EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
QMS Plazomicin Immunoassay
DECISION SUMMARY

A. DEN Number:

DEN180030

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation of the QMS Plazomicin Immunoassay

C. Measurand:

Plazomicin

D. Type of Test:

Quantitative, homogenous particle-enhanced competitive turbidimetric immunoassay

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

QMS Plazomicin Immunoassay

G. Regulatory Information:

1. Regulation Section:

   21 CFR 862.3460

2. Classification:

   Class II, Special Controls

3. Product Code(s):

   QDR

4. Panel:

   Toxicology (91)

H. Indications for use:

1. Indication(s) for use:

   QMS Plazomicin Immunoassay:
   The QMS Plazomicin Immunoassay is intended for the quantitative determination of plazomicin in human K2-EDTA plasma on automated clinical chemistry analyzers. The assay results obtained should only be used as an aid in the management of patients with complicated urinary tract infection (cUTI) receiving plazomicin therapy.

   The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

2. Special conditions for use statement(s):

   For prescription use only.

3. Special instrument requirements:

   Performance is evaluated on the Beckman Coulter AU680 Chemistry Analyzer.

I. Device Description:

The QMS Plazomicin Immunoassay system is a homogeneous assay utilizing particle agglutination technology and it is based on the competitive binding principle. The assay consists of liquid ready-to-use reagents R1 (anti-plazomicin mouse monoclonal antibody) and R2 (plazomicin-coated microparticles).

J. Standard/Guidance Document Referenced:

- CLSI EP05-A3 – Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.
- CLSI EP06-A – Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.
- CLSI EP07-A2 – Interference Testing In Clinical Chemistry; Approved Guideline – Second Edition.
- CLSI EP14-A3 – Evaluation of Commutability of Processed Samples; Approved Guideline – Third Edition.
- CLSI EP15-A3 – User Verification of Precision and Estimation of Bias; Approved Guideline – Third Edition.
- CLSI EP17-A2 – Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition.
- CLSI EP25-A – Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

K. Test Principle:

The QMS Plazomicin Immunoassay is a homogeneous particle-enhanced turbidimetric immunoassay. The assay is based on competition between drug in the sample and drug coated onto microparticles for antibody binding sites of the anti-plazomicin antibody reagent (R1). The plazomicin-coated microparticle reagent (R2) is rapidly agglutinated in the presence of the anti-plazomicin antibody reagent and in the absence of any competing drug in the sample. The assay is based on the rate of absorbance change, which is measured photometrically. When a sample containing plazomicin is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent agglutination inhibition curve is obtained, where the maximum rate of agglutination occurs at the lowest sample plazomicin concentration and the lowest agglutination rate occurs at the highest sample plazomicin concentration.

L. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility:

Internal Precision Study

An internal precision study was conducted according to CLSI Document EP05-A3 by measuring trilevel quality control (QC) materials, spiked plasma samples, and patient plasma pools. Each spiked and QC material sample was tested in two replicates per run, two runs per day for 20 days (n=80 per sample). Patient pools were tested for two replicates per run, two runs per day for five days (n=20 per sample). The following results were obtained.

Sample Description	N	Mean (µg/mL)	Within-Run SD	Within-Run %CV	Between-Run SD	Between-Run %CV	Total-Run SD	Total-Run %CV
Quality Control 1	80	2.5	0.1	2%	0.1	4%	0.1	5%
Quality Control 2	80	8.1	0.2	2%	0.3	4%	0.3	4%
Quality Control 3	80	29.6	1.2	4%	0.8	3%	1.7	6%
Plasma Patient Pool 1	20	2.3	0.1	2%	0.1	4%	0.1	5%
Plasma Patient Pool 2	20	8.0	0.2	2%	0.2	2%	0.3	4%
Plasma Patient Pool 3	20	27.3	0.7	3%	0.9	3%	1.2	4%
Plasma Spiked 1	80	2.3	0.1	3%	0.1	4%	0.1	6%
Plasma Spiked 2	80	7.8	0.1	2%	0.3	4%	0.5	6%
Plasma Spiked 3	80	14.8	0.3	2%	0.8	5%	1.0	7%
Plasma Spiked 4	80	28.4	0.9	3%	1.1	4%	1.9	7%

