Variations in Pharmacokinetic-Pharmacodynamic Target Value Across Minimum Inhibitory Concentrations and Its Impact on Determination of Susceptibility Test Interpretive Criteria

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Introduction

• The determination of an antibacterial drug's Susceptibility Test Interpretive Criteria (STIC), which classifies bacterial isolates as susceptible to a drug or not, is based on clinical, microbiological, and pharmacokinetic-pharmacodynamic (PK-PD) data.

• Probability of Target Attainment (PTA) analysis, which may play a pivotal or supportive role in determination of a STIC, is heavily dependent on the PK-PD target values determined from animal PK-PD studies.

• Animal PK-PD study findings are utilized to identify a PK-PD index (Cmax/MIC, AUC/MIC, or %T>MIC) and a PK-PD target value, which is then used to extrapolate a drug's activity up to the determination of the STIC.

Specific Objectives:

1) To analyze relationships between PK-PD target values and MIC values for each bacterial species (Referred to as: PK-PD Target Value vs. MIC Analysis)
2) To evaluate the ranges of MICs for isolates used in animal PK-PD studies and their comparison with the proposed/target STICs in their respective NDA (Referred to as: MIC Range vs. Proposed STIC Analysis)

Methods

| Dataset Preparation Steps	Dataset

Identify antibacterial drugs which received an FDA approval between 2010 and 2019 ↓ Remove combination drug ↓ Collect data from animal PK/PD studies	• 10 single-drug NDAs that included 22 animal PK-PD studies
	• PK-PD index usage:
	  • 2 drugs used %T>MIC
	  • 8 drugs used AUC/MIC (7 drugs with adequate data for analysis)

Analysis Steps

PK-PD Target Value vs. MIC Analysis: Drugs with AUC/MIC as PK-PD index were selected as it was the most used PK-PD index. PK-PD target values were compiled and grouped based on drug, bacterial species, and PD target (e.g., net-stasis), i.e., DBPT group. To allow comparisons across NDAs, AUC/MIC values were normalized by dividing each AUC/MIC value by the average AUC/MIC within each DBPT group and normalized AUC/MIC values were compared across DBPT groups.

MIC Range vs. Proposed STIC Analysis: Data from all NDAs were used and MIC values for each bacterial isolate were normalized by the number of 2-fold dilutions between the isolate MIC and the Applicant's proposed STIC for the respective drug-bacterial group, i.e., DB group. Normalized values from each DB group were compared to the highest MIC values evaluated in the animal PK-PD studies.

Results: PK-PD Target Value vs. MIC Analysis
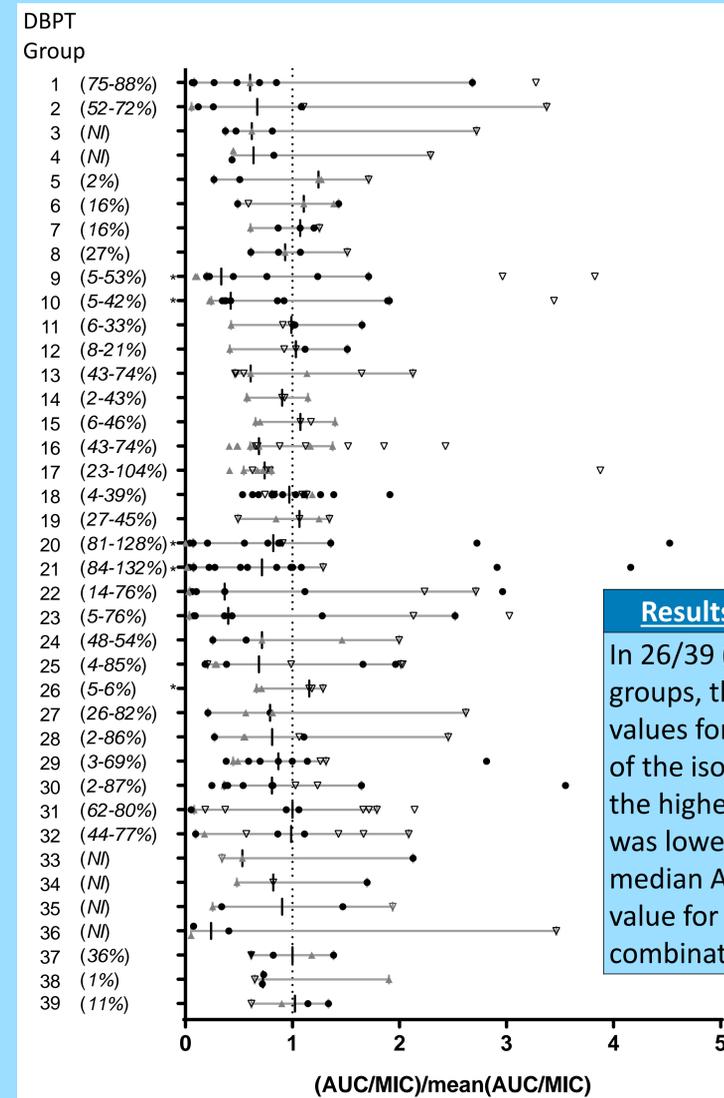
Results Summary

