Penicillin G Procaine Depletion from Tissues of Heavy Sows

David J. Smith[1], Sara J. Lupton[1], Weilin L. Shelver[1], David Newman[2], Steve Larsen[3]

[1]USDA ARS Biosciences Lab, Fargo ND

[2]North Dakota State University, Fargo ND

[3]National Pork Board, Des Moines, IA

Background

- Under AMDUCA, the off-label use of approved veterinary drugs is allowed
- Veterinarians must recommend withdrawal periods that are sufficient to allow drug residues to deplete from edible tissues
- Few data exist for off-label use of most drugs
- FARAD recommends withdrawal periods based on the best available evidence

Background

- Penicillin-G procaine is an important antibiotic for use in heavy sows
- In May of 2011, FSIS changed screening methods and the incidence of penicillin-G detections spiked significantly
- FARAD recommended 15-d withdrawal period appeared to be insufficient

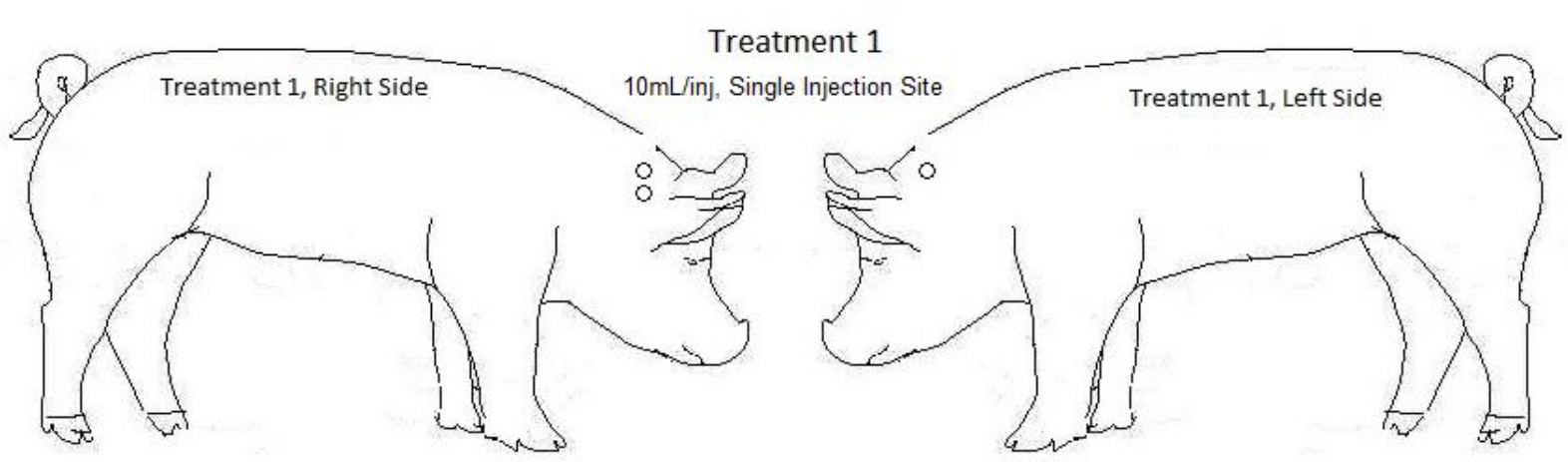
Objectives

- Determine pre-slaughter withdrawal periods for heavy sows treated with a 5x IM penicillin-G procaine dose for 3 consecutive days
- Determine most appropriate pattern (site and volume) of intramuscular (IM) penicillin-G procaine administration
- Determine the incidence of false-positives returned by the Charm-KIS microbial inhibition test (used by the US FSIS)

Animals/Dosing

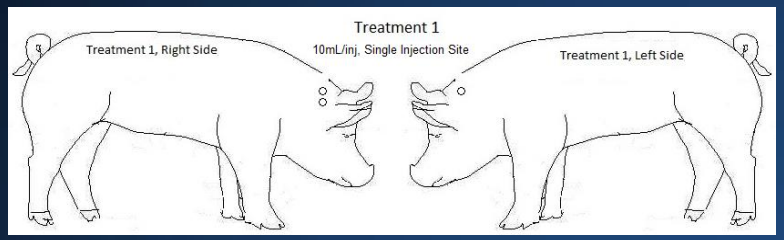
- Heavy sows, n = 126
  - Starting weight: 228.3 ± 30.1 kg
  - Ending weight: 230.9 ± 30.1 kg
- Penicillin-G procaine administration
  - Intramuscular in neck
  - 33,000 U per kg BW (5x label dose)
    - 5 mL/100 lb BW or 11 mL/100 kg BW
  - 3 consecutive days
- Three administration patterns (treatments)

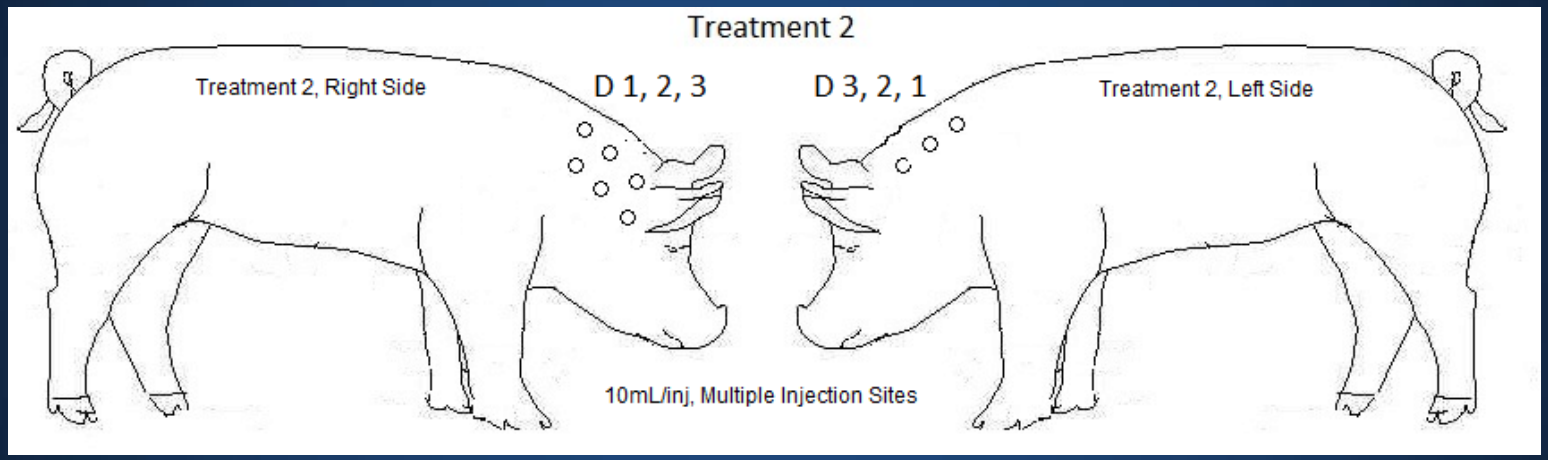
Treatment 1



- Maximum injection volume of 10 mL
- 10 mL in right & left sides, >20 mL in right side
- Same injection sites each day
- For 250 kg sow
  - 10 mL R, 10 mL L, 7.5 mL R

