choice because this may best demonstrate the pharmacological effects in a clinical setting. However, a lower dose on the steep part of the exposure–response curve may be appropriate when PD is being measured or when healthy subjects are selected for evaluation.

In certain cases, a dose selected from a range of doses may be useful for a clinical PK and PD similarity assessment. For example, if the concentration–effect relationship of the reference product is known to be highly variable or nonlinear, a range of doses can be used to assess dose–response.

If the product can be administered only to patients, an alternative dosing regimen, such as a single dose for a chronic indication or a lower dose than the approved dose, may be acceptable if the approved dose results in nonlinear PK or exceeds the dose required for maximal PD effect and therefore will not allow the detection of differences. However, the appropriateness of an alternative dosing regimen will depend on certain factors, e.g., the lower dose is known to have the same effect as the approved dose, or if it is ethically acceptable to give lower doses notwithstanding differences in effect. Adequate justification for the selection of an alternative dosing regimen should be provided in written communication to the Agency.

When appropriate, PD markers should be used to assess PK/PD similarity between a proposed biosimilar product and the reference product. Development of a dose–response profile that includes the steep part of the dose–response curve is a sensitive test for similarity between products, and if clinical pharmacology similarity between products is demonstrated, in some instances, this may complete the clinical evaluation, and in others it may support a more targeted clinical development program.

3.8.5.5 Route of administration Human PK and PD studies should be conducted using the same route of administration for the proposed biological product and the reference product. If more than one route of administration (e.g., both intravenous and subcutaneous) is approved for the reference product, the route selected for the assessment of PK and PD similarity should be the one most sensitive for detecting clinically meaningful differences. In most cases, this is likely to be the subcutaneous or other extravascular routes of administration, because extravascular routes can provide insight into potential PK differences during the absorption phase in addition to the distribution and elimination phases.

3.8.5.6 PK measures All PK steps should be obtained for the proposed biosimilar product and the reference product. The sponsor should obtain measures of C_{max} and total exposure (AUC) in a relevant biological fluid. For single-dose studies, total exposure should be calculated as the area under the biological product concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$