Multi-Laboratory Precision:

The manufacturer also conducted precision studies at external sites, using tri-level quality control (QC) material, spiked plasma pools, and patient plasma pools. Each spiked and QC material sample was tested in two replicates per run, 2 runs per day for 20 days (n=80 per sample). Patient pools were tested for two replicates per run, 2 runs per day for 5 days (n=20 per sample). The multi-laboratory total repeatability and reproducibility were calculated from combining precision results across three sites. The overall precision study results are shown below:

Sample	N	Grand Mean (µg/mL)	Total Repeatability		Total Between-Run		Total Between-Day		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
QC1	240	2.5	0.1	2%	0.1	4%	0.0	1%	0.1	5%
QC 2	240	8.2	0.1	2%	0.2	3%	0.1	1%	0.3	4%
QC 3	240	29.6	0.9	3%	0.7	2%	0.6	2%	1.2	4%
Patient Pool 1	60	2.4	0.1	5%	0.0	0%	0.0	0%	0.2	7%
Patient Pool 2	60	8.4	0.4	4%	0.0	0%	0.2	2%	0.6	7%
Patient Pool 3	60	28.8	1.0	4%	0.5	2%	0.7	2%	2.4	8%
Spiked 1	240	2.4	0.1	3%	0.1	3%	0.1	2%	0.2	6%
Spiked 2	240	8.1	0.2	3%	0.2	3%	0.3	3%	0.5	6%
Spiked 3	240	15.4	0.6	4%	0.5	3%	0.4	3%	1.1	7%
Spiked 4	240	29.7	1.1	4%	0.8	3%	0.6	2%	2.2	8%

b. Linearity/assay reportable range:

The linearity of the QMS Plazomicin Immunoassay was assessed with two different types of samples; plazomicin-spiked human plasma K2-EDTA, and plazomicin patient pooled plasma K2 EDTA samples. For spiked samples, a high concentration plazomicin stock solution (approximately 1.0 mg/mL) was added to drug-free human K2-EDTA plasma to create a spiked sample with high plazomicin of 34.0 µg/mL. A patient pooled plasma sample was created by pooling patient plasma samples with high plazomicin concentrations to create a sample with concentration of 34.0 µg/mL. The high concentration spiked and pooled patient samples were then diluted with drug-free K2-EDTA plasma to create lower concentrations ranging from 0 µg/mL to 34.0 µg/mL. Nine (9) levels of samples, including concentrations between 0.3 µg/mL and 34.0 µg/mL, were tested in five replicates in a single run.

Regression analysis was performed between the measured mean plazomicin and assigned values for each dilution. The linear regression results from a representative kit lot are shown below:

Plasma K2EDTA (spiked)

Site	Slope	Intercept	r
A	1.04	0.32	1.00
B	0.98	0.36	1.00
C	1.02	0.34	1.00

Patient Pooled Plasma

Site	Slope	Intercept	r
A	0.98	0.23	1.00

These results support the claimed measuring range of 0.8 to 34.0 µg/mL, where the lower end of the measuring range is defined by the LoQ.

Analytical Recovery:
Accuracy by recovery was performed following CLSI standard EP15-A3. Two sample panels were prepared by spiking known amounts of plazomicin into negative human K2-EDTA plasma at concentrations throughout the assay range. Each sample was analyzed over a course of five days with four replicates each day for a total of 20 measurements. The mean measured concentration was compared to the gravimetric target concentration for percent recovery. Recovery ranged between 97% and 104% throughout the claimed measuring interval of the device (0.3 to 34.0 µg/mL)

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

A six-level kit of QMS Plazomicin Immunoassay Calibrators (A through F) is used to calibrate the assay. A three-level kit of QMS Plazomicin Immunoassay Controls (1 through 3) is used establish control limits. The kits of calibrators and controls are sold separately.