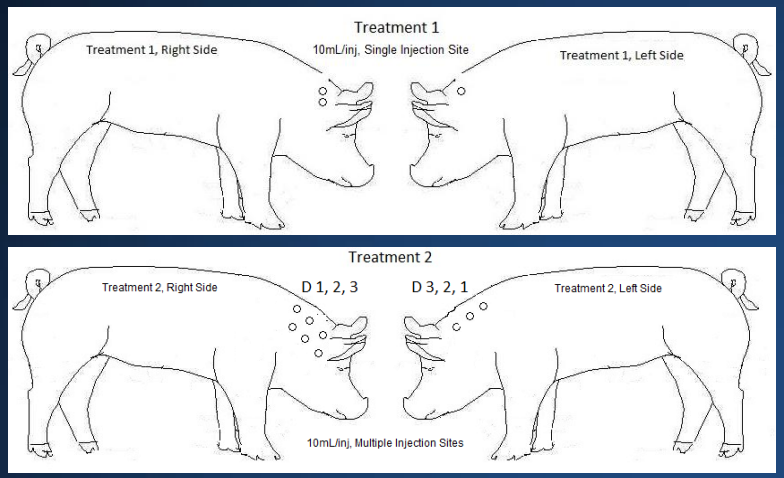
Treatment 2



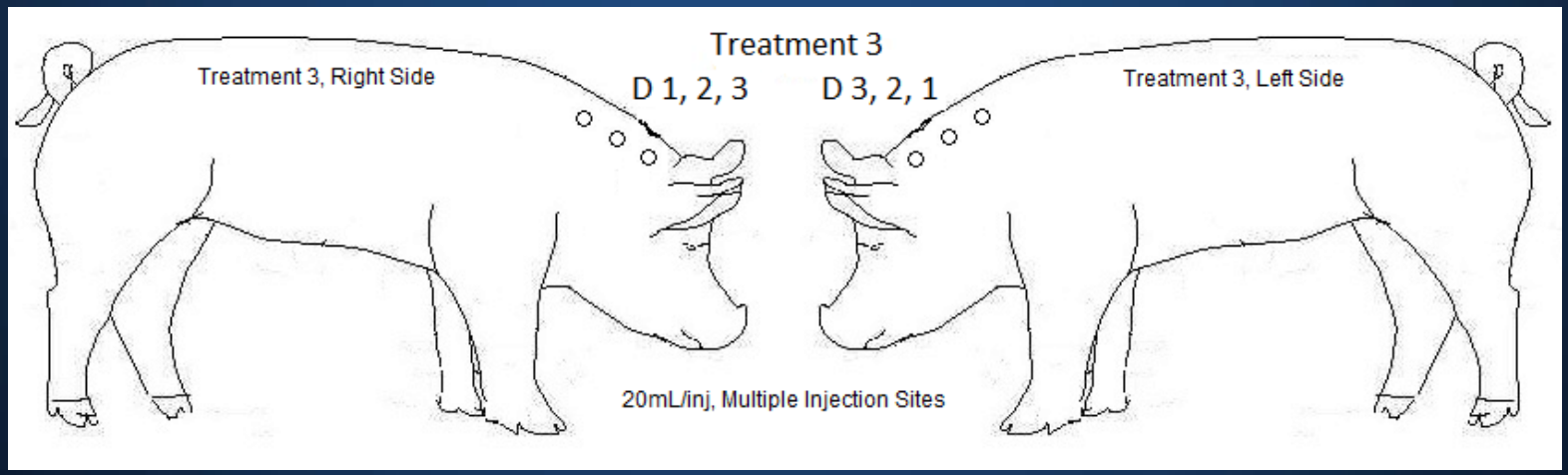


- Maximum injection volume of 10 mL
- 10 mL in right & left sides, >20 mL in right side
- Across day- injection sites separated by ~2 inches

Treatment 3



- Max injection volume of 20 mL
- 20 mL in right side, volume >20 mL in left side
- Across day- injection sites separated by ~2 inches



Slaughter/Tissue Collection

- Withdrawal Periods: 5, 10, 15, 20, 25, 32, 39 d
- Tissues:
  - Kidney, muscle (longissimus), liver, adipose tissue
- Other:
  - Urine, serum
  - Injection site

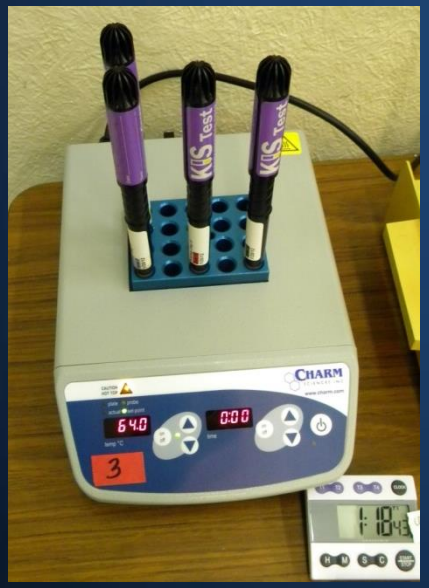
Design Summary

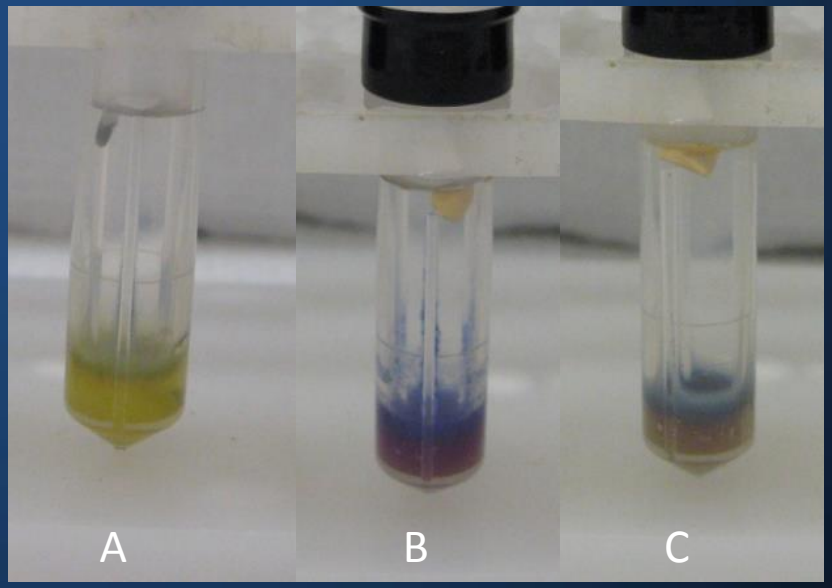
Replication of treatment and withdrawal times

Withdrawal	Trial 1			Trial 2			
time	Trt 1	Trt 2	Trt 3	Trt 1	Trt 2	Trt 3	
d	*sows*	*sows*	*sows*	*sows*	*sows*	*sows*	*total*
5	3	3	3	3	3	3	18
10	3	3	3	3	3	3	18
15	3	3	3	3	3	3	18
20	3	3	3	3	3	3	18
25	3	3	3	3	3	3	18
32	3	3	3	3	3	3	18
39	3	3	3	3	3	3	18
Totals:	21	21	21	21	21	21	126

Endpoints: Qualitative Screen

- Charm-KIS rapid screen:
  - Kidney samples on the kill floor
  - Muscle, kidney, liver, serum, urine, injection site in laboratory



