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4 Concept Paper on revision of the points to consider on 5 pharmacokinetics and pharmacodynamics in the 6 development of antibacterial medicinal products 7 (CHMP/EWP/2655/99) and conversion to a CHMP 8 guideline

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11 The proposed guideline will replace CPMP/EWP/2655/99

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

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1. Introduction

This Concept Paper proposes a revision of the CHMP's Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CPMP/EWP/2655/99) and its conversion into a full guideline.

CPMP/EWP/2655/99 was developed at a time when the application of analyses of pharmacokinetic (PK) and pharmacodynamic (PD) relationships was gaining importance as a component of antibacterial drug development. This Points to consider document lays out some principles for use of analyses of PK/PD relationships to identify potentially effective dose regimens and discusses their possible impact on the overall clinical data requirements. All of the principles discussed in this document remain applicable to current antibacterial development programmes.

Since adoption of CPMP/EWP/2655/99 in 2000 there have been several important advances in the field of PK/PD analyses and recognition of the wider applicability of knowledge of PK/PD relationships beyond identification of potentially useful regimens for clinical evaluation. It is proposed to revise the existing document to reflect these advances and to provide more detailed guidance on expectations for the assessment and analysis of PK/PD and exposure-response relationships (i.e. the application of pharmacometrics) in application dossiers.

The use of techniques such as hollow fibre models has been of particular assistance in identifying combination regimens, including doses of beta-lactamase inhibitors required for protection of partner beta-lactam agents from hydrolysis. There have also been advances in the use of PK/PD analyses to select regimens that may minimise the risk of selecting for resistant organisms. In addition to these clinical applications, the selection of interpretive criteria for susceptibility testing is very predominantly driven by PK/PD analyses.

Another important aspect concerns the prospective validation of the correlation between the PK/PD relationship and clinical and bacteriological outcomes. CPMP/EWP/2655/99 encourages attempts to validate and confirm the PK/PD concept during the clinical development programme. This can be accomplished by detailed analyses of exposure-response relationships. Experience gained since 2000 has demonstrated how knowledge of the exposure-response relationship can provide insight into issues such as reasons for failure, adequacy of doses and dose adjustments in specific patient populations.

Finally, in the case of antibacterial agents that can address an unmet need, in particular with potential to be clinically active against multidrug-resistant pathogens, the Addendum to CPMP/EWP/558/95 rev 2 stresses the undoubted importance of the contribution of PK/PD analyses to substantiate the dose and to assist in the overall assessment of the clinical utility of new agents when the efficacy data that can be obtained may be very limited.

For all these reasons and to provide a sound basis for the provision of CHMP scientific advice, there is a pressing need to revise CPMP/EWP/2655/99 to clarify the EU regulatory expectations with regard to the data that should be generated to support robust PK/PD analyses and to evaluate exposure-response relationships during clinical studies, including situations in which the pre-licensure clinical development programme may be very limited.

2. Problem statement

The content of CPMP/EWP/2655/99 covers the principles and the general approach to the use of analyses of PK/PD relationships in the development of antibacterial agents. The content of this document remains correct and wholly applicable. However, this document does not provide detailed

guidance on the expectations with regard to the data required to support robust conclusions from these analyses. In addition, it does not reflect the various uses that have been and may be made of detailed PK/PD and exposure-response analyses, including their role in the development programmes for antibacterial agents with potential to address unmet needs. It is now apparent that such guidance is needed in order to describe and clarify the CHMP's position on various matters.

3. Discussion (on the problem statement)

Most sponsors involved in developing new antibacterial agents and extending the indications or modifying the dose regimens for approved agents have in-house or seek external expertise when performing analyses of PK/PD relationships. Nevertheless, there are some crucial aspects of the data, analyses and interpretation of the findings that deserve attention in a regulatory guidance document. For example, a critically important factor is the probability of target attainment (PTA) that would be considered acceptable to support selection of a dose regimen for clinical evaluation. To some extent this is a matter of opinion. Also, a given dose may provide very different PTA estimates for individual pathogens and sometimes suggest the use of indication-specific regimens.

Relatively few application dossiers have included detailed and robust analyses of exposure-response relationships but, when they have been done, they have been very helpful in providing support for dose regimens and in the investigation of possible reasons for variable cure rates in patient subsets. These analyses may be of particular use in assessing the appropriateness of dose adjustments (such as in renal insufficiency), doses for special populations (including paediatric doses) and the potential clinical importance of drug-drug-interactions.

