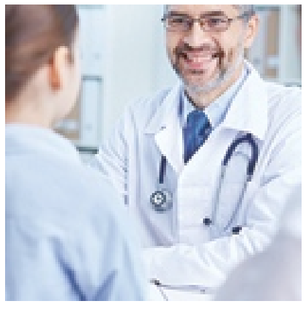
European Federation of Pharmaceutical Industries and Associations

Beta-lactamase Inhibitors – Topic 5, Section 4.6

Shampa Das, *on behalf of the EFPIA team*





EMA PK-PD Workshop

12-13 Nov 2015

Defining PD Index of Inhibitor

- *Section 4.6.1 and 4.6.2*
  - PK/PD (and hence dose regimen) needs to be defined for each BL

- **EFPIA recommendation: Agree, and propose the following modification to line 549-551:**
  - A PK-PD index that expresses the relationship between drug exposures and antibacterial effects in preclinical models should be established for each BLI. The PK-PD index should be established using bacterial strains that have been characterized for type of beta-lactamases and other relevant resistant mechanisms to the beta-lactam and/or inhibitor (e.g., permeability-based) to understand the impact of varying organisms and beta-lactamase types on the PDT for the BLI.

Defining PD Index of Inhibitor

Section 4.6.2 Line 552-554:

- In non-clinical infection models the BL/BLI should be administered to mimic the anticipated mode(s) of clinical use

- **EFPIA Comment: Agree, however:**
  - Some studies used during development of PK/PD understanding may not represent mode of clinical use (e.g. continuous infusion for dose fractionation, keeping one component as continuous dosing etc)
- **EFPIA recommendation:**
  - **Modify of lines 552 to 554 to read:**
  - **“In establishing the PK-PD index, studies should be included in non-clinical infection models wherein the BL/BLI** should be administered to mimic the anticipated mode(s) of clinical use……."

Defining PD Index of Inhibitor

Section 4.6.2 line 554

- The BLI PK parameters of potential interest **should be indexed to the potentiated MICs**

- **EFPIA comment:**
  - PK/PD index for BLI should be based on data and **may not be indexed to MIC** of the combination
    - Eg: PDT for avibactam (T>threshold concentration) and relebactam (AUC) is directly a PK parameter not linked to MIC, whereas for tazobactam (T>threshold) which is indexed to the MIC of the combination (potentiated MIC)
    - MIC is not only a function of the amount of beta lactamase produced, there are other resistance mechanisms
    - The PD Index should cover extremes of MICs that the BL-BLI is intended to treat
- **EFPIA Suggestion: Change language on lines 554 to allow for exploration of whether PK/PD index of BLI is linked to MIC, and remove reference to "potentiated" MIC**
  - **For example: How the BLI PK parameters of interest (e.g. C_{max}, AUC, T>threshold) should be indexed to in vitro data should be driven by the data.**

Susceptibility Testing and PK/PD Target Concentrations

Currently no mention in the guidance document

- The concentration used to create stable susceptibility testing does not necessarily map to threshold concentrations that are derived from PK/PD studies and lead to dose selection in man

- **EFPIA Suggestion: Include text on this in background section to make the principle clear**
  - **For example: The fixed concentration of BLI used in in vitro susceptibility testing does not necessarily relate to target threshold concentrations from PK/PD experiments that describe the PDT.**

Non-clinical activity data

Section 4.6.1 and 4.6.3

- Confirmation of activity across multiple strains/enzyme types from nonclinical data (in vitro and in vivo models)
  - Supports use when you have limited clinical data (e.g. little or no pathogens that are BL-R but BL/BLI-S) [4.6.3 of guidance]
  - In the setting of robust nonclinical data, limited clinical data can support extrapolation to other pathogens

- **EFPIA recommendation: This information should be reflected in the SmPC. A section to say what pre-clinical data are available - examples of US labels shown on next slide.**

As clinical data will not provide data on everything, non-clinical data is needed in the label

Examples from AVYCAZ and ZERBAXA labels in the US:

- Example of animal efficacy and PK/PD data
  - Avibactam restored activity of ceftazidime in animal models of infection (e.g. thigh infection, pyelonephritis, systemic infection induced by intraperitoneal injection) caused by ceftazidime non-susceptible beta-lactamase producing (e.g., ESBL, KPC and AmpC) gram-negative bacteria
- Examples of in vitro data across multiple strains/enzymes:
  - ZERBAXA demonstrated in vitro activity against Enterobacteriaceae in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, and OXA. ZERBAXA is not active against bacteria that produce serine carbapenemases [*K. pneumoniae* carbapenemase (KPC)], and metallo-beta lactamases

PK/PD target attainment simulations

Section 4.6.2 line 559-566

- Joint target attainment for inhibitor and beta lactam
  - Different approaches can be taken (e.g. deriving a relationship between BLI PK and the MIC, resulting in a time-varying MIC that the PTA of the BL can be assessed against)
- Accounting for correlation between beta lactam and inhibitor random effects and other dependencies
  - Simultaneous model of BL and BLI
  - Parallel models with joint covariate structures
  - May be covered in popPK guidances, avoid being too prescriptive here
- **EFPIA Comment: We agree with the points above and acknowledge that different approaches can be taken to address them. No change is suggested.**

Renal dose adjustments

Section 4.6.2 lines 567-572

- Renal dose adjustments for fixed dose combinations
  - Important to understand PK of both BL and BLI as a function of degree of renal impairment
  - Different renal clearance of BL/BLI combination **should not** preclude use of a fixed dose combination, especially if combination remains within therapeutic window
  - Appropriate guidance on antibiotic dosing should be available, where justifiable, for treatment of subjects with renal impairment

- **EFPIA Recommendation: Modify lines 570-572 to indicate that renal dose adjustments should be based on the therapeutic window and change “will preclude” to “may preclude”**

PK/PD and Clinical studies

Section 4.6.3

- PK/PD in nonclinical models is used to predict what we <u>expect</u> to see in humans
- Data from clinical studies may be limited for the most relevant pathogens (BL resistant, BL-BLI susceptible)
- Different clinical study types:
    - Traditional pivotal non-inferiority study design
        - Demonstrates efficacy/safety in a large-powered study
        - Provides limited data on BL-resistant organisms
    - Small study in patients with confirmed BL non-susceptible pathogens
        - Not powered for statistical analyses, long time to enroll
        - Specifically shows contribution of BLI to efficacy of BL
        - Generates clinical data that can be used to relate efficacy to PD results from nonclinical studies
- **EFPIA Recommendation: Reinforce that the list of isolates in the label shouldn't be limited to what was in clinical studies, and that nonclinical data could be leveraged to include additional pathogens**

Summary

- Draft guidance provides valuable information on selecting dose regimens for BL/BLI combinations and recognizes that limited clinical data may be available for the most relevant pathogens (BL-resistant, BL-BLI susceptible)
- Dose regimen should take into consideration unique characteristics of each combination (e.g. PD driver, renal dose adjustments)
- Even if limited, data (nonclinical and clinical) on pathogens that produce specific beta-lactamases is useful to include in labelling

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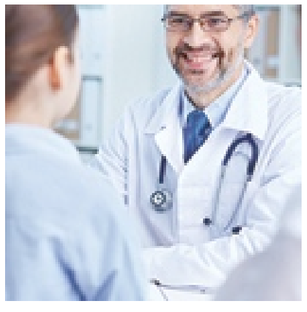
Thank you!





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