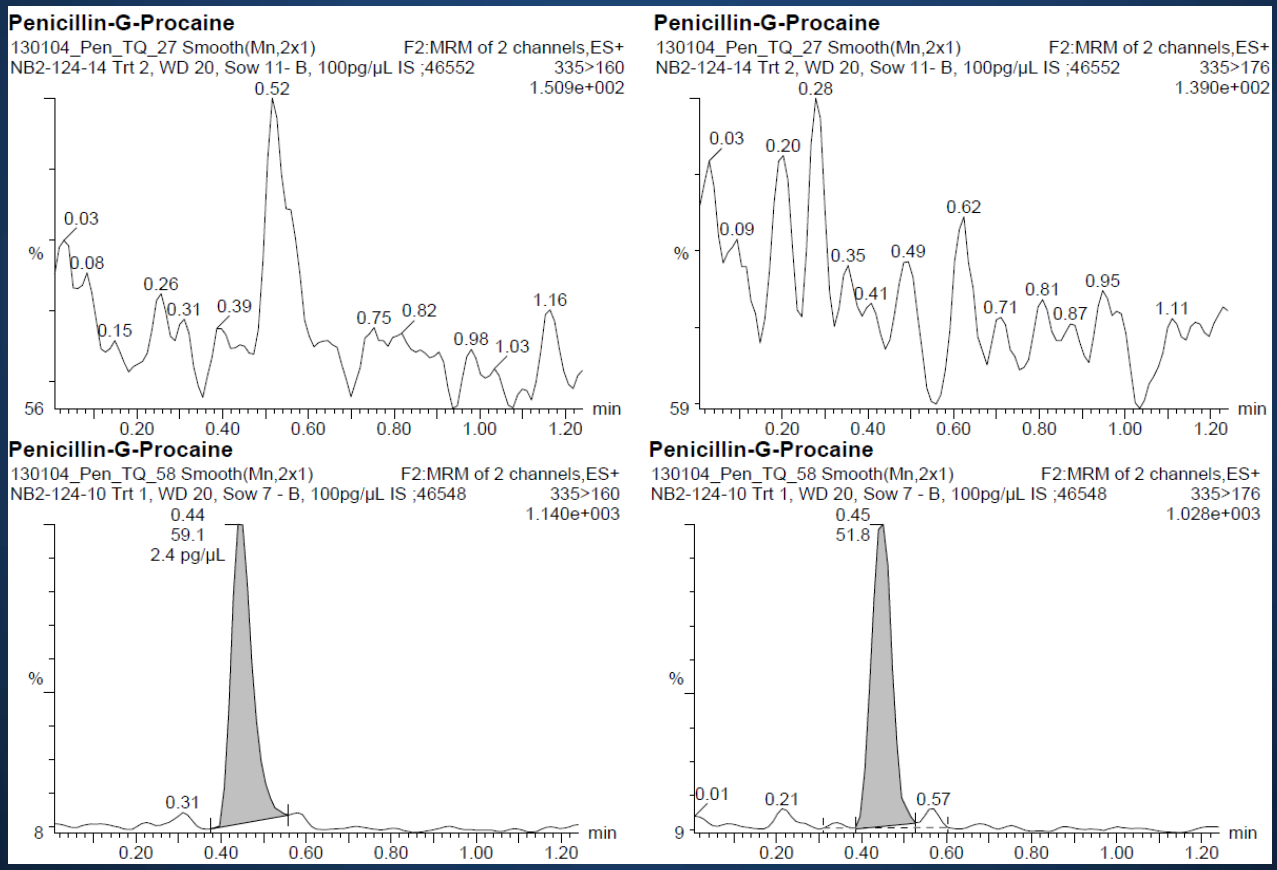


Endpoints: Quantitative/Confirmatory

UPLC-Mass Spectrometry:

20-d Kidney Sow – 11B

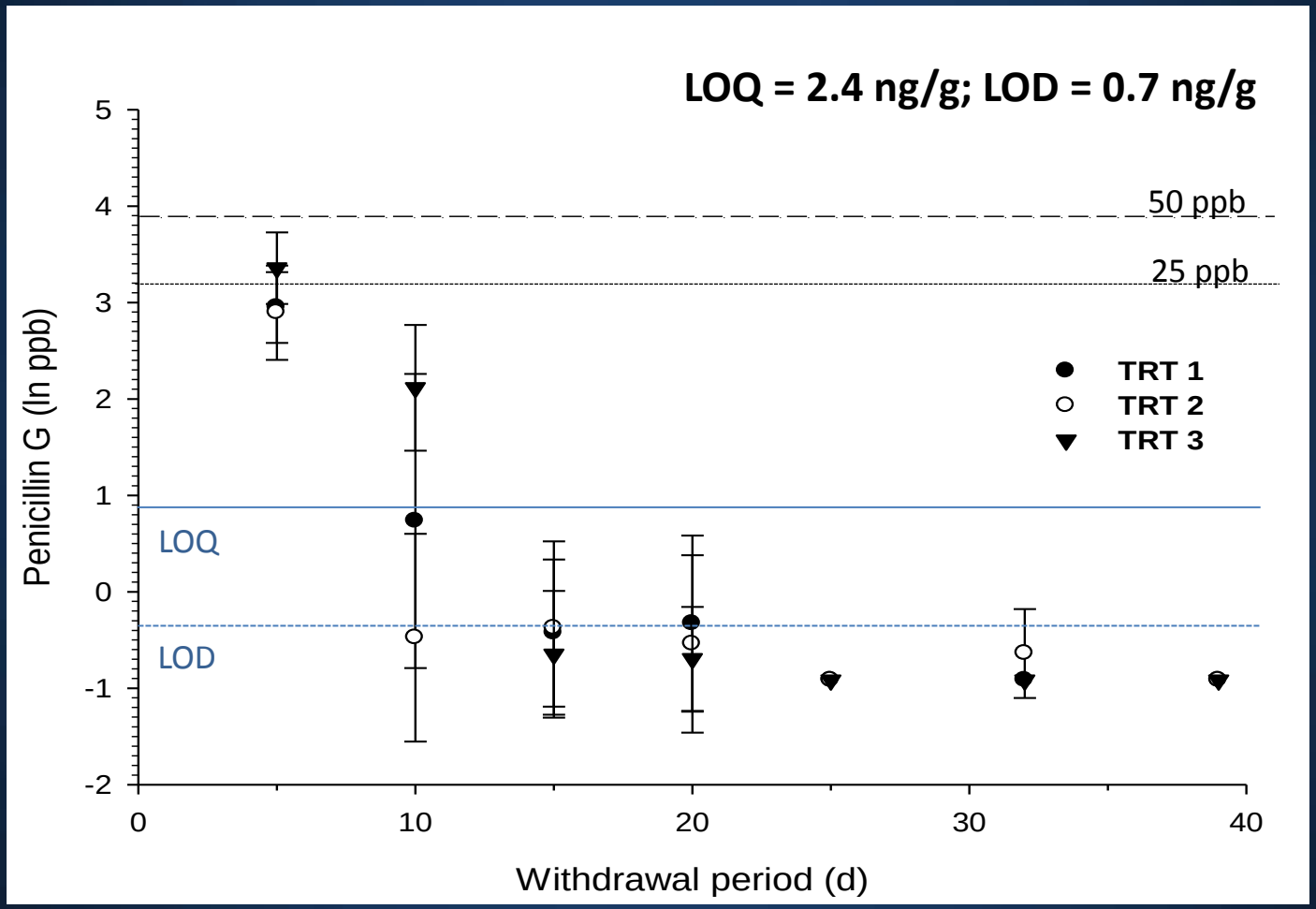
20-d Kidney Sow-7B



Summary of Qualitative Results

- Charm-KIS performed well for kidney tissues
  - No false-positives
  - Sensitive to ~20 ppb in our hands
  - Predicted presence of UPLC-MS positive samples well
- Skeletal muscle was a poor matrix
- Charm-KIS of urine correlated very well with Charm-KIS of kidney residues