The QMS Plazomicin Immunoassay is traceable to plazomicin reference calibrators which are gravimetrically prepared with plazomicin sulfate in the human serum and value confirmed by LC-MS/MS.

d. *Detection limit:*

Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) studies were performed and analyzed as described below.

LoB Test Protocol
To estimate the LoB, (b) (4) K2-EDTA samples were tested in replicates of (b) (4) over (b) (4) days. Three reagent lots and one Beckman Coulter AU680 instrument was used. A total of (b) (4) replicates were obtained on a given

instrument/reagent lot combination. The LoB was determined to be (b) (4) ng/L, using the non-parametric option.

LoD Test Protocol

(b) (4) blank plasma K2-EDTA samples, spiked gravimetrically to (b) (4) of plazomicin, were tested in replicates of five in one run over three days. Three reagent lots and one Beckman Coulter AU680 instrument was used. A total of (b) (4) replicates were obtained on a given instrument/reagent lot combination. The LoD was determined to be 0.4 ug/mL using the parametric option.

LoQ Test Protocol

The LoQ of the assay was determined based on the guidelines from CLSI standard EP17- A02. The LoQ is defined as the lowest concentration which results in inter-assay precision ≤ 20%CV and bias ≤ 15%. The LoQ was determined to be ≤ 0.8 µg/mL for K2-EDTA plasma samples.

e. *Analytical specificity:*

Endogenous interference:

Interference studies were conducted using CLSI standard protocol EP07-A2 as a guideline. The following endogenous substances, when tested with the QMS Plazomicin Immunoassay at the concentrations indicated, resulted in less than or equal to 10% bias in detecting plazomicin. The results are shown below:

Endogenous Substances	Concentration
Albumin	6 g/dL
Unconjugated Bilirubin	30 mg/dL
Conjugated Bilirubin	30 mg/dL
Cholesterol	500 mg/dL
Creatinine	5 mg/dL
Gamma Globulin	10 g/dL
Human Anti-Mouse Antibody (HAMA) Type 1&2	20 ng/mL
Hemoglobin	1000 mg/dL
Rheumatoid Factor*	1080 IU/mL
Triglyceride	1000 mg/dL
Uric Acid	30 mg/dL

* Naturally existing substance

Exogenous interference

Specificity studies were conducted using CLSI standard protocol EP07-A2 as a guideline. Positive and negative interference effects were evaluated for clinically-

relevant concentrations of potential cross-reactants that are either concomitant medications or are structurally similar to plazomicin. None of the compounds, when added into the plasma pool containing 2.5 or 30 µg/mL plazomicin at the concentrations listed below, caused greater than or equal to 10% bias in plazomicin measurement. The results are shown below:

Concomitant Medication/ Structurally Similar Compounds	**Concentration (µg/mL)**
Acetyl-Salicylic Acid	750
Amikacin	200
Amiodarone	50
Amlodipine	5
Amphotericin	20
Ampicillin/ Sulbactam*	500
	500
Azithromycin	50
Aztreonam	750
Carvedilol	5
Cefazolin	1250
Cefepime	500
Ceftaroline fosamil	100
Ceftazidime	550
Ceftazidime/ Avibactam*	300
	100
Ceftolozane/ Tazobactam*	300
	100
Ceftriaxone sodium	1000
Ciprofloxacin	100
Cisatracurium	20
Laudanosine (Cisatracurium metabolite)	3.5
MQA metabolite (Cisatracurium metabolite)	20
Clonidine	5
Colistimethate Sodium (Colistin)	100
Daptomycin	700
Dexmedetomidine	5
Diltiazem hydrochloride	20
Dobutamine hydrochloride	20
Dopamine hydrochloride	5
Doripenem	100
Enoxaparin	200
Epinephrine hydrochloride	20
Ertapenem	500
Erythromycin	100
Esmolol	20
Esomeprazole	20
Ethacrynic Acid	100
Fentanyl	2