There is now sufficient experience in these fields to support provision of more definitive guidance on methodologies, interpretation and scope of use of PK/PD and exposure-response analyses as integral parts of the development programme. CHMP advice is frequently sought on these matters and establishing a clear position in a guideline would be helpful to both sponsors and regulators.

It should be noted that PK/PD analyses are at the cornerstone of setting interpretive criteria for susceptibility testing, which is currently undertaken by EUCAST. However, the very same data needed to support analyses to identify clinical doses are used to form the basis of analyses to support setting interpretive criteria. EUCAST has already published guidance regarding their expectations for PK/PD analyses and these recommendations will be taken into account.

4. Recommendation

The CHMP recommends that the existing *Points to Consider* document (CPMP/EWP/2655/99) should be revised and converted into a full CHMP guideline to incorporate guidance on the following matters:

i. *In-vitro* and *in-vivo* (animal) models

The neutropenic mouse thigh (NMT) model is the standard/reference model for determining both the PK/PD driver and the magnitude of the PK/PD driver. Guidance is needed on the use of other models and how their use could be justified based on how the model translates to clinical efficacy.

For example, to discuss the acceptability of the NMT, other animal models or *in vitro* hollow fibre models to establish the PK/PD targets for application to specific or across several different infection types. Also, to consider the value of a model that mimics the clinical indication, such as a pneumonia model when selecting regimens to treat lung infections.

Acceptability of PK/PD data from immunocompetent models requires discussion, including justifying their use based on a strong rationale that they would predict efficacy in man (e.g. as applied to evaluations of fluoroquinolones against pneumococci).

ii. Efficacy targets

The selection of targets and application of indication-specific efficacy targets should be addressed, including (as a minimum) the following matters:

To consider when it may be appropriate to estimate PTA to achieve stasis (e.g. perhaps for infections with low bacterial burden and those treated in part by surgical intervention)

To consider the adequacy of 1-log kill as opposed to the very stringent 2-log kill target.

iii. Extrapolating PK/PD from one pathogen to another

To develop expectations for provision of PK/PD analyses for the key pathogens involved in the clinical indication(s) to be sought. For example, for indications in which many individual species within a large grouping (e.g. Enterobacteriaceae) are relevant, to clarify expectations for PK/PD (e.g. confining to a few representative species).

iv. Human PK data for use in Monte-Carlo simulations (MCS)

There is a need to discuss the use of patient PK data in the model and/or to consider applying inflated variance to healthy volunteer PK data if no PK data from relevant patient populations are available when first selecting a possible dose regimen. For example, when using MCS to identify doses for treating infections that most often occur in ICU (and especially ventilated) patients.

v. PTA rates

Dose regimens for which MCS predict less than 90% PTA for one or more of the most important target pathogens are sometimes proposed by sponsors. On occasion this is due to safety concerns at higher doses. There is a need to discuss the preferred PTA rates and the issues that may arise when the dose proposed for an indication may not be optimal for all infections.

vi. Exposure-response analyses

Analysing clinical and bacteriological outcomes by MIC or by dose are not usually helpful in confirming the suitability of the selected dose regimen. There is a need to discuss the value (including the various ways in which the analyses can be used) and feasibility (including the collection of adequate PK and clinical status data) of incorporating analyses of exposure-response relationships into clinical studies. In particular, to discuss the importance of these analyses in very limited clinical development programmes (such as may apply to new agents that can address unmet need) and to assist in identifying relationships between exposure and standard as well as exploratory outcome measures (e.g. faster resolution of signs and symptoms or effects on laboratory biomarkers).

5. Proposed timetable

Adoption of Concept Paper by IDWP/CHMP by Q1 2014.

First draft revision agreed by IDWP and released for consultation by Q4 2014.

Finalisation during Q2-Q3 2015.

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.

7. Impact assessment (anticipated)

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

8. Interested parties

The International Society of Anti-infective Pharmacology (ISAP)

EFPIA

9. References to literature, guidelines, etc.

1. CPMP/EWP/2655/99

2. CPMP/EWP/558/95 rev 2 and Addendum

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