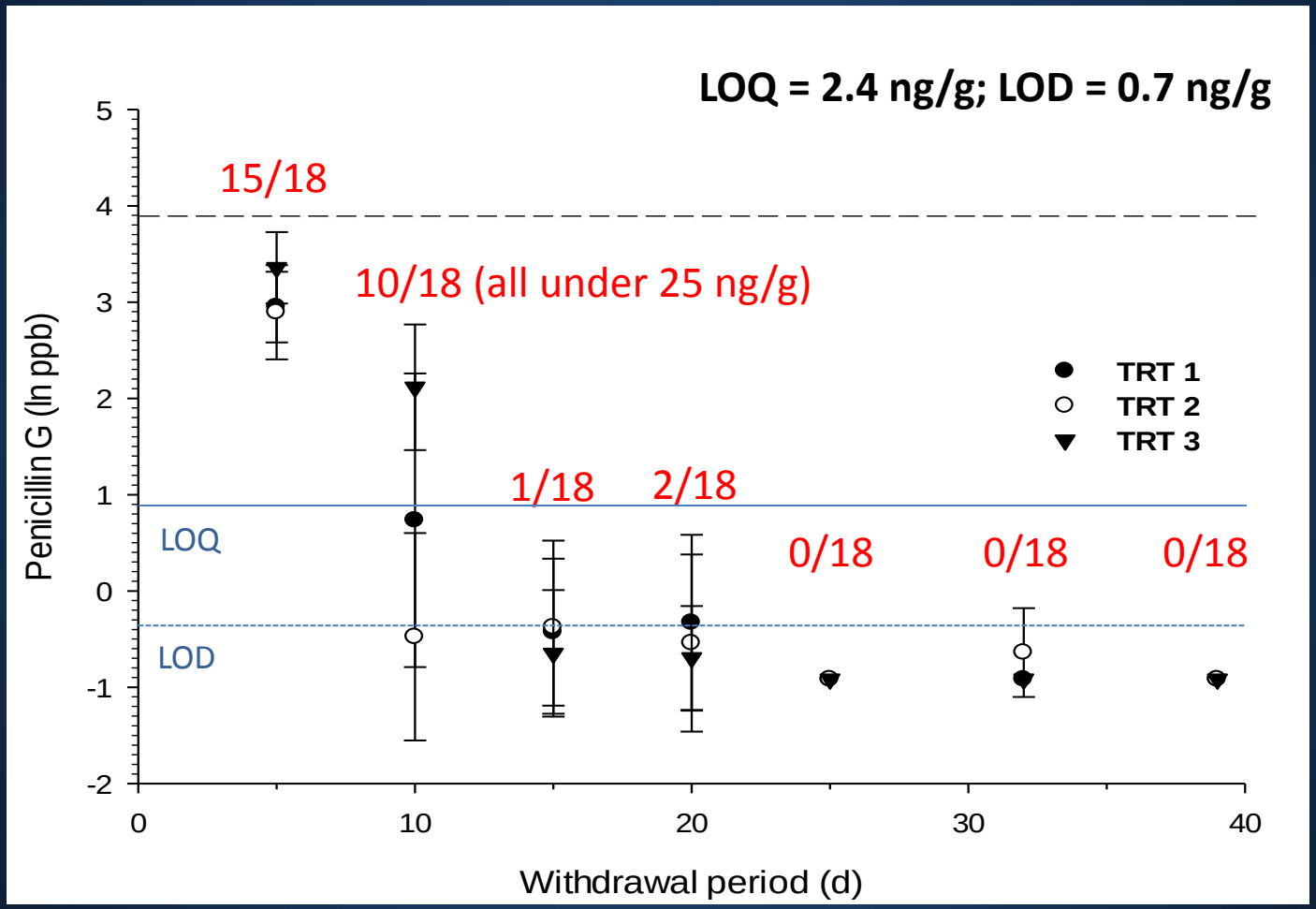
Quantitative Results: Skeletal Muscle



To Calculate a Withdrawal Period

- FDA Requires:
  - Use portion of depletion curve which is linear with time ($P < 0.05$)
  - Normal distribution of residue data
  - Constant variance over time
  - Time point should have at least “3 acceptable observations”
    - FDA suggests excluding data below the method LOQ or LOD
    - (EU includes data below the method LOQ or LOD, ie. ½ method LOD)

Quantitative Results: Skeletal Muscle



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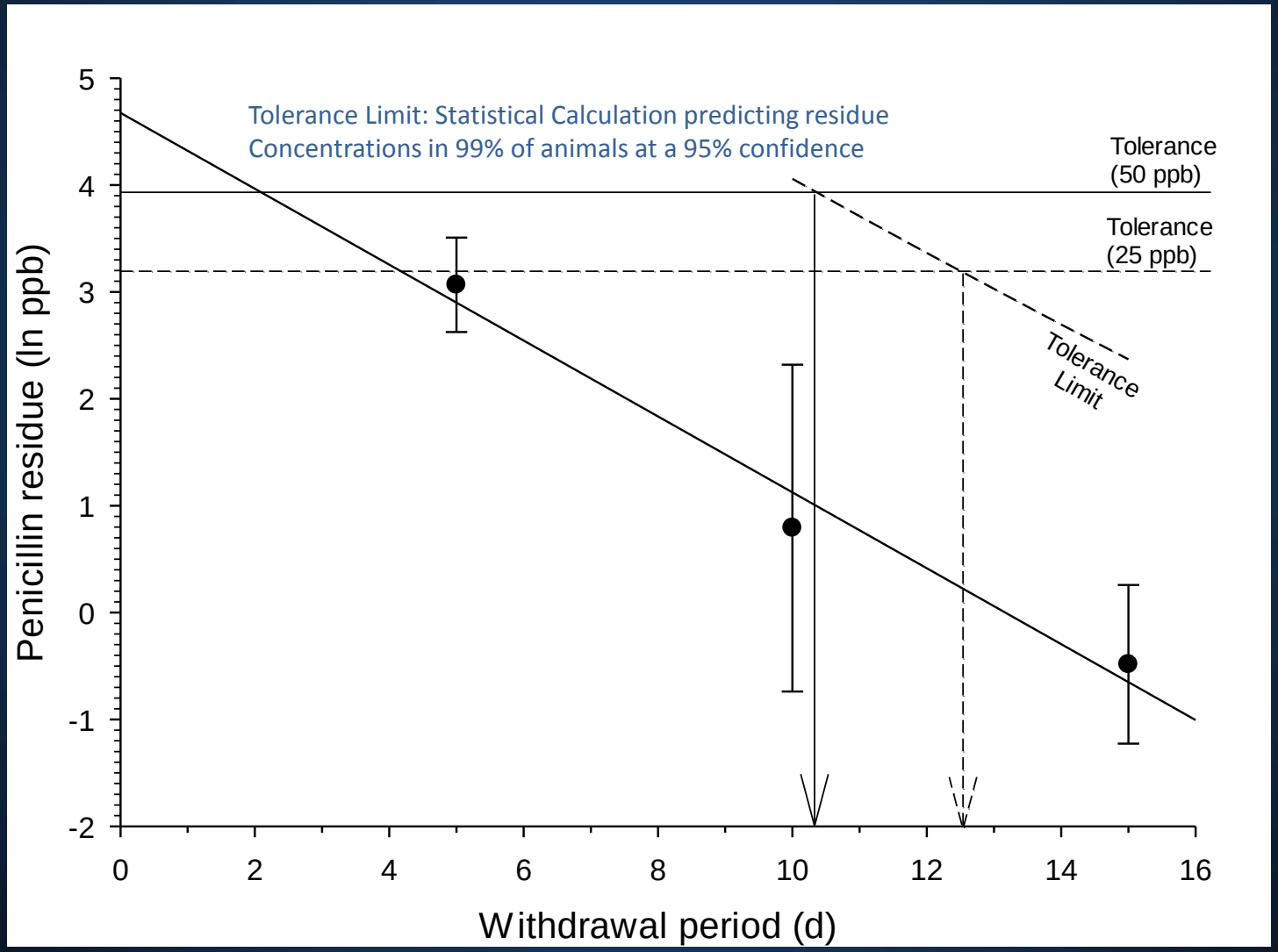

