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## New EU guidance for the evaluation of medicinal products with modified drug release will be finished by the middle of 2014

The guideline 'Note for guidance on modified release oral and transdermal dosage forms: Section II (Pharmacokinetic and clinical evaluation)' [1] was issued over 10 years ago, and the need for revision was recognized in 2010. An international group of experts, led by Austrian members of the Pharmacokinetics Working Party, is responsible for its implementation. They have joined forces with the Quality Working Party, which revises guidelines on the quality of such products, and various other expert groups of the European Medicines Agency (EMA). A draft version was recently produced and approval obtained from EMA's Committee for Medicinal Products for Human Use; it was then posted on the EMA website for feedback [2].

This guideline deals specifically with medicinal products that use a modified drug release mechanism. Several different product groups, in particular all modified oral dosage forms, all transdermal delivery systems, as well as subcutaneous or intramuscular depot formulations, are covered by the recommendations.

Two principles of the modification can be distinguished:

1. Delayed drug release products: those with enteric coating, for example, that either protects the drug from the acidic pH in the stomach or protects the stomach from a potentially harmful drug. Other products target a specific location in the lower digestive tract for time-dependent, belated drug release, thereby significantly increasing the efficiency of certain drugs.
2. Prolonged release products: those products that release quantities of the active ingredient continuously over a certain time period. Peaks in drug concentrations in the blood can be flattened by this mechanism, and more uniform drug concentrations are achieved in contrast to immediate release formulations. Therefore, the incidence and intensity of undesired, concentration-dependent side effects can be reduced and dosing frequency decreased. The reduction in dosing frequency can also lead to improved patient compliance or adherence.

Today, numerous different release mechanisms are increasingly being incorporated into new products. The simultaneous use of galenic components with both immediate and prolonged release properties achieves a rapid onset of action combined with a prolonged duration of effects. In people suffering from chronic diseases where treatment needs to be adjusted to a circadian rhythm of their symptoms, a time-related single or multiple drug release, a so-called pulsatile release, from a single tablet might lead to improved treatment outcome.

The new guideline will provide detailed rules for the conduct of clinical trials of these drug products. These guidelines will include:

- Approval of a new drug with a modified release mechanism.
- Approval of an already known active ingredient, with a new modified release mechanism.

- Approval of a generic version of an already approved product that uses a modified release mechanism.

Two new, additional pharmacokinetic parameters to be used for the evaluation and comparison of the plasma profile of drugs were established during the guideline revision process:  $C_{\tau}$  (concentration at the end of the dosing interval) and  $AUC_{\text{partial}}$  (the area under the concentration time curve during a predefined and relevant portion of the whole AUC).

The necessity and usefulness of conducting bioequivalence studies after repeated dosing (steady-state or multiple dose studies) was discussed in detail, and the latest scientific publications related to this topic were also taken into account. In contrast to applicable US FDA guidelines, it was decided to continue to request these studies as a requirement for the approval of certain generic drugs [3]. The failure to conduct such a study, however, can be justified by proving that no or negligible accumulation of the active substance will occur in patients following the recommended dosage regimen.

The intensity of the discussions is reflected in the fact that 22 draft versions were developed before publication of internal draft 23 on 15 March 2013. The deadline for receipt of comments closed on 15 September 2013. Over 400 pages containing thousands of comments have been received from industry representatives, doctors and patient organizations, and these are now being carefully evaluated, discussed and responded to. By the middle of 2014, a new version of the guideline, incorporating these discussions and comments, will be made available.

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