Concomitant Medication/ Structurally Similar Compounds	Concentration (µg/mL)
Fluconazole	100
Fondaparinux	20
Fosfomycin	100
Furosemide	100
Gentamicin	50
Haloperidol	20
Hydrocortisone	20
Imipenem/ Cilastatin*	300
	300
Insulin human regular	20
Kanamycin B	100
Levetiracetam	300
Levofloxacin	100
Linezolid	100
Lorazepam	2
Meropenem	600
Metamizole (Dipyrone)	100
Metformin	100
Methylprednisolone sodium succinate	100
Metoclopramide	2
Metoprolol	20
Metronidazole	300
Micafungin	100
Midazolam	5
Morphine sulfate	20
Nafcillin	100
N-desethylamiodarone (metabolite of Amiodarone)	20
Netilmicin	100
Norepinephrine Bitartrate (Noradrenaline)	5
Omeprazole	20
Pantoprazole	20
Paracetamol (acetaminophen)	500
Phenylephrine hydrochloride	5
Phenytoin (Fosphenytoin IV)	20
Phenytoin sodium	50
Piperacillin	1300
Propofol	100
Ramipril	5
Ranitidine	20
Sisomicin	20
Spectinomycin	500
Streptomycin	300
Tamsulosin	5
Tazobactam	200

Concomitant Medication/ Structurally Similar Compounds	Concentration (µg/mL)
Tedizolid	50
Tigecycline	20
Tobramycin	100
Tramadol	20
Vancomycin	200
Vasopressin	5
Vecuronium bromide	20

* Tested as combination drugs

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison study:

A total of 134 K2-EDTA plasma samples from patients taking plazomicin, within the measuring range of the QMS Plazomicin Immunoassay, were measured by the QMS Plazomicin Immunoassay in singlicate, over the course of 4 to 5 days and across 3 test laboratories. Data from the candidate device were compared with results from a validated LC-MS/MS method using Passing-Bablok regression analysis (similar data were obtained using a second lot of reagents; not shown).

QMS Plazomicin Immunoassay vs. Comparator LC-MS/MS Method

N	Deming		Passing-Bablok		Correlation (R)
	Slope	Intercept	Slope	Intercept	
134	1.007	0.72	1.039	0.41	0.983

b. Matrix comparison:

Not applicable. The claimed matrix is K2-EDTA human plasma.

3. Clinical studies:

A clinical study was conducted to support approval of Plazomicin that included (b) (4) randomized adults hospitalized with Complicate Urinary Tract Infections (cUTI), in a multinational, double-blind, noninferiority trial comparing plazomicin to (b) (4) No therapeutic drug monitoring (TDM) was used to adjust patient dosing in the drug trial. However, data from the trial were retrospectively correlated to drug concentrations determined by the candidate device to establish the likelihood of an increase in nephrotoxicity associated with plazomicin trough values greater than (b) (4) in patients with renal impairment. As such, TDM is recommended in the plazomicin drug label for

patients with renal impairment. The candidate device was evaluated based on this recommended plasma trough concentration of (b) (4) and determined to have adequate performance characteristics for plazomicin TDM.

4. Clinical cut-off:

   Not applicable.

5. Expected values/Reference range:

   Not applicable.

M. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

N. Identified Risks and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
Incorrect test results	General controls and special controls (1) and (2)
Incorrect interpretation of test results	General controls and special controls (1) and (2)

O. Benefit/Risk Analysis:

Summary of the Assessment of the Benefit
For the Proposed Indications for Use

Plazomicin is an intravenous aminoglycoside antibiotic indicated for treatment of complicated Urinary Tract Infections (cUTI) including (b) (4) Due to evidence of increased nephrotoxicity (i.e. creatinine increase of ≥ 0.5 mg/dL from baseline) in the drug trials, plazomicin exposure-response analysis was performed which targeted a trough concentration of (b) (4) to prompt adjustment of the plazomicin dose regimen prior to a second dose. Dosing adjustment of patients over this trough concentration, based on therapeutic drug monitoring (TDM), involves extending dosing intervals by 1.5-fold (i.e., from every 24 hours to every 36 hours or from every 48 hours to every 72 hours) for moderate to severe renal impairment patients (i.e. creatinine clearance <90 and ≥ 15 mL/min). Since the drug label recommends dosing adjustments based on TDM to decrease the incidence of nephrotoxicity, there is a clear clinical need for a plazomicin TDM device.