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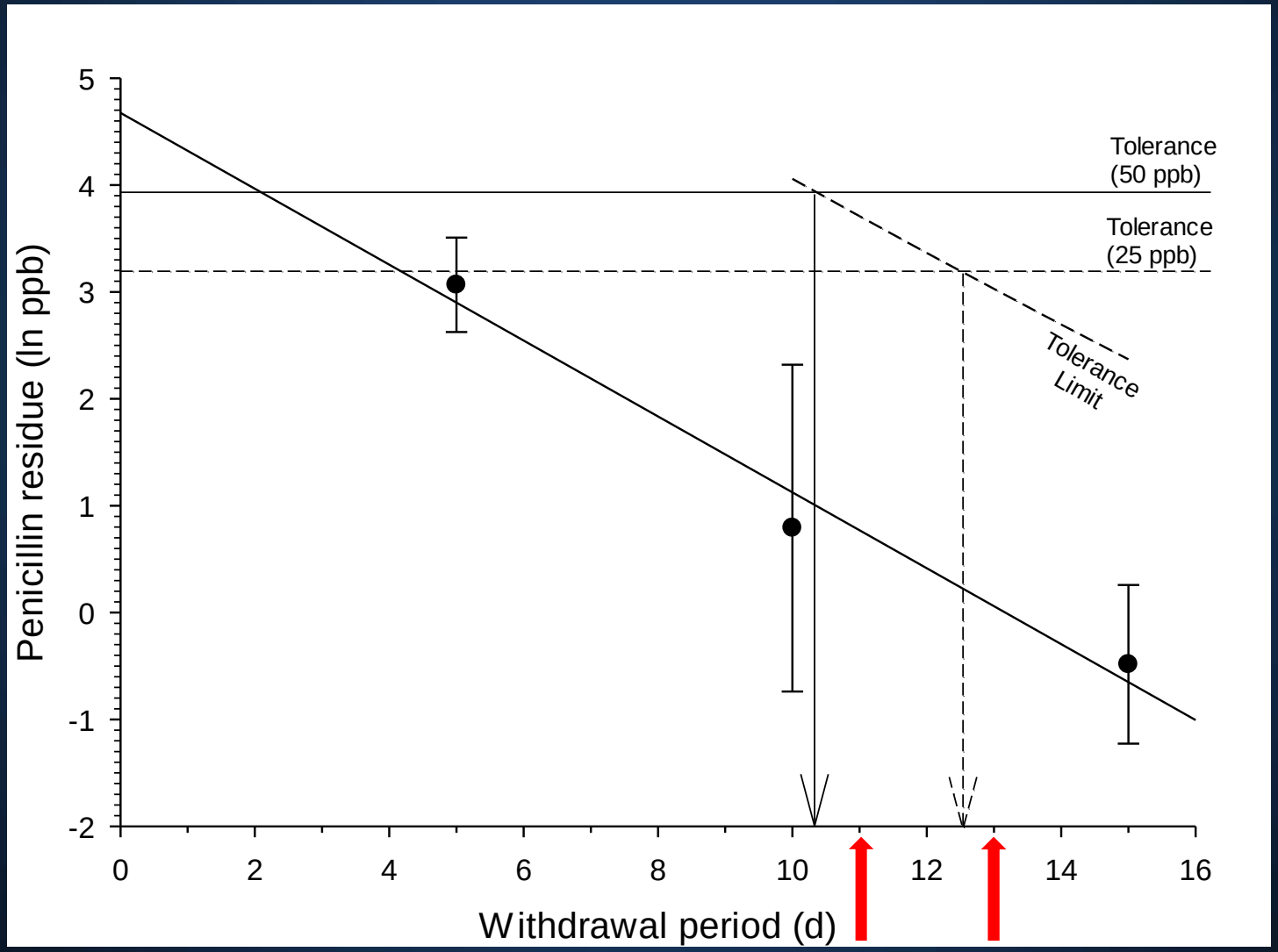
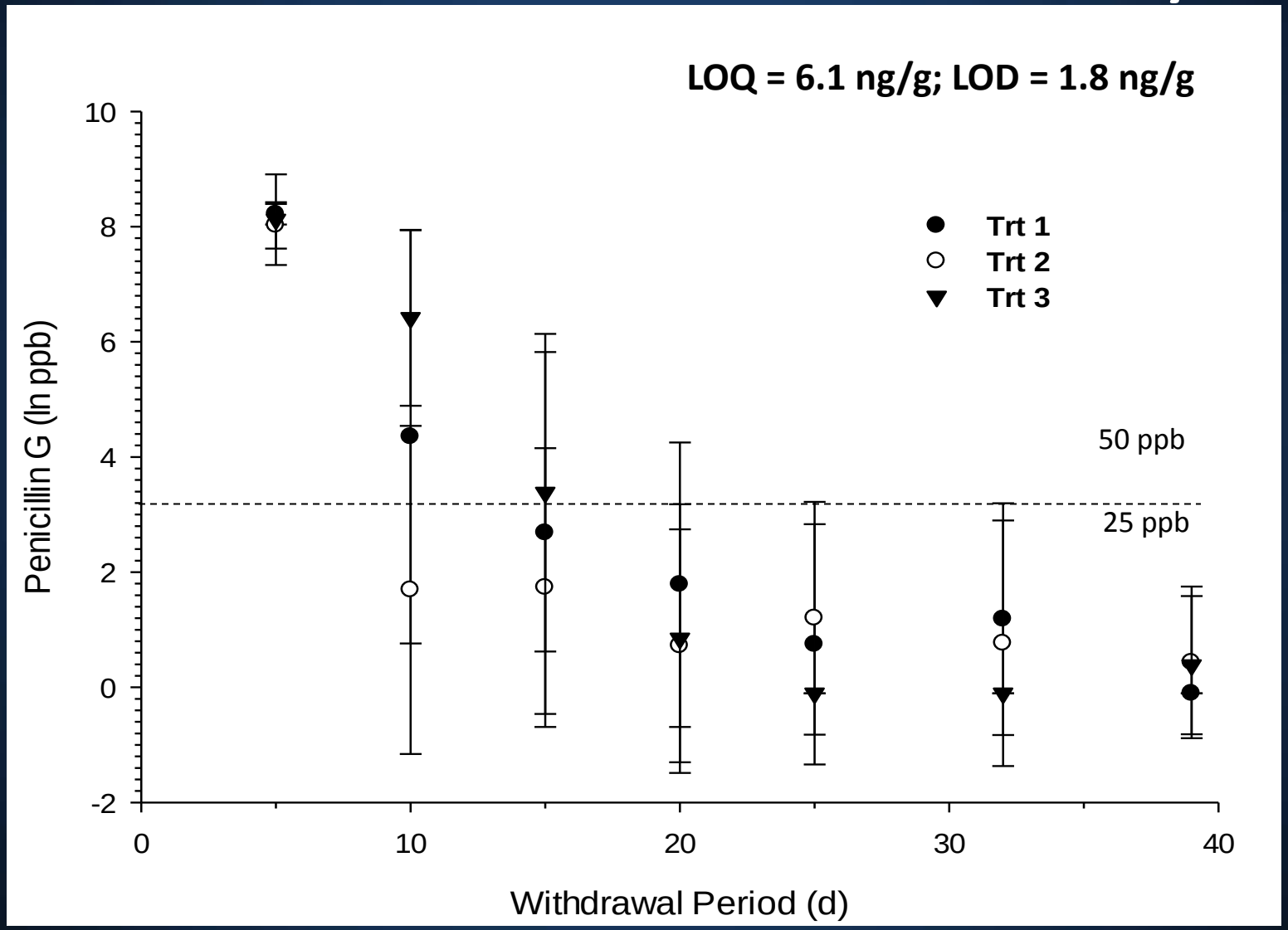


