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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

combinations are given in the dosage instructions. The design of texts for *the information and direction for use leaflets* was harmonised and stipulated by developing a Guidance Document (''PtC on wording of helicobacter pylori eradication therapy in selected SPC sections''). However, there exists one *combination medicinal product*, which has obtained an approval as the result of a completed regulatory process: The preparation Zac-Pac® is a free combination of three substances for eradication therapy (Pantoprazole, Amoxicillin and Clarithromycin) with a common summary of product characteristics (SmPC) [19]. In France, the medicinal products applied together are usually combined in one blister [15].

The FDA has already recognised the need for the development of combination medicinal products, and has therefore published the Guidance on ''Fixed Dose Combinations, Co-Packaged Drug Products, for the Treatment of HIV'' in October 2006 [4], which has been supplemented by another Guidance on the co-development of pharmaceutical substances in June 2013 [5]. The second Guidance explains strategies for the approval of new active substances in combination products. It carries the intention to limit approvals to those combinations for the treatment of severe diseases, which are justified by strong scientific and biological evidence, as, for example the tuberculosis therapy or the combination of Levodopa and Carbidopa. All other products will be handled very restrictively. Especially the requirements to substantiate the combination, as demanded by the German Drug Law as well,[1] are difficult to meet. For the assessment of fixed combinations the so-called Crout[2] criteria of 1979 have become an international standard. They meet the requirements of efficacy and safety for medicinal products and, at the same time, address the problem of abuse and advantages of compliance. Concluding, the Crout criteria do not at all have the intention to prevent the use of fixed combination products. According to these criteria, the combination of active substances in medicinal products is justified, when it can be proven that each single substance has a therapeutic effect in the indication and the dosage of each single substance has been allocated — regarding maximum dose, frequency and duration of use — to meet the requirements for efficacy and safety on a risk-benefit-ratio and a significant number of patients will benefit from this fixed combination. Furthermore, the active substances amended increases the efficacy and/or safety of the main pharmaceutical ingredient or decrease the abuse potential of the main pharmaceutical ingredient or the fixed combination of active substances increases the therapeutic effect or offers more safety than each active substance regarded separately.

Two related and interlocking spheres of activity with respect to combination drugs, the sphere of theoretical debate and the sphere of actual use, must be considered. Debate and learned opinion serves to strengthen the scientific basis for the development and prescribing of combination drugs [10].

This led to the following theses from the physician's point of view [2]:

1. Medication management has become a complex process over the past 10 years and therefore cannot be left to chance any longer.
2. Patients know the full details about their own medication only in exceptional cases. This applies in particular to medications which consist of more than two to three active substances. With respect to compliance, there is no difference between university graduates and craftsmen.
3. Physicians do not have an exact knowledge about the daily medication of their patients. Furthermore, they are not aware about the knowledge of their patients on the medicinal products and whether they remember the information given to them at the time of writing the prescription.
4. Polypharmacotherapy is today commonly used in many widespread diseases. The structure of our society concerning morbidity and age as well as the clear tendency towards multi-medication represent a challenge on modern medication management which is difficult to handle. Without appropriate support, the single physician will be overwhelmed by these tasks.

Therapeutic regimes with a long lasting combination medication in constant dosages over long periods of time, after a run-in-phase, are nowadays state of the art for many diseases [17]. Scientific research on compliance [6] indicates that each reduction of numbers of medication packages will optimise the patient's compliance and the therapeutic success.

The most common concern raised against the combination of medicinal products is the potential medication risk. On the other hand, it can be assumed that multiple options for interaction, especially in multi-medications, with 20 or more single pharmaceuticals have never been investigated.

2. Conclusion

Very different combinations of medicinal products are presently used in pharmacotherapy. A new strategy has apparently evolved for ''traditional'', mostly chemically defined pharmaceuticals. After years of demonisation, *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 takes the leading role. But it is still unsolved how patient safety can be secured in free recommended combinations. A shift of paradigms to an approval of therapeutic concepts might be a solution.

Author contributions

Both authors conceived the idea to the article and structured and wrote the article jointly.

[1] If a medicinal product consists of more than one active substance, a combination statement needs to be given according to § 22 (3a) AMG in order to prove that each pharmaceutically active ingredient participates to the positive effect of the medicinal product. Without a combination statement, the application for an authorisation may be refused according to § 25 (2) No. 1 AMG.

[2] J. R. Crout was the director of the US competent authority Food and Drug Administration (FDA) in the 1970s.

Infobox A: Phytopharmaceuticals

The regulatory situation for conventionally manufactured phytopharmaceuticals/herbal medicinal products is different from the one described. Herbal medicinal products consist of one or several active substances, according to the German Drug Law. Those active substances are generally composed of a complex mixture of various herbal ingredients. A distinction can be made between main ingredients, lead compounds, attendant substances and structural materials. Main ingredients are those herbal ingredients which determine the effect of the medicinal product. Attendant substances are used for phytochemical identification in the chemical analyses. Although lead compounds do not have a direct impact on the effect of a phytopharmaceutical, they can influence the effect of main ingredients, for example, by exerting influence on its pharmacokinetics. Herbal ingredients, originating from the cellular or extra-cellular matrix and responsible for structure and stability of the former plant, are named structural materials.