In 26/39 (66.7%) DBPT groups, the AUC/MIC values for at least one of the isolates with the highest MIC value was lower than the median AUC/MIC value for that combination.

Figure 1. Distribution of normalized AUC/MIC values across DBPT groups. For cross-study comparison, the value of AUC/MIC for each isolate divided by the mean AUC/MIC value for all isolates within each DBPT group was plotted. The DBPT group is a unique combination of a drug, bacterial species, and PK-PD target. The short vertical line represents the median value for each DBPT group. The horizontal line in each DBPT group represents the 95% confidence interval around the mean for each group. A dotted line at 1 represents the expected median value. Grey triangles and open downward facing triangles indicate values from bacterial isolates with the highest and lowest MIC, respectively. * indicates the AUC/MIC for isolate with the highest MIC in each DBPT group was lower than the 95% CI. The numbers in italics following the DBPT group number represent the range of CV% of AUC/MIC values for the MIC values within the DBPT group. NI indicates it was not possible to calculate any CV% for AUC/MIC values for any MICs within the DBPT group.

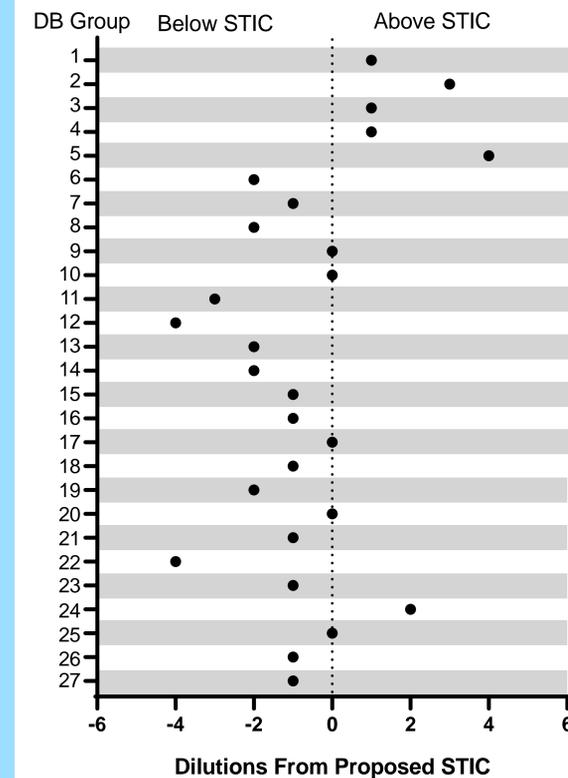## Results: MIC Range vs. Proposed STIC Analysis

Figure 2. Comparison of Highest MIC to the Proposed Respective STIC per Experiment Group. The highest MIC tested from each bacterial species was plotted as the number of 2-fold dilutions away from the Applicant's proposed STIC. Only bacterial species for which the Applicant proposed a STIC were included. DB Group – a unique combination of a drug and bacterial species.

Results Summary

Category	Number of Drugs
Below STIC	16 (59%)
At STIC	5 (19%)
Above STIC	6 (22%)

Conclusion

• AUC/MIC values were variable over a range of MIC values and for most of the bacterial species examined, the AUC/MIC values tended to decrease with an increase of MIC values.

• The range of MICs tested in most NDAs did not include the respective Applicant-proposed STIC, resulting in a potential knowledge gap in supporting the drug's activity.

• These findings suggest that considerations towards selection of bacterial isolates and expanding MIC range for animal PK-PD study appears to be of value as such an approach may allow better informed trend analysis between normalized PK-PD target values and MIC values at individual drug level.

Acknowledgement