Quantitative Results: Kidney



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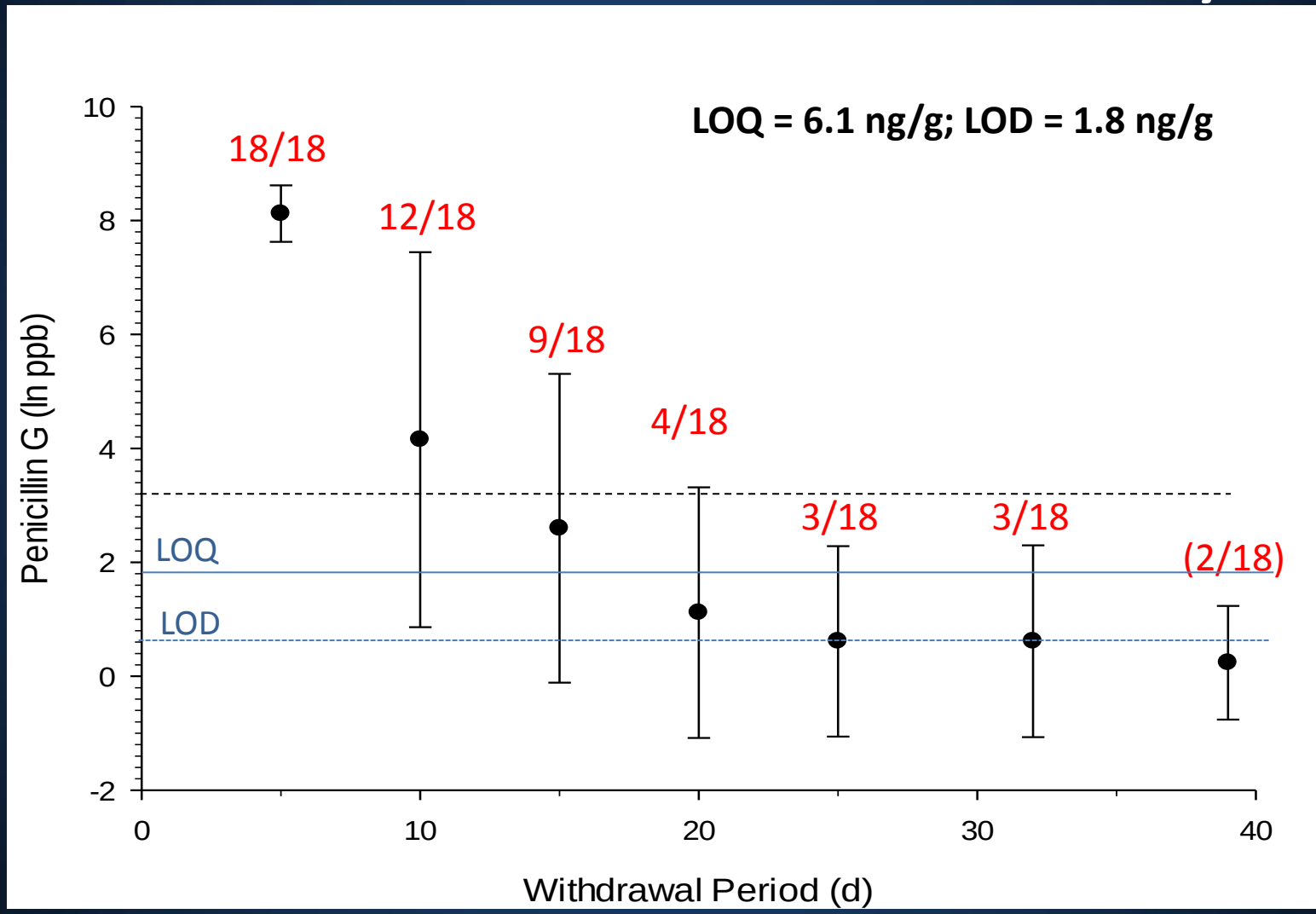

