2 mg ceftiofur/kg of body weight.

Treatment Group	Slaughter Time (Days After Last Treatment)	Kidney DCA Concentration (ppm)
A	1	0.99 ± 0.14
B	2	0.32 ± 0.13
C	3	0.12 ± 0.02
D	4	0.08 ± 0.002
E	5	BLOQ[1]

[1] BLOQ, Below the limit of quantification (0.075 ppm)

The upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence was less than the codified kidney tolerance in cattle at 3 days after the last injection.

Conclusion: The data from Study #026/15 support assigning a 3-day withdrawal period to Cefenil® RTU for cattle treated with an intramuscular injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).

Study Title: A Tissue Residue Study to Determine the Levels of Ceftiofur (Measured as Desfuroylceftiofur Acetamide Derivative) in cattle 1, 2, 3, 4 and 5 Days Following the Subcutaneous Administration of Ceftiofur Hydrochloride Injection (Study No. 025/15)

Study Dates: September 30, 2015 to February 26, 2016

Study Location:
Animal phase: Rostrevor, Co. Down, Northern Ireland
Bioanalytical testing: Newry, Co. Down, Northern Ireland

Study Design:

Objective: The objective of the study was to determine the concentration of ceftiofur and desfuroylceftiofur-related residues, as measured by the marker residue DCA, in kidney samples from cattle treated with five daily subcutaneous injections of Cefenil® RTU at a dose of 2.2 mg ceftiofur/kg of body weight. This study was conducted in accordance with GLPs (21 CFR §58).

Study Animals: Twenty cattle, weighing 33 to 381 kg at the time of administration.

Experimental Design: Cattle were assigned randomly to one of five groups (Table V.3) such that each group contained two males and two females (n = 4 *per* group).

Drug Administration: Cattle were treated once daily for five consecutive days with a subcutaneous injection of 2.2 mg ceftiofur/kg of body weight in the following

sequence of injection sites: right rib cage (dorsal), left neck, right rib cage (ventral), left rib cage, and finally right neck.

Measurements and Observations: At the assigned time (Table V.3), cattle were slaughtered, and kidney samples were collected. The kidney samples were assayed for concentrations of ceftiofur and desfuroylceftiofur-related residues, measured as DCA, by a validated HPLC-UV procedure. The method's LOQ was 0.075 ppm. Kidney concentrations of DCA less than the method LOQ were excluded from the analyses.

Statistical Method: The residue data from Study 025/15 were analyzed using a statistical algorithm that calculated the upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence.

Results: Mean (± standard deviation) concentrations of DCA in kidney samples are presented in Table V.3.

Table V.3. Mean (± standard deviation) concentrations of ceftiofur residues (measured as desfuroylceftiofur acetamide (DCA)) in kidney tissues from cattle subcutaneously injected once daily for five consecutive days with 2.2 mg ceftiofur/kg of body weight.

Treatment Group	Slaughter Time (Days After Last Treatment)	Kidney DCA Concentration (ppm)
A	1	0.87 ± 0.14
B	2	0.26 ± 0.06
C	3	0.13 ± 0.02
D	4	BLOQ[1]
E	5	BLOQ

[1] BLOQ, Below the limit of quantification (0.075 ppm)

The upper tolerance limit for kidney DCA concentrations for the 99th percentile of the population with 95% confidence was less than the codified kidney tolerance in cattle at 3 days after the last injection.

Conclusion: The data from Study 025/15 support assigning a 3-day withdrawal period to Cefenil® RTU for cattle treated with a subcutaneous injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).

Study Title: A Pharmacokinetic Study to Determine the Plasma Levels of Ceftiofur (Measured as Ceftiofur Free Acid Equivalents) in Cattle Following the Intramuscular Administration of a Formulation of Ceftiofur Hydrochloride Injection (Norbrook Laboratories Limited, Product Code P-CEFT 020) and Excenel® RTU (Pfizer Limited, NADA 140-890; Study No. 046/14)

See Section II. Bioequivalence for a description of this study.

Results: Plasma concentrations of ceftiofur (measured as ceftiofur free acid equivalents) were greater than the LOQ of the analytical method (0.234 µg/mL) for the duration of the milk discard time assigned to the RLNAD

(*i.e.*, 0-day (12 hours)). In addition, the data from Study 046/14 demonstrated bioequivalence between Cefenil® RTU and the RLNAD.

Conclusion: The data from Study 046/14 support assigning Cefenil® RTU the milk discard time previously assigned to the RLNAD for an intramuscular injection in lactating dairy cows: 0-day milk discard time for lactating dairy cows treated with an intramuscular injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).

Study Title: A Pharmacokinetic Study to Determine the Plasma Levels of Ceftiofur (Measured as Ceftiofur Free Acid Equivalents) in Cattle Following the Subcutaneous Administration of a Formulation of Ceftiofur Hydrochloride Injection (Norbrook Laboratories Limited, Product Code P-CEFT 020) and Excenel® RTU (Pfizer Limited, NADA 140-890; Study No. 001/15)

See Section II. Bioequivalence for a description of this study.

Results: Plasma concentrations of ceftiofur (measured as ceftiofur free acid equivalents) were greater than the LOQ of the analytical method (0.234 µg/mL) for the duration of the milk discard time assigned to the RLNAD (*i.e.*, 0-day (12 hours)). In addition, the data from Study 001/15 demonstrated bioequivalence between Cefenil® RTU and the RLNAD.

Conclusion: The data from Study 001/15 support assigning Cefenil® RTU the milk discard time previously assigned to the RLNAD for a subcutaneous injection in lactating dairy cows: 0-day milk discard time for lactating dairy cows treated with a subcutaneous injection of 0.5 to 1.0 mg ceftiofur equivalents/lb. body weight (1.1 to 2.2 mg/kg) for up to five consecutive days or 1.0 mg ceftiofur equivalents/lb. body weight (2.2 mg/kg) every other day on Days 1 and 3 (48-hour interval).

C. Analytical Method for Residues

The validated analytical method for analysis of residues of ceftiofur is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

VI. USER SAFETY

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Cefenil® RTU:

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.
Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to

sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing. Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention. The safety data sheet contains more detailed occupational safety information. To obtain a safety data sheet (SDS) or to report any adverse event please call 1-866-591-5777.

VII. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that Cefenil® RTU, when used according to the label, is safe and effective.

Additionally, data demonstrate that residues in food products derived from species treated with Cefenil® RTU will not represent a public health concern when the product is used according to the label.