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2 EMA/CHMP/792679/2013
3 Committee for Medicinal Products for Human Use (CHMP)

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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Agreed by Infectious Diseases Working Party	November 2013
Adopted by CHMP for release for consultation	20 February 2014
Start of public consultation	28 February 2014
End of consultation (deadline for comments)	31 May 2014

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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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Keywords	Pharmacokinetics; pharmacodynamics; exposure-response; target attainment
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16 **1. Introduction**

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

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

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

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

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

44 Finally, in the case of antibacterial agents that can address an unmet need, in particular with potential
45 to be clinically active against multidrug-resistant pathogens, the Addendum to CPMP/EWP/558/95 rev
46 2 stresses the undoubted importance of the contribution of PK/PD analyses to substantiate the dose
47 and to assist in the overall assessment of the clinical utility of new agents when the efficacy data that
48 can be obtained may be very limited.

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

54 **2. Problem statement**

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

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

63 **3. Discussion (on the problem statement)**

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

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

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

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

87 **4. Recommendation**

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

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

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

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

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

101 ii. Efficacy targets

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

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

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

107 iii. Extrapolating PK/PD from one pathogen to another

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

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

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

117 v. PTA rates

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

122 vi. Exposure-response analyses

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

131 **5. Proposed timetable**

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

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

134 Finalisation during Q2-Q3 2015.

135 **6. Resource requirements for preparation**

136 The resources needed for this addendum relate to IDWP members who will develop the draft
137 addendum and proceed to develop a final version after the consultation period.

138 **7. Impact assessment (anticipated)**

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

141 **8. Interested parties**

142 The International Society of Anti-infective Pharmacology (ISAP)

143 EFPIA

9. References to literature, guidelines, etc.

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