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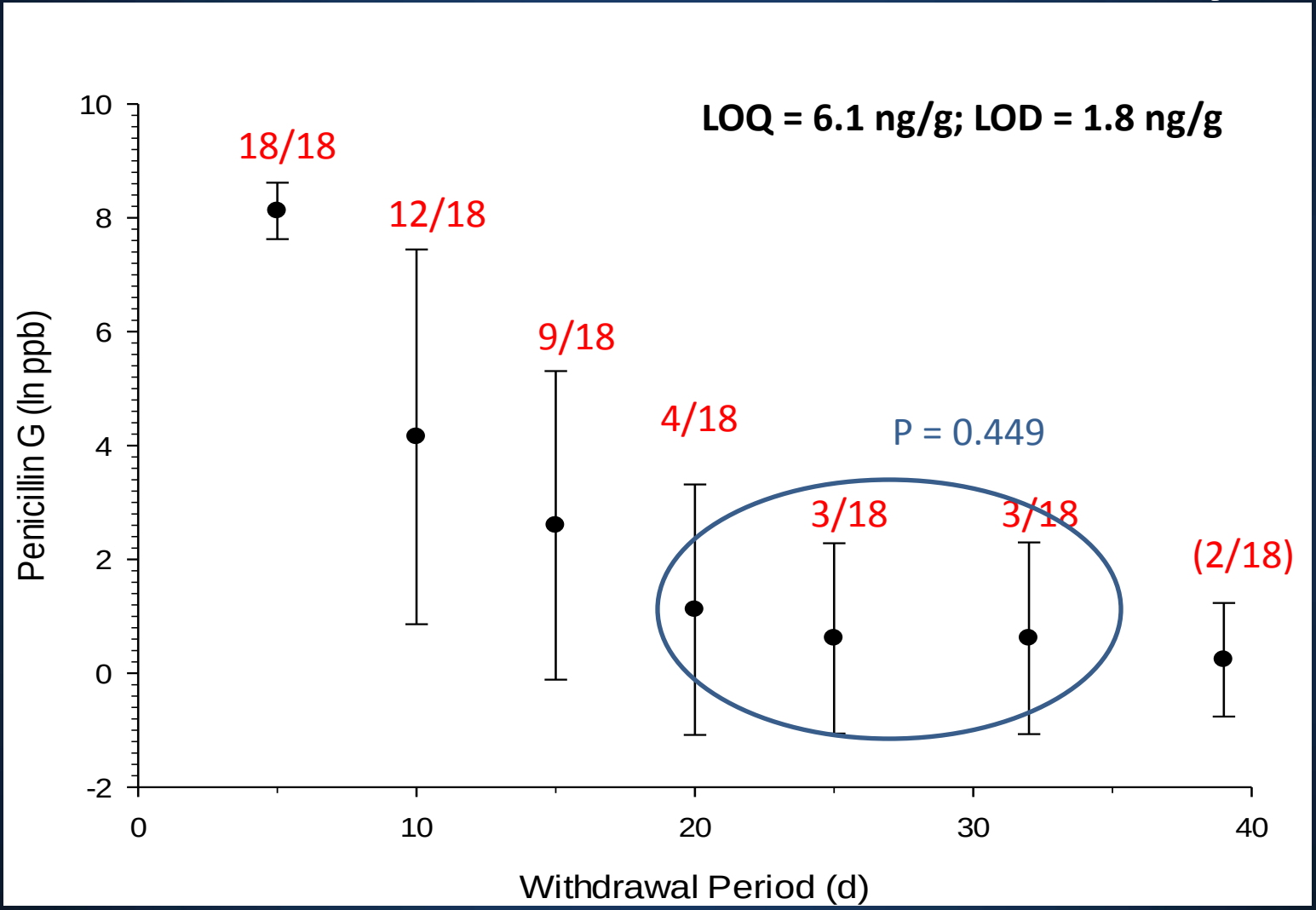

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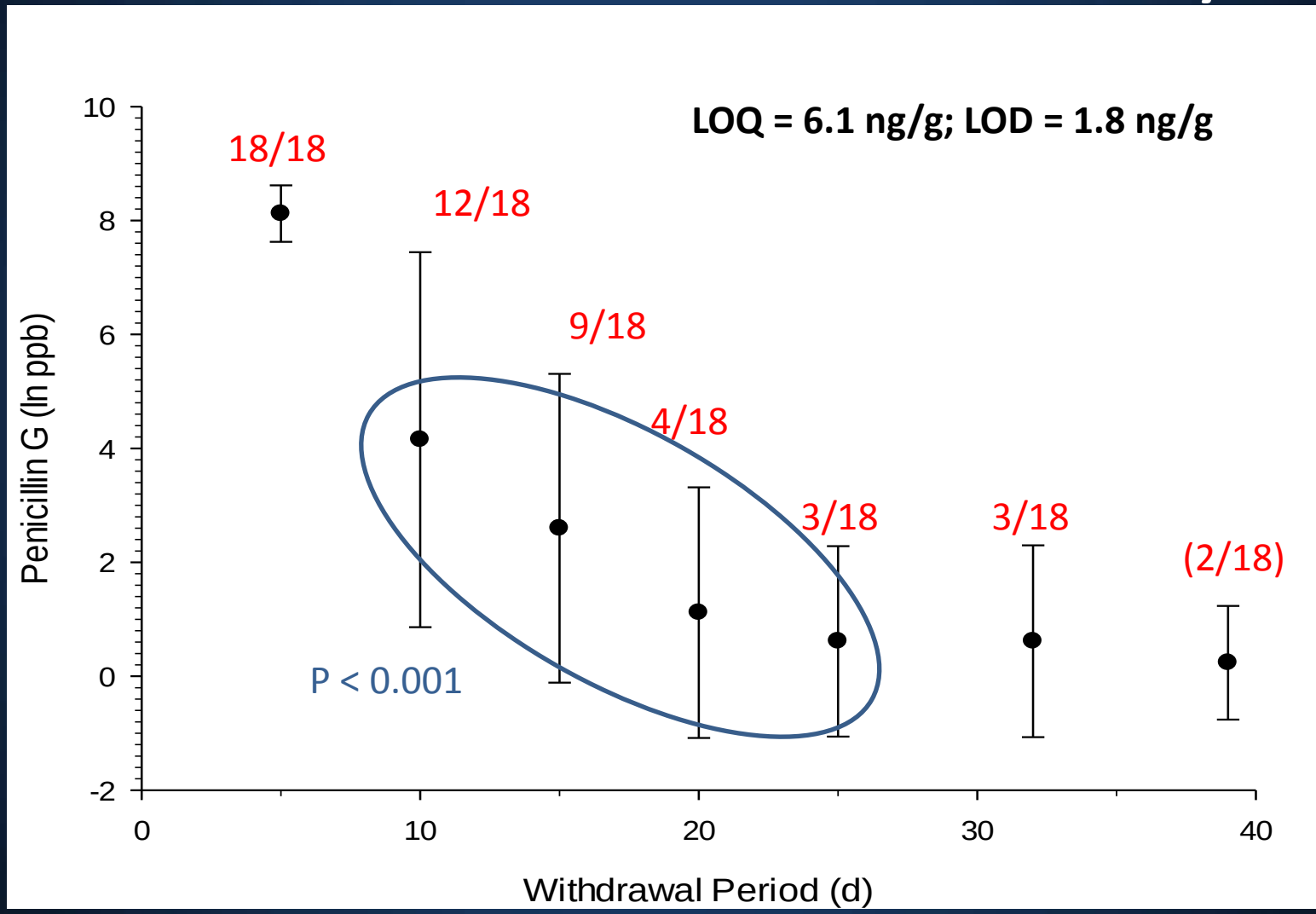
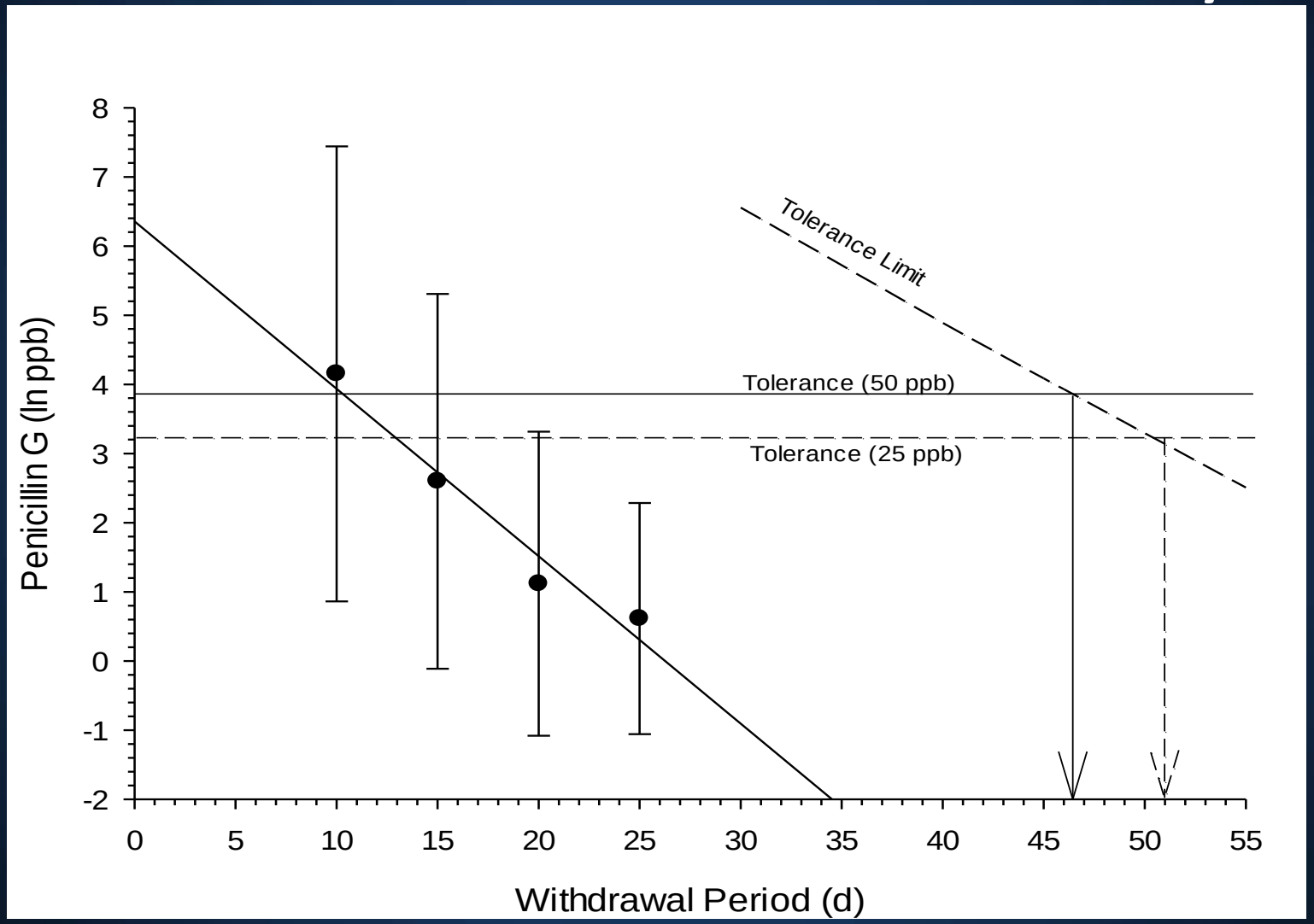


