EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/644851/2014
Committee for Human Medicinal Products (CHMP)

Concept Paper on revision of the Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to mycobacterium tuberculosis

Agreed by IDWP	September 2014
Adopted by CHMP for release for consultation	20 November 2014
Start of public consultation	30 November 2014
End of consultation (deadline for comments)	28 February 2015

The proposed guideline will replace EMA/CHMP/EWP/14377/2008

Comments should be provided using this template. The completed comments form should be sent to idwpsecretariat@ema.europa.eu

Keywords	*Mycobacterium tuberculosis, tuberculosis, combination regimens, multi-drug resistant and extensively resistant M. tuberculosis (MDR-TB, XDR-TB), early bactericidal activity (EBA), sputum culture conversion (SCC), biomarkers*

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1. Introduction

This Concept Paper proposes a revision of the CHMP's Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to *Mycobacterium tuberculosis* (EMA/CHMP/EWP/14377/2008). This Addendum came into force 1 August 2010.

EMA/CHMP/EWP/14377/2008 was developed during the period 2008-2010 and at a time when new anti-tuberculosis agents under clinical investigation were proposed mainly for inclusion in shortened regimens to treat fully susceptible tuberculosis (DS-TB) or for addition to optimised background regimens for treatment of multi-drug-resistant tuberculosis (MDR-TB and/or XDR-TB). Hence the guidance provided was tailored towards such programmes.

Developments in the field since that time point to the need to consider several other types of drug development programmes, such as those intended to lead to approval of entire new regimens, and to re-evaluate the feasibility of some types of studies suggested in the current version in light of the availability of some recently approved agents.

For these reasons and to provide a sound basis for the provision of CHMP scientific advice, there is a need to revise EMA/CHMP/EWP/14377/2008 to clarify the EU regulatory expectations with regard to the data that should be generated to support the approval of individual new agents and/or new regimens comprising wholly novel or a mixture of novel and licensed agents (which may be used at doses that differ from those currently approved).

2. Problem statement

The content of EMA/CHMP/EWP/14377/2008 covers the principles and the general approach to the investigation of the antimycobacterial activity of new agents. Since adoption of the current guidance there has been progress in assessing the PK/PD relationship for anti-tuberculosis agents in non-clinical studies. Some of the clinical study designs suggested, such as those intended to demonstrate superiority of a new agent vs. placebo when each is added to optimised background regimens for patients with MDR/XDR-TB, may not be feasible any more. In addition, there has been a move towards developing whole new shorter regimens rather than approaching drug development on an individual agent basis and to focus on the susceptibility pattern of patients' organisms rather than approaching studies in terms of patient populations with DS-TB and MDR/XDR-TB. Thus, some of the sections of the current Addendum require revision.

3. Discussion (on the problem statement)

The focus of the current addendum is on the evaluation of a single test agent within regimens that contain licensed anti-tuberculosis agents. It is assumed that test combination regimens (i.e. including at least one test agent) will initially comprise at least three potentially active agents with the possibility of reduction to a minimum of two agents after a defined period of time.

Brief guidance is provided on the range of in-vitro and in-vivo non-clinical studies that may provide at least an indication of the range of doses and/or durations of therapy that might be suitable for evaluation in clinical studies. Due to the studies ongoing or planned at the time of drafting the current version the text pays particular attention to:

- The investigation of agents potentially suitable for use in shortened regimens for the treatment of disease due to susceptible *M. tuberculosis* (i.e. susceptible to first line agents)

- The investigation of agents potentially suitable for use in the treatment of drug-resistant *M. tuberculosis.*

Other possible scenarios for clinical development (e.g. to identify regimens that provide an improved safety profile, a lower risk of drug-drug interactions or a simplified regimen or address other objectives) are not covered in detail.

With the advent of new approved agents, advances in PK/PD-related techniques and analyses relevant to tuberculosis and emerging data on relationships between early sputum culture conversion and final outcomes there are several matters that are either not adequately covered in the current document or require updating.

For example, the recent approvals of bedaquiline and delamanid have implications for the likely success of new studies that seek to demonstrate superiority of a new agent vs. placebo when added to optimised background regimens that include one or both of these agents. In terms of PK/PD there has been expanded use of techniques such as hollow fibre models, including factors such as growth phases and intracellular accumulations. Experience from clinical studies, both successful and failed, have enhanced our understanding of the predictive value of various biomarkers for ultimate clinical cure.

In addition, there have been shifts to developing entirely new regimens rather than focussing on the efficacy of individual new agents. Also, to test these regimens in patient populations that have pathogens susceptible to all agents in the test (and control) regimens rather than defining patients according to the DS, MDR and XDR-TB definitions. In this regard the current text states that it is not possible to extrapolate the results of clinical studies with a new agent in the treatment of drug-susceptible *M. tuberculosis* to the treatment of drug-resistant organisms or *vice versa*. This position reflected expert opinion at the time but it requires reconsideration taking into account both scientific and feasibility issues.

Other matters that require reconsideration include the number of studies and duration of post-treatment follow-up before filing an application dossier as well as the use of rapid diagnostic tests to detect tuberculosis and to detect certain types of resistance mechanisms.

4. Recommendation

The Working Party recommends that the existing Addendum EMA/CHMP/EWP/14377/2008 should be revised to incorporate guidance on the following matters:

1. To address feasible development programmes (including clinical study designs and number of studies) to evaluate the efficacy of individual new agents in light of the recent approval of some new anti-tuberculosis agents.

2. To consider clinical development programmes (including clinical study designs and number of studies) to evaluate new regimens incorporating at least one new agent, with or without licensed agents used at the approved or alternative doses.

3. To update the section on the use of PK/PD for rational dose selection for new agents and regimens, including models that can take into account the effects of growth phases and intracellular accumulation.

4. To update considerations of the predictive value of various biomarkers for ultimate clinical cure.

5. To discuss patient selection and categorisation that is focussed on the susceptibility of their infecting organisms to specific agents and to consider how best to reflect the populations studied in the indication for use.

6. To elaborate on the number of studies required and duration of post-treatment follow-up before filing an application dossier.

7. To provide guidance on the use of rapid diagnostic tests to detect tuberculosis and to detect certain types of resistance mechanisms.

5. Proposed timetable

Adoption of Concept Paper by IDWP/CHMP during 3Q2014.

First draft revision agreed by IDWP and released for consultation by end 2Q2015.

Finalisation during 1Q2016.

6. Resource requirements for preparation

The resources needed for this addendum relate to IDWP members who will develop the draft addendum and proceed to develop a final version after the consultation period. The current version was developed after two consultation meetings with the SAG on anti-infective agents plus extra invited experts in tuberculosis and it seems likely that such a meeting could be needed. This could also take the opportunity to consult with the Industry and TB Global Alliance.

7. Impact assessment (anticipated)

The most important impact is expected to be on clinical development programmes for antimycobacterial agents.

8. Interested parties

The International Society of Anti-infective Pharmacology (ISAP)

EFPIA

The Global TB Alliance