How VetCAST will define veterinary clinical breakpoints

VetCAST
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VETCAST modus operandi: A risk analysis approach

Risk assessment

Risk management

Risk communication

Cut-offs

BP for a Substance often shared by several companies
BP for a given substance may have a large impact on the market of alternative AMDs

Independency
Transparency, Consensus

Science

Decision

Harmonisation

CLSI/EUCAST/CEESA...

Academia/Industry/CEESA/
Development of a (clinical) Breakpoint (BP)

- Clinical BP
  - $C_0_{W_T}$
  - $E_C O_F F_S$
  - $C_0_{P_K/P_D}$
  - $C_0_{C_L}$

Some issues to discuss
The setting of a PK/PD cutoff
The setting of a PK/PD CO

Step 1
Selection of a PK/PD index predictive of clinical efficacy and/or prevention of resistance

Step 2
Determination of the critical value (size) of the selected PK/PD index

Step 3
Computation, for a given animal species and for all possible (not probable) MICs of the percentage (proportion) of animals able to achieve the critical value of the selected PK/PD index (computation of so-called Target Attainment Rates (or TAR))
Step 1: Selection of a PK/PD index

- $\frac{fAUC_{24h}}{MIC}$
- $\frac{fC_{max}}{MIC}$
- $fT>MIC$

Specific veterinary issues:
- many modalities of oral drug administration
- Long-acting formulations
The case of $fT>MIC$

- For a given dose, $T>MIC$ is dependent on the shape of the curve and its variability
  - Influence of modalities of administration
    - E.g. dosage interval
    - Top feeding vs. pump
  - Influence of the formulation
    - Short vs LA formulations
Human vs. veterinary medicine: the case of oral administration
T>MIC for a single dose of a LA formulation vs. daily dose for the same drug (same total dose)
T>MIC for 40-50% of the dosing interval: Daily dosing vs. long-acting drug

Both treatments ensure plasma concentrations above MIC for 50% of the dosing interval (1 or 14 days) but they are not equivalent.
T>MIC: possible options

• Likely impossible to release several BP for different modalities of drug administration for a given substance
• Select an other PK/PD index not dependent of the shape of the internal exposure
AUC/MIC: an universal PK/PD index for veterinary medicine?

It is quoted: For drugs like the b-lactams where the efficacy generally have been found to be correlated to $T_{MIC}$, the best PK/PD index shifts toward AUC/MIC dependence as the half-life increase, as seen in patients with a reduced renal function e.g., elderly or neonates.
The setting of a PK/PD CO

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Step 3
Computation, for a given animal species and for all possible (not probable) MICs of the percentage (proportion) of animals able to achieve the critical value of the selected PK/PD index (computation of so-called Target Attainment Rates (or TAR))
Step 3: Computation of the TAR (%) for the critical value of the selected index for the different possible MICs (TAR are stratified by MIC)

PK raw data (meta-analysis)

Population modeling

Monte Carlo Simulation (n=5000 animals)

TAR(%)
A Vetcast guideline to collect, handle, analyse, report and archive pharmacokinetic data for VetCAST
Vetcast guideline (draft version 1)

• Collection, archiving and analysis AND reporting of individual pharmacokinetic (PK) data

• The VetCAST modellers will use the latest version of Phoenix© NLME (Pharsight Corporation; 5520 Dillard Drive, Suite 260 Cary, North Carolina 27518) for PPK modelling and Monte Carlo simulations, following population estimations, and Oracle Crystal Ball will be used for other Monte Carlo simulations when required.

• The provisions made to guarantee the confidentiality and safety of data shared by drug companies volunteering to help VetCAST.
A VETCAST Pop PK/PD population workshop for those who are motivated to compute PK/PD cutoffs following the Vetcast SOP
Development of a (clinical) Breakpoint (BP)

Clinical BP

- $CO_{WT}$
- $ECOFFs$
- $CO_{PK/PD}$
- $CO_{CL}$
Clinical breakpoint vs ECOFF

Fig. 1. Ciprofloxacin MIC distribution of *Escherichia coli* isolates (http://www.eucast.org). Epidemiological cut-off (ECOFF) values and clinical susceptible (S) and resistant (R) breakpoints from CLSI and EUCAST committees are indicated. The clinically susceptible population (below the clinical susceptible breakpoint) includes part of the microbiologically resistant population (low-level resistant bacteria, presumably expressing *qnr*-like genes or other PMQR mechanisms or first step *gyrA* mutations) and the wild-type population (below the ECOFF value and presumably without resistance mechanisms). The clinically resistant population (beyond the clinical resistant breakpoint) includes isolates with high-level resistance mechanisms (most probably double-step *gyrA* mutants or a combination of *gyrA* with *parC* mutations).
The clinical CO (CO\textsubscript{CL})

The CO\textsubscript{CL} is based upon the collection of isolates obtained during the clinical effectiveness studies.

CO\textsubscript{CL} reflects the upper limit of the MIC values associated with a high likelihood of clinical success [probability of cure (POC)].

There is no set method for establishing the CO\textsubscript{CL}, and no hard target for POC.
Issues for to determine the clinical cutoff

• No *public* data relating MIC to outcome
  – Rem: EMA, not FDA require to sample isolates during clinical trials

• An assumption that needs to be consolidated
  – It exist a relationship between MIC and clinical outcome or between AST results (S,I,R) and clinical outcomes
MIC distributions

Q for clinician: what is the clinical cutoff?

Diagramtitel

Clinical CO=ECOFF
MIC distribution: What is the clinical cutoff?
Assumption: MIC vs. clinical cure (POC)?

Sensitive strains (n=160) for a quinolone
## AST results and clinical outcomes

(Merged results for 4 AMDs from 3 different classes)

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>(n=364)</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>(n=23)</td>
</tr>
<tr>
<td><strong>R</strong></td>
<td>(n=17)</td>
</tr>
</tbody>
</table>

Pulmonary conditions; Pasteurella multocida and Manheimia haemolytica
MIC distribution: What is the clinical cutoff?

- POC
- CLSI: Window & MaxDiff
- ECOFF
- Clinical CO
Clinical cutoff and clinical breakpoint

• Curative vs. metaphylactic treatment
  – Same BP for the two conditions?
    • Quid of the inoculum effect?
Diameters vs. MICs

• Diameter is a surrogate of MIC
• What is the value of this surrogate?
  – Convenience
  – Reliability?
  – For harmonisation
For a quinolone: MIC vs. Diameters

For a quinolone: MIC vs. Diameters

\[ y = -79.464x + 41.618 \]

\[ R^2 = 0.2876 \]

MIC should be the independent variable when discussing this relationship.
Impact of VETCAST Breakpoint on Microbiology Laboratories and Antimicrobial Stewardship Programs

Impact of CLSI Breakpoint Changes on Microbiology Laboratories and Antimicrobial Stewardship Programs

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Others issue

• MIC in serum vs MHB
  – Tulathromycin (as for azithromycin):
    • MIC in serum 50 times lower than in MHB
    • MIC in MHB much higher than in vivo plasma concentration
    • MIC in serum consistent with in vivo plasma con
  – Oxytetracycline:
    • MIC in serum 25 times higher than in MHB
Conclusion

• More data are needed
  – Epidemiology
  – For population PK meta-analysis
  – To establish the clinical cutoff
  – To assess the value of diameters

• Consequences of our activity should be anticipated in terms of stewardship, epidemiology, financial cost......