Quantitative Results: Kidney



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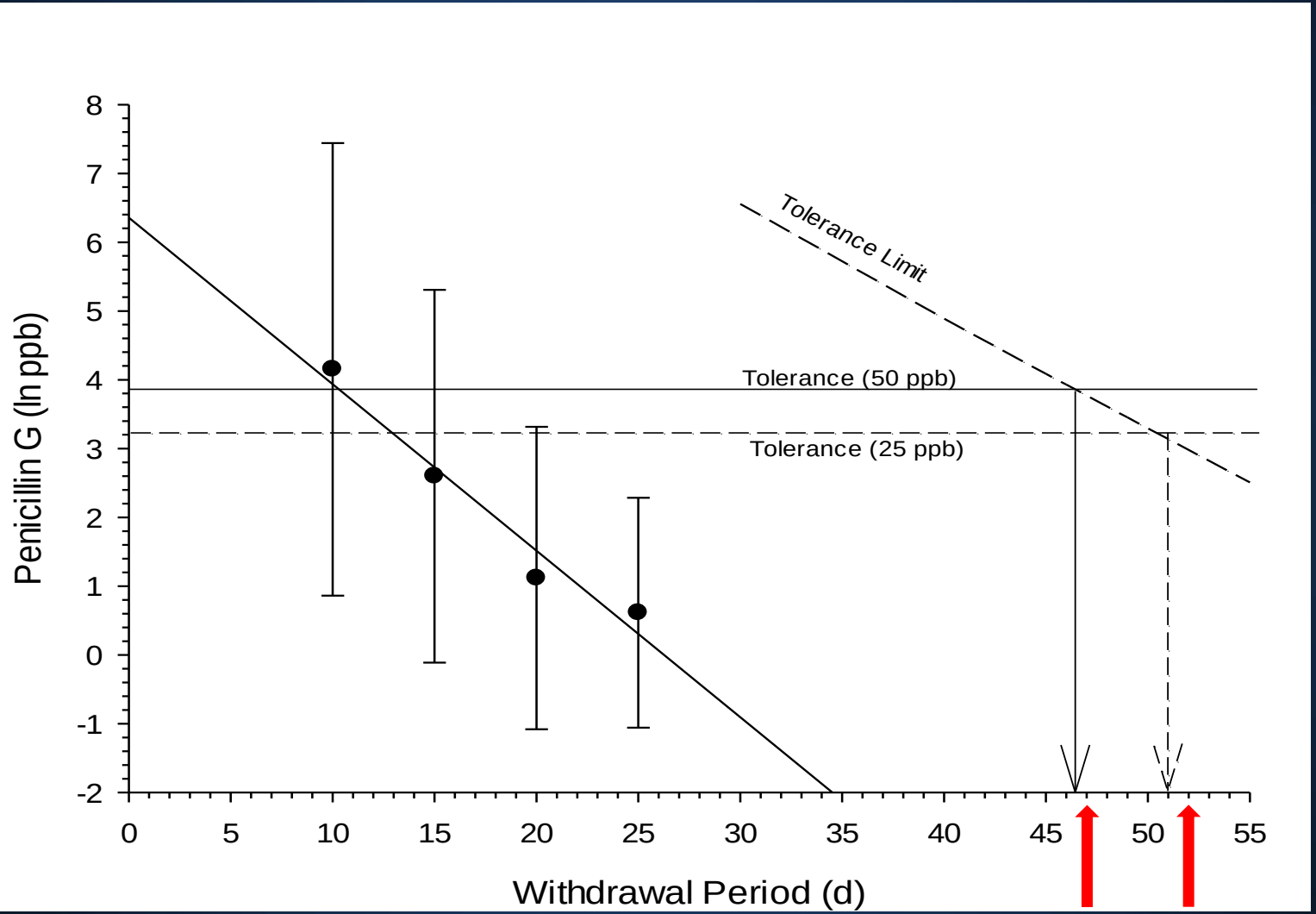

Conclusions

- Treatment pattern had little discernible effect on muscle or kidney penicillin-G residues
- Penicillin-G residues deplete rapidly from skeletal muscle
  - Estimated withdrawal days for skeletal muscle were 11 and 13 days (50 and 25 ppb MRL)
  - FARAD recommended 15-d withdrawal period is adequate
- Penicillin-G residues deplete slowly from kidney
  - Estimated withdrawal days for kidney were 47 and 52 days (50 and 25 ppb MRL)
  - FARAD recommended 15-d withdrawal period is inadequate

Recommendations

- Producer use of the Charm-KIS to screen urine from treated animals
  - $2 to $3 per assay
  - ~1500 set-up expenses
- Establish a kidney discard at the packing plant for penicillin-G treated sows