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Status quo and future developments of *combinations of medicinal products*

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Summary *Combinations of medicinal products* were in common use during the 1950s and 1960s. These combinations were rarely a result of a rational development, but rather based on empirical experience. Following the German Drug Law (AMG) in 1976, a rational pharmacological justification for *combinations of medicinal products* became mandatory. Simultaneously cases of certain fixed combinations were found to possess high health risks, leading to the opinion that an effective and safe therapy requires an individual dosing of each drug. Today with the advanced knowledge about multifactorial causes of diseases, patients and physicians are increasingly confronted with an existing polypharmacotherapy, but the regulatory framework for the authorisation of *combination medicinal products* is lagging behind. The article describes in concrete examples the present status for the authorisation of *combination medicinal products* and offers suggestions for future developments based on the recent advancements in science. It further describes the special legal situation for phytopharmaceuticals and the present status for the reimbursability of fixed *medicinal product combinations*.

1. General considerations

During the 1950s and 1960s of the last century, the combination of drugs or medicinal products in various constellations was very common on the pharmaceutical market. These combinations were rarely a result of rational development, but rather based on empirical experiences. Previous to the introduction of the German Drug Law (AMG) of 1976, no necessity for a rational pharmacological justifications existed. But also after the AMG had been established, the authorisation of some combinations was heavily criticised, e.g. the combination of analgetics with caffeine was criticised for their addictive potential [3]. In the 1970s and 1980s fixed combinations of two or even more medicinal products or drugs were therefore judged as medicines with a high risk

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potential. The major argument was, however, that the different ingredients of a fixed combination could have different courses or durations of action, which could cause an overdose or underdosage of one or another ingredient [13,14]. From the perspective of the school of thoughts of pharmacology during that time, fixed combinations of medicinal products offered in most cases no advantages compared to formulations with a single therapeutic agent: ''Effective pharmaceutical therapy regularly requires the individual dosing of each single active ingredient, even when several active ingredients are used simultaneously''.

A great challenge in the development of fixed combinations is the synchronisation of the bioavailability of both single substances in order to meet the requirements of the European ''Combination Guideline'' [8]. Is this the case, the common argument of an improved titration of single substances in comparison to fixed combinations is inapplicable.

The bioavailability is a pharmacological unit for the percentage of an active substance that will be available in an unmodified form in the systemic circulation. It indicates the rate and the amount of the active substance absorbed and available at the site of action. Therefore, the challenge of different half-life periods of the active substances has to be taken into consideration, especially if the implementation of the ''pro-drug-concept'' is required. A Pro-drug is an inactive or less active pharmacological ingredient which will be transformed into an active substance during one or more metabolic steps in the organism. In cases where the active substance, if commonly applied, does not reach the site of action e.g. because it reaches not or only in marginal amounts or not with the appropriate selectivity the site of action, the pro-drug-concept gains strategic importance. This concept mainly tends to improve the pharmacokinetic characteristics of the substance. The application of pro-drugs can improve the oral bioavailability or enable a medicinal substance to pass the blood brain barrier, just to mention two examples.

The distribution of a medicinal substance begins in the moment it enters the blood circulation. In the context of pharmacokinetics distribution means the transportation of substances between different body fluids and tissues. This transport process is caused by the concentration gradient between the different distribution areas. Pharmaceutical characteristics of the substance such as solubility, chemical structure, binding capacity to plasma proteins and other physiological conditions influence the distribution. The blood—brain-barrier for example is encircled by a membrane. This membrane is difficult to penetrate, and therefore may prevent or reduce central side effects. All processes of biochemical degradation and reconstruction affecting the medicinal substance, are designated as metabolism or biotransformation. Their aim is to improve the excretion from the body.

The advanced knowledge about multifactorial causes of diseases demands factually the intake of an increasing number of medicinal products simultaneously, especially in an ageing society. This development points already towards the growing challenge which comes along with the demographic change of certain societies today and in future. ''Normal'' parameters, such as renal and heart functions, decline with advancing age due to biological reasons. Therefore, the consumption of a ''basic medication'' of an elderly person can be regarded as quite common. This will be accompanied by ''acute medications'' in cases of illness. Surveys showed that a daily intake of about ten medicinal products is quite common [1,22], in some individual cases patients had to take up to 21 different medications [16] per day (thus patients and physicians are increasingly confronted with a polypharmacology).

For many patients it is already highly demanding to take their medications regularly under general conditions, but a multiplicity of medicinal products leads to serious compliance problems [11]. Only about 35% of patients are successful in taking their medication regularly and correctly [21]. French researchers investigated the compliance of 556 chronically ill patients between 20 and 70 years of age in Norway, the Netherlands and France by using a special questionnaire: They found that the intake of multiple tablets from several packages is too demanding for most patients. Another survey [20] demonstrated earlier that 30% of patients who had to take medications twice a day, forgot about a quarter of the prescribed intakes; this also applied for 70% of the patients who had to take their medicinal products four times a day. Therefore it can be expected that any decline in the number of packages to be handled by the patient will substantially increase the compliance. Thus, *combination medicinal products* (*drug combinations*) are medically necessary in order to treat complex diseases or multiple morbidities according to the present state of medical knowledge.

When approving medicinal products, the competent authority currently assesses the efficacy and safety of only *one* pharmaceutical. Although there is an awareness of the fact that the intake of *combination medicinal products* is reasonable or indispensable for many diseases, regulatory rules do not provide a ''co-approval'' of free combinations of medicinal products. Therefore the current state of authority approval seems to have reached its limit. In order to close the gap between approval and medication practice, the authors suggest the ''approval of therapeutic concepts''. This strategy shall enable the approval of *combination medicinal products* intended for the use in special patient groups [12].

A therapeutic concept means the approval of a pharmaceutical regime, which must not be mistaken for a fixed combination in a single pharmaceutical form. Medicinal products belonging to an approved therapeutic concept must not be marketed in a co-package, but shall be dispensed separately. When approving therapeutic concepts, it is aimed to adapt the dosage of each medicinal product to the needs of the patient. This appears to be easier with separated medicinal products in different dosages. So each constituent can be given to the patient in the appropriate dose.

A well-known example for a *combination of medicinal products* is the eradication therapy used for combating the Helicobacter pylori bacteria: This triple-therapy combines the administration of two different antibiotics (Amoxicillin or Metronidazole with Clarithromycin) and a proton pump inhibitor (PPI) over a short period of seven days. Until today, the regulatory problems linked to this combination therapy are visible on the instruction leaflets of the particular medicinal products. The texts for both PPIs — Omeprazole and Lansoprazole — were designed for the approval in such a way that they mention in the section ''field of application'' not only the aim and the purpose of the therapy, but also the combinations to be applied (without dosage information, but naming the combination partners). Further information on the