Minutes of VetCAST meeting in Schiphol Airport, Amsterdam, 27th of March 2017, 10am-4pm.

Attending: Dik Mevius (DM), Renata Karpiskova, Pavla Novotna, Hana Pratova, Andrea Fessler, Heike Kaspar, Jürgen Wallmann, Simone Dore, Stefano Lollai (SL), Christophe Hugnet, Alain Bousquet-Melou, Kees Veldman, Johan W Mouton (JWM), Annet Heuvelink, Peter Lees, Pierre-Louis Toutain (PLT), Peter Damborg (PD), Gunnar Kahlmeter (GK), Lina Cavaco (LC), Ludovic Pelligand (LP), Zrinka Stritof.

VetCAST position paper
- Pierre-Louis Toutain (PLT) explained the process of writing the position paper on how VetCAST will establish clinical breakpoints (CBPs) in veterinary medicine. Some output/notes from the discussion:
  - It was agreed that the position paper should include general statements on how to set CBPs and the reasoning behind. In other words; the paper will not be an SOP.
  - GK emphasized that all EUCAST subcommittees have to follow the EUCAST terminology.
  - The paper is crucial for the process of VetCAST being officially recognized by EMA and (subsequently) the industry.
  - VetCAST cannot discuss decisions with all national breakpoint committees, but expert advice/input should always be considered irrespective of origin.
  - EUCAST has regular contacts with CLSI and has on occasion collaborated on breakpoint developments and revision (e.g. colistin), and VetCAST should continue collaborating with CLSI-VAST although it is crucial that we make our own decisions and have our own CBP table.
  - EUCAST breakpoints are set for humans. They are species specific so that Enterobacteriaceae, staphylococci etc. mostly have different breakpoints. On occasion the breakpoint is related to a specific dose or infection site.
  - JWM: It is okay to use AUC/MIC as the single PK/PD index for all antimicrobial agents, in particular if there are few doses only, but it is important to emphasize that this is only true for efficacy of drugs. T>MIC may be important for other purposes, for example when considering development of resistance.
  - EUCAST states that “PD data” are needed for thresholds. It was clarified that PK data are used for reaching thresholds.
  - EUCAST has major challenges in getting PK data from industry partners;’, old data of good quality especially may be impossible to obtain.
  - VetCAST should not use the term “Clinical Cutoff” as it is not part of the EUCAST terminology. Similarly, VetCAST should use “PK/PD breakpoint” instead of “PK/PD cutoff”.
  - It was agreed that an ECOFF should be determined before and independently of determining a CBP.
  - Section 9, presentation of EUCAST breakpoints: the word “generally” refers to the fact that the target (e.g. gram-positive vs. gram-negative bacteria) may vary, whereas the approach to obtain PK/PD breakpoints is always the same.
- PLT will now revise the draft position paper rapidly and send it to the EUCAST Steering Committee within the next 3 weeks (preferably early April so we can discuss further at ECCMID). After ECCMID and new revision we will send to EMA.
- Input from VetCAST members is still encouraged.
Conflicts of Interest policy

- DM summarized the current draft of a VetCAST COI policy and explained that VetCAST intends to stick to ESCMID system for declaration of conflicts.
- We hope that EMA will accept this procedure, which is similar to the one used by EUCAST members.
- Agreed that – prior to ECCMID - DM writes to Christian Giske exactly to ask which 2-4 points we want EUCAST input on. After ECCMID, the document will be adjusted based on input from EUCAST, and subsequently sent to EMA for approval.

PK data collection

- LP described the efforts and achievements so far. The following 3 documents have been prepared:
  - Letter to industry (invitation to provide PK data).
  - Excel spreadsheet for inserting PK data. The sheet takes into account many factors, e.g. different technology to capture data; hence it is very flexible although a video on how to use it may be needed.
  - A general guideline on how VetCAST will collect, archive, handle, and analyze PK data (it was not clear whether this had been reviewed by EUCAST).
- LP: we need individual concentration-time curves in as many animals as possible and will use “non-linear mixed effect” modelling which can provide quite robust data even if only from a few individual animals (JWM: a non-parametric model may be considered as well, so we shouldn’t restrict ourselves to only one method).
  - Potential effect of animal race. GK: we have to be practical and have some sort of balance
  - We may discover inappropriate dosages. JWM: we should strive to change such dosages.
  - PLT: currently we are not intending to discuss dosages as they comprise a critical point for the industry.
- JWM/GK: in general try to avoid too many complex breakpoints (e.g. for young and old animals) as it makes our lives too complicated.
- JWM: we can start by not using a co-variate analysis when we calculate the PK/PD breakpoint and just do a structural model (much easier, will save time).
- JWM: PK data from only 50 individuals or less in human medicine is normal and still useful for modeling, hence we shouldn’t be afraid of sparse data.
- GK/JWM: for human generics, usually PK data are only available from the mother/pioneer company. A better strategy to obtain PK data is often to contact authors of papers. For new human drugs, companies either provide entire PK/PD data sets or their own CBP that EUCAST then reviews.
- EUCAST uses a prediction interval (= target attainment rate) between 95% to 99% and not a confidence interval afterwards. EUCAST selects the percentage based on individual drugs (e.g. can you afford to have treatment failure or not?).
  - Comment from Peter Lees: if we use those PTAs of 95% or 99%, then that would change the dosage for almost all drugs except fluoroquinolones.
- PLT questioned if we need to have an SOP on minimum requirements for doing population analysis as the approach may vary a lot by software and the computing person. PLT/JWM suggest Phoenix followed by a sensitivity analysis. The only way to control for data generated using other software is to re-analyze from raw data.
- EUCAST-approaches (GK/JWM):
GI-infections: Oral treatment is considered “topical treatment”, hence no PK/PD breakpoints are set, but rather ECOFFs and clinical experience are used (because of shortage of data).