Summary of the Assessment of Risk
For the Proposed Indications for Use

The risk of a falsely elevated plazomicin result is potentially decreased efficacy of the drug due to unnecessary lengthening of the dosing interval. Loss of drug efficacy may present in clinical deterioration leading to a change in antimicrobial regimen (in most cases changing to a broader regimen or possibly a more toxic regimen), clinical deterioration leading to longer

hospitalization and possible clinical complications associated with longer hospitalization, and clinical deterioration leading to significant morbidity or even mortality. Therapeutic drug monitoring (TDM) was not used during the clinical trial for plazomicin. However, based on the observed levels of plazomicin in the majority of subjects in the clinical study who still showed adequate efficacy, it is uncertain that lengthening the dosing interval will result in compromised efficacy in moderately to severely renal impaired subjects given that the drug is primarily excreted through the urine; reductions in efficacy would likely be relative to the degree of bias of the false result.

The risk of a falsely low plazomicin result is a missed indicator to avoid potential nephrotoxicity in complicated UTI patients by increasing the dosing interval, as falsely low results may lead the clinician to erroneously believe that the plazomicin trough is below the threshold level (≤3 μg/mL) associated with an increased incidence of nephrotoxicity. Therefore, a falsely low plazomicin result could lead to a clinician incorrectly maintaining the dosing interval for cUTI patients. According to the exposure response analysis (as described in the drug label), the incidence of nephrotoxicity (defined as serum creatinine increase of 0.5 mg/dL from baseline) was higher in patients with plazomicin trough concentration ≥ 3μ/mL (36%, 10/28) compared to patients with plazomicin trough concentration < 3 μg/mL (5%, 11/215). Acute kidney injury is a known risk factor for the aminoglycoside class of drugs. Typically, renal parameters such as serum creatinine and urine output are monitored carefully during aminoglycoside administration, especially in patients with underlying moderate or severe kidney insufficiency. Monitoring serum creatinine and urine output may serve as a mitigation to the potential for nephrotoxicity due to an erroneous assay result. Additionally, although a creatinine increase of 0.5 mg/dL may indicate acute kidney injury, the injury may be reversible after discontinuation of the drug.

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use

The benefit of the proposed assay does not outweigh the risk.

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use

Overall, the probable benefits outweigh the probable risks of this device after considering the mitigations provided by the special controls in addition to the general controls.

Patient Perspectives:

Plazomicin is reserved for use in patients with complicated urinary tract infection who have limited or no alternative treatment options. FDA considered the clinical need for this device in this patient population.

P. Conclusion:

The information provided in this de novo submission is sufficient to classify this device into class II under regulation 21 CFR 862.3460. FDA believes that the special controls, in

combination with the general controls provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QDR
Device Type: Plazomicin test system
Class: II (special controls)
Regulation: 862.3460

a) *Identification.*
A plazomicin test system is a device intended to measure plazomicin in human specimens. Measurements obtained by this device are used in monitoring levels of plazomicin to ensure appropriate therapy in patients with complicated urinary tract infection.

b) *Classification*. Class II (special controls). A plazomicin test system must comply with the following special controls:

(1) Design verification and validation must include the following:
   (i) Precision study data that demonstrates clinically appropriate precision of the plazomicin test system, as determined by FDA. Precision studies must include a minimum of three samples containing different concentrations of plazomicin, including near medical decision points throughout the expected therapeutic range of plazomicin. Samples near the medical decision points must be clinical specimens collected from patients taking plazomicin.
   (ii) Method comparison data that demonstrates clinically appropriate accuracy of the plazomicin test system, as determined by FDA. Method comparison data must be collected at a minimum of three laboratory sites.
   (iii) Data from studies appropriate to demonstrate that the device is free from clinically significant interference from co-administered medications that are used in patients with complicated urinary tract infection, as determined by FDA.

(2) The device's 809.10 labeling must include a warning statement that reads: "The assay should only be used in conjunction with information available from clinical evaluations and other diagnostic procedures."