

Annex to UNITAID EB17 Resolution 11 (TB Alliance)

Clarifications/ Issues to be addressed:

Notwithstanding other information and clarifications that may be sought as part of the grant agreement and project plan development process, the Secretariat and/or the PRC specifically requires:

- 1. The feasibility of a strategy directly engaging current manufacturers of pre-qualified paediatric FDCs needs to be considered.** Two companies currently provide pre-qualified paediatric dispersible products as FDCs of the same APIs that would be required for the new formulations. The companies have the know-how to successfully formulate and manufacture quality dispersible tablets for TB, and they would need to make only slight modifications to the current dosage. Therefore, TBA should explain how they will consider the cost- and time-saving implications of more focused manufacturer engagement.
- 2. The requested budget of almost US\$17 million should be further justified** with discussion of potential cost-savings through more targeted manufacturer engagement (as above) and comparative cost analysis. The proponent should justify the budget needed for lobbying. Many countries have already adopted the new treatment recommendations, implying that the budget needed for lobbying should be minimal.
- 3. The proponents need to clarify what level of cost to UNITAID would specifically serve the novel compound development objective, if at all.** The main aim of the proposal is to rapidly and efficiently enable global access to quality-assured, newly WHO-recommended paediatric dosage forms. However, in several instances, reference is also made to preparing the market for potential new drug combinations for the treatment of TB that might be composed of novel drug agents. If both focus areas are to be pursued simultaneously, two distinct strategies should be proposed. Currently, these are rolled into one. Clearly, there will be areas of overlap, but in certain respects, new combinations based on novel agents will require more demanding development activity (e.g. clinical phase 3 trials for regulatory approval, as opposed to clinical phase 1 or 2 for generic agents that are well-established in the clinical environment). Intellectual property issues, policy guideline development, WHO endorsement, cost issues, manufacturing challenges, etc. will all present major challenges in terms of timelines, resources, and cost.
- 4. The proponent needs to explain why a special effort will be made to define the dosage needs for children with body-mass less than 5kg** (see Activity 2.2 Why would it be suspected that infants in the first weeks after birth would have significantly different PK profiles to anti-TB medications than slightly older infants with higher body-mass? What body-mass range has already been investigated in the studies that led to the revised dosage recommendations of the WHO? Evidence supports a linear relationship between body-mass and dose-effect of PK parameters for all anti-TB compounds. Why would it not be possible to scale the dosage for under-5 kg body-mass on the basis of existing information, and devise a relevant dosage indication for infants, using the proposed formulations under consideration here for body-mass range 5-30 kg? There are several more associated questions, e.g. how quickly do infants grow from under 5 kg to over 5 kg (seen against the period of treatment required to cure TB), how many infants develop active TB in the first weeks of life (i.e. how big is the market), is a special product dosage form really required for this very restricted patient cohort?

5. **Consideration should be given for more comprehensive multi-dose PK studies of the higher-dose regimens, especially in children with TB under 5 years of age, and activities defined accordingly.** In addition to single-dose PK studies, multi-centre tolerability studies of multiple dosing strategies in patient populations from different parts of the world are essential to understand the safety profile of the higher doses recommended by WHO for new formulations. Such data would may be required by regulatory authorities for licensing of the new dosage forms.

Secondary points for clarification

6. Clarification required as to why there is a **WHO cost linked to Activities 2.2 and 2.3.**
7. South African reported case-rates for paediatric TB are, by far, the highest of all (50 474 cases in 2010). Manufacturers in South Africa – a well-developed market for TB medicines, supported by a stringent regulatory authority, and providing a near-to-market opportunity – should be considered.
8. **What will be the role of the Paediatric TB Centre of Excellence once the project is completed?** Additional justification should be provided for the Centre, addressing the added value and sustainability of this element (vs. a strictly time-limited project).