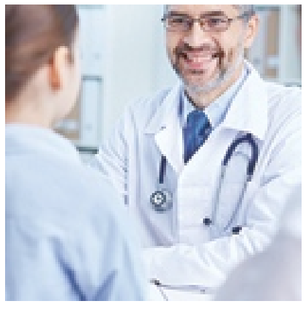
European Federation of Pharmaceutical Industries and Associations

Determination of the probability of target attainment (PTA) – Topic 3b Section 4.4

Matthew Rizk, *on behalf of the EFPIA team*





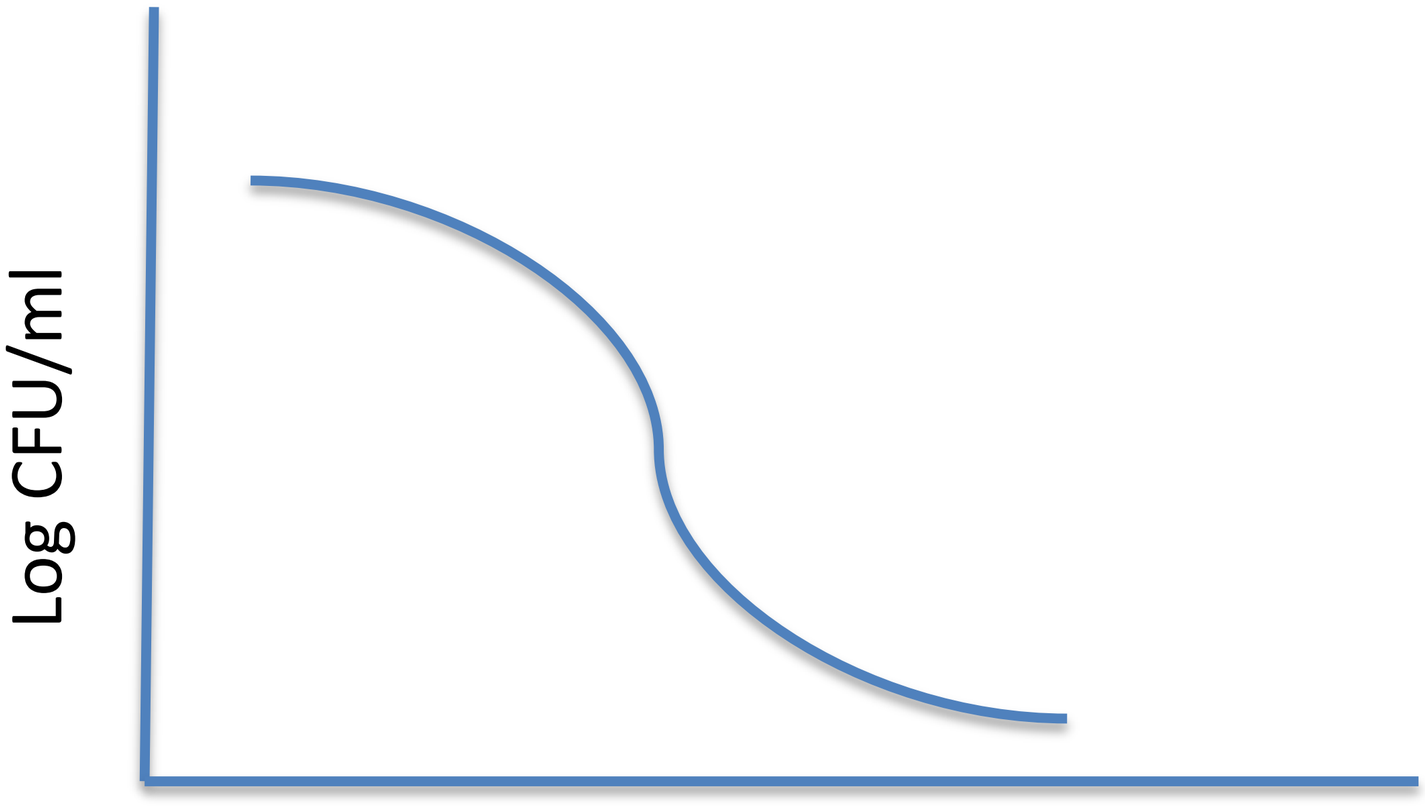
EMA PK-PD Workshop

12-13 Nov 2015

Framing of Topics 3a and 3b

Topic 3a:

- *How Much Killing?*



Topic 3b:

- *How much PK-PD exposure (PDT)?*
- *How often should we expect to get it given a dose, PK, and MIC in a patient population? (PTA)*

Executive Summary: PTA

- Generally agree with the tone and content of Section 4.4; root of concerns primarily regarding choice of PDT (as discussed in Topic 3a)
- Most would agree that ***more*** PTA coverage ***is better****!*
- But, let's not be too prescriptive about the magnitude…
  - Important to consider unmet medical need and risk:benefit (therapeutic window) of the agent
  - Consider in context of other agents within the class and their degree of PTA for the same indications
  - While a good guidepost, 90% PTA should not be treated as a strict threshold
  - PTA should be considered as one part of the totality of the data to justify the dose

Sources of Data for Simulations

- Agree to begin with healthy volunteer PK data and incorporate patient PK data as becomes available
- *Lines 393-395 and 409-411: "sponsor should describe the underlying population distributions*"
- **EFPIA suggestion: No changes requested; text leaves an appropriate amount of flexibility for sponsors to sample from covariate distributions or sample from the acquired patient database**