Mastitis: intramammary treatment is considered “topical treatment”, hence no PK/PD breakpoints are set, but rather ECOFFs and clinical experience (because of shortage of data).

- LP emphasized that VetCAST volunteers are needed to:
  o Approach pharmaceutical companies.
  o Develop population PK models (competencies needed, NB: Toulouse workshop).
  o Agree on and define PK/PD targets.

MIC data collection

- KV presented the status of MIC data collection
- Now 668 tetracycline MIC distributions (based on almost 270000 observations).
- 448 aggregated distributions
  o GK: the biggest problem is that we tend to have truncated data, which are generally not acceptable for aggregation in the EUCAST database.
  o Still 22 species without ECOFFs (including for some important species like Bordetella bronchiseptica and Actinobacillus pleuropneumoniae).
  o Specific distribution acceptance criteria were mentioned (e.g. minimum 15 observations per distribution).
  o Tentative ECOFFs (“TECOFFs”) were presented for A. pleuropneumoniae and S. suis. Although fewer data are needed for TECOFFs, we still need at least 3 distributions from 2 labs.
  o Kees has used the Eyeball method for setting ECOFFs.
  o We are not sure how to deal with CEESA data, even if they are already published.
  o GK comments on future MIC data:
    ▪ Avoid E-test data.
    ▪ Agar dilution data are OK as long as the method has been calibrated.
  o GK: we should make a priority list of bacterial species and antibiotics for which we need more data. His lab may have available slots in MIC plates for testing some animal pathogens against drugs used both in veterinary and human medicine.

Presentation by GK on EUCAST activities and TECOFF

- EUCAST now has several national AST Committees outside Europe, e.g. USA, China, Australia etc.
- The EUCAST decision process on setting/revising CBPs was reviewed.
- The method for setting ECOFFs was reviewed. EUCAST uses a combination of the Eyeball method and ECOFFinder. Other methods/software are evaluated regularly (e.g. NRI by Göran Kronvall)
- Tentative ECOFFs
  o Less stringently defined ECOFF. These are clearly marked on the EUCAST homepage.
- New for EUCAST
  o New organisms with CBPs (Aerococcus etc).
  o Revised breakpoints (e.g. colistin and fluoroquinolones).
- S. pseudintermedius: oxacillin disk test (1 ug) is now preferred over cefoxitin for detection of MRSP.
Roundtable discussion about data collection

- DM asked everyone attending to support with data they have or know of.
- MIC data
  - Should be sorted according to year.
  - PLT/LP: only limited data from France and the UK (more labs/vet schools could be asked).
  - KV will ensure that requirements for data are clear whenever requests are circulated.
- PK data
  - Generics: data are only acceptable if bioequivalence studies have been done.
  - A pharmaceutical company in a certain country should be contacted by a VetCAST member representing that country. Preferably, companies should be contacted in parallel rather than sequentially.
  - LP will re-circulate any needed documents in advance.
  - LP: the FARAD database headed by Jim Riviere has almost any kind of data needed, but we need a dedicated person to mine data from there. Maybe a Masters student?
  - We may apply for European Training Networks grant for PhD students who can then go and do data mining.

Presentation by Stefano Lollai

- SL presented the recently started project “Setting antimicrobial resistance breakpoints in sheep with particular reference to mammary gland infections”.
- The consortium comprises 8 research groups/units, and DM, KV, and LP from VetCAST have been enrolled as experts.
- The project comprises preliminary/pilot studies on;
  - Oxytetracycline against S. uberis.
  - Cloxacillin (and other beta-lactams) against CoNS, Pasteurella (drugs mainly used for dry therapy).
- Naturally diseased animals will be included (no experimental studies).
- MICs will be tested in broth, serum and milk.


- PLT presented the course structure and programme.
- The 1st day will include a broad introduction to susceptibility testing etc., and around 40-50 participants are expected.
- Day 2-4 will be more specialized and will require a minimum insight into PK: max 35 participants.
- The budget is currently being sorted, and attendees will benefit from the support of the JPIAMR VetCAST project and sponsorship from bioMerieux.
- JWM asked for more teaching on pharmacodynamics targets. PLT will see if this wish can be fulfilled, e.g. by asking John Turnidge to cover it.
- The workshop will be widely advertised soon.
Presentation on COST-Action proposal

- PD presented past and current ideas for a COST-Action VetCAST project.
- It was agreed that as many European countries as possible must be included. LC may assist in identifying clinical microbiology labs, and LP and PLT may assist in identifying pharmacologists.
- The importance of dissemination was stressed. Chantal Britt (Communications and Publications manager from ESCMID) will be on board and play a key role on this matter.

Any other business

- LP: will check if any VetCAST members are missing on the Google group.

/Peter Damborg