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Short communication

Statement to the future of combination medicinal products [1]

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During the 50 s and 60 s of the last century, combination medicinal products in various constellations were very common on the pharmaceutical market. They were rarely a result of rational development, but rather basing on empirical experiences, no necessity for rational pharmacological justifications existed. But also after the German Drug Law (AMG) had been established, the authorisation of some combination medicinal products were judged as "medicines of risk" [1,2]. From the perspective of pharmacology teaching during that time only formulations with a single therapeutic agent were accepted. The only "exception" were phytoproducts with their (often) natural "multicomponent" action.

But even at that time it was commonly known that – in some cases – diseases could only be cured with combination of drugs, e.g. tuberculosis. In the following years the disease needing combination-therapy increased: e.g. human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) or helicobacter pylori eradication.

Additionally, the today knowledge about multifactorial reasons for diseases and the necessity of multi-medication, especially in an ageing society, points to the growing problem of demographic change. "Normal" parameters, such as renal and heart functions, decline with advancing age for biological reasons. Therefore, a "basic medication" of an ageing 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 usual [3], in some individual cases patients have to take up to 21 different medications [4] per day.

Indeed, it is a great challenge to synchronize the bioavailability of both single substances in order to meet the requirements of the European "Combination Guideline" [5]. In this case, the common argument of an improved titration of single substances in comparison to fixed combinations is inapplicable.

So my thesis: The combination guideline in this strict reading is "outdated", it must be replaced by a more flexible system.

When approving medicinal products, the competent authority currently assesses the efficacy and safety of only **one** pharmaceutical. Although there is awareness of the fact that the application 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. This is why the current state of authority approval seems to have come to its limit. To close the gap between approval and therapy in practice, one way could be the "approval of therapeutic concepts [6]" and the other way the use of synergistic effects: Therapy of complex diseases; dose reduction; less adverse drug events (ADE); improvement of efficacy and often less resistance problems.

1. Conclusion

Very different combinations of medicinal products are presently used in pharmacotherapy. A new strategy has to be evolved. After years of "demonization", combination medicinal products experience a renaissance. Professional circles have realised that various diseases cannot be treated with single active substances successfully. Recommended free combinations, co-packaging and "real" multi-component products are the methods of choice. Parameters for efficacy and bioavailability are still subject to strict rational criteria. For the development of new combination medicinal products, the FDA Guidance of 2013 [7] took the leading role. Europe is on the way to follow (??). But it is still unsolved how patient safety can be secured in free recommended combinations.

The mentioned strategies shall enable the approval of combination medicinal products intended for the use in special patient groups.

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