Plasma Protein Binding in Simulations

- *Lines 396-398: "Unless otherwise justified, adjustments should be made for the degree of human plasma protein binding."*
  - Simulations appropriately utilize plasma PK, as plasma provides most robust assessment of PK characteristics and variability
  - Appropriate to rely on plasma PK and to appropriately adjust PDTs for differences in target site penetration between preclinical models and human (as discussed in Topic 2)
- **EFPIA suggestion: For drugs with low PPB, practically speaking incorporation may have little impact as variability in MIC and PK is much greater. Suggested language: *"Unless otherwise justified (e.g., for drugs with low plasma protein binding), adjustments should be made for the degree of human plasma protein binding."***

Incorporation of Creatinine Clearance in Simulations (1 of 2)

- *Lines 407-408: "It is also necessary to include a distribution for creatinine clearance that is usually found in the target population"*
  - While relevant for renally cleared drugs, no allowance made for drugs not impacted by renal function
- **EFPIA suggestion: revise lines 407-408 to state *"For renally cleared drugs, including a distribution for creatinine clearance that is usually found in the target population should be considered"***

Incorporation of Creatinine Clearance in Simulations (2 of 2)

- *Lines 407-408: "It is also necessary to include a distribution for creatinine clearance that is usually found in the target population"*
  - Does this speak to renal insufficiency or to augmented renal clearance (ARC)? For ARC, how do we better understand and predict this phenomenon?
  - The use of the Cockcroft- Gault equation may a be less precise estimate of creatinine clearance in certain circumstances such as when renal function is not stable.
  - Methods of estimated creatinine clearance should be clear/justified. Sponsor should consider whether using existing methods for estimation of creatinine clearance is an appropriate approach vs. an independent population PK derived approach for predicting the drug's clearance.
- **EFPIA suggestion: The Agency is requested to speak to strengths/limitations of methods of estimating creatinine clearance for simulation purposes and insights on predicting individuals with ARC**

Virtual Patient Database

- Simulation database: a standard population for simulations of each indication [e.g. with standardized distributions for common PopPK model parameters such as height, weight, ClCr, age etc.] would allow better head to head comparisons between agents.

- **EFPIA suggestion: Not in scope for the guidance, but a suggestion for the agency to consider as a resource for sponsors [an industry working group, or professional society could take a lead with endorsement from agency]**

Selection and Justification of PDTs for Probability of Target Attainment (PTA) 1 of 2

- *Lines 419-429: Link severity of infection type with PDT*
- Recap of Topic 3a:
  - Many considerations preclude designation of specific target levels of bacterial reduction and linkage to clinical outcomes in human infection. Thus, final guidance should avoid prescribing specific thresholds in nonclinical models for specific infection sites or indications in humans
  - Prior experience from both nonclinical and clinical studies can benchmark existing classes and can help bridge to new agents from these existing drug classes
  - Sponsor has burden of developing justification for specific levels of bacterial killing based on the totality of data, which would include both nonclinical and clinical data
- **EFPIA suggestion: Recommend lines 419-435 be replaced with suggested text (see Topic 3a).**

Selection and Justification of PDTs for Probability of Target Attainment (PTA) 2 of 2

- *Lines 417-418: PTA to be shown by MIC and by PDT associated with stasis, 1-log_{10} and 2-log_{10} kill*
- *Lines 430-435: Additional PDTs may be considered in analyses of PTA (in vitro resistance, rapid response, neutropenic patients, etc.)*
  - *Sponsor should consider incorporating these factors into the core justification of the PDT(s) used in simulations, instead of increasing the number of PTA analyses*
  - *Consider slope of exposure-response (E-R) relationship. a steep E-R relationship may justify increasing dose more readily than a shallow E-R curve.*
- Can PTA assessments be used to recommend doses for groups without clinical data, if appropriate validity/confidence in the extrapolation of PK is supported? (May be appropriately addressed in section 4.7)
- **EFPIA suggestion:**
  - **Sections above raise issue of generating multitudes of tables/figures. Suggest to highlight PTA for relevant PDT for indication and population, incorporating specific treatment aims to streamline presentation and focus on assessment of interest.**

Appropriateness of 90% PTA Threshold

- *Lines 438-449: At least 90% PTA is commonly expected, but <90% may be acceptable in certain situations*
  - Appropriate that risk:benefit be considered
  - Focus is primarily on 90% PTA at the MIC90
  - No mention of how to handle combinations (e.g. BL/BLIs) and if joint PTA preferred method versus other integrated approach (see topic 5 as well)
- **EFPIA suggestion:**
  - **Suggest to emphasize value of PTA as tool for *relative comparison* with known members of the class, other internal controls, or between organs, indications, pathogens or PDTs, instead of focusing on a specific numerical PTA cut off (i.e. 90%)**

Achieving PTA through Personalized Dosing

- In certain circumstances, consideration of a precision medicine approach with personalized, exposure-targeted dosing recommendation may enable achieving high PTA
- **EFPIA suggestion:**
  - **Recommend adding language following line 449: *'A personalized dosing approach to achieve target exposures may be considered, instead of a fixed dosing recommendation based on a population-derived PTA threshold, in patient populations with a high unmet medical need and highly variable PK properties, such as the critically ill. Individualized pharmacology dosing support, or if available, therapeutic drug management, may be tools to achieve individually optimized target attainment'***

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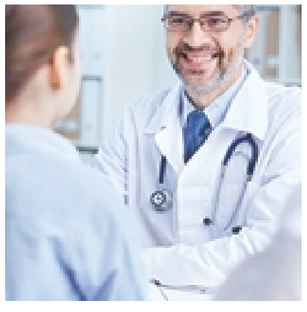
Thank you!





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