In general, phytopharmaceuticals are multi-component systems and — as the oldest class of medicinal products — they can be regarded as the "prototype" of *combination medicinal products*. While pharmacologists of former times considered the phytopharmaceutical only to be a "transit" on the way to the isolated active principle (=pure substance), the opinion of today is that the complex matrix of the herbal extract is protected within the extract and can be effective especially if the pure substance cannot or can only hardly be isolated due to instability. Artemisinin, which originates from the blossom and leaves of sweet wormwood (*Artemisia annua*), was an important stage of development, although partial synthetic modifications and biotechnological innovations have changed the image. Characteristics of the artemisinin structure are a trioxan ring system and a very sensitive peroxide bridge (e.g. towards iron). It is used worldwide for the treatment of infections with multiresistent strains of plasmodium falciparum, the agent of malaria tropica [23].

In 2013, Paddon et al. released a publication on the process for manufacturing artemisinin acid using genetically modified brewer's yeast [18].

Either the (dried) plant itself or the extract derived from the plant is considered by definition to be the "active substance", which is manufactured in a "standardised manner". If possible, it is standardised to the value-determining ingredient (=active substance), but it can also be standardised on other ingredients (=lead compounds), if the active substance is unknown.

The manufacturing of a so-called special extract is a complex and multi-step process of extraction and purification. Undesirable ingredients are removed and the desirable ingredients, that determine the efficacy of the phytopharmaceutical, are enhanced by this procedure. The use of special extracts has several advantages: In the special extract, the concentration of active substances can be raised and smaller amounts of the substance are needed to achieve an impact. Undesirable byproducts can be removed by the process of extraction, so that the phytopharmaceutical will be better tolerated. Composition and amount of ingredients are standardised. Then, a consistent quality can be guaranteed [7].

Today, the basic principle of phytopharmaceuticals — multi-component mixtures in complex matrices with synergistic or antagonistic, partially unknown single components, which are protected e.g. by reductones — is acknowledged throughout the world. By the specific definition of a phytopharmaceutical it becomes obvious why it cannot be manufactured as a generic drug since the (specific) process of manufacturing the extract has a significant impact on the efficacy. There is a growing awareness on the influence of the cultivation, cultivar, method and daytime of harvesting etc. on the quality of the herbal material. If, for example, the alkaloid content in a plant fluctuates during the circadian rhythm, the wrong time of harvesting could result in extracts poor or even free of active substances. Some purists even work on cloned plants with illumination for the exact hour, nutrient solution etc.

A.1. Conclusion

The oldest group of medicinal products — the phytopharmaceuticals — are multi-component mixtures of natural origin and their use increases due to advantages in the therapy of several diseases such as good tolerability. They need to fulfill the same requirements as other medicinal products concerning the "three pillars" of authority approval — safety, efficacy and (consistent) quality — in order to enjoy broad acceptance. The German Society for psychiatry and psychotherapy, psychosomatic and neurology (DGPPN), for example, recommends the use of Saint John's wort on level 0 as a possibility of a first therapy attempt for mild to moderate depression in the S3-Guideline on unipolar depression. The decretionary clause implies expert reports or judgments and/or clinical experience of recognised authorities (category of evidence IV or extrapolation of evidence level IIa, IIb or III).

Future development will especially focus on the quality of products ("special extracts") and hopefully lead to new medicinal products, e.g. by ethnobotanical screening.[3]

Infobox B: Reimbursability of fixed medicinal product combinations

According to § 92 (1) 1 of the German Social Security Code V (SGB V), the Federal Joint Committee (G-BA) is allowed to provide binding administrative regulations on the scope and the modalities of the supply of medicinal products for contractual physicians, health insurance companies and the insurants in order to substantiate the efficiency principle. For this reason the G-BA might restrict or suspend the prescription of medicinal products, if it is proven to be inappropriate or another treatment option, that is economically more efficient and has a similar diagnostic or therapeutic approach, is available (§ 92 (1) 1 hs. 4 SGB V). Making use of this authorisation, the G-BA has regulated in Annex III No. 18 of the administrative Guideline for Medicinal Products

[3] In the late 1960s, Monroe E. Wall and M. C. Wani did an intensive research for anti-cancer substances. In 1971 they succeeded for the first time to isolate and characterise the substance Paclitaxel by extracting the bark of pacific yew (Taxus brevifolia) and investigated its effect to inhibit the proliferation of cells, e.g. cancer cells.

(AM-RL) that fixed combinations of antiphlogistics or antirheumatic drugs with other active substances will not be reimbursable. The reasons for this decision against the fixed combination of active substances are:

1. The number of side effects, especially the number of allergic reactions, tends to be higher when several active substances are ingested by the patient at the same time,
2. only in exceptional cases, the active substances have the same pharmacokinetics and duration of action, which also might change and develop differently during therapy due to enzyme induction or inhibition, and
3. therapy and potential interactions lack transparency if several active substances are used at the same time.

The legal basis for the suspension to prescribe medicinal products in fixed combination with other active substances can be found in § 92 (1) 1 hs. 3 SGB V and § 16 (1), (2) AM-RL. According to § 16 (1) AM-RL, medicinal products may not be claimed by insurants, prescribed by physicians and reimbursed by health insurance companies, if

1. the diagnostic or therapeutic benefit or,
2. the medical need or,
3. the economical efficiency

is not proven corresponding to the generally accepted state of medicinal knowledge. These conditions are met in particular, if the treatment goal can be reached more medically appropriate and/or cost-effective when using therapeutically equivalent mono-preparations (§ 16 (2) no. 5 AM-RL).

But the situation has slightly changed since a fixed combination of a non-steroidal anti-inflammatory drug (NSAID) (Naproxen) and a proton pump inhibitor (PPI) (Esomeprazole) has been approved and marketed on 12th April 2012. As a consequence, the regulation in Annex III No. 18 AM-RL had to be amended [9]: The G-BA has constituted a derogation in the AM-RL (last updated version as of 20th February 2014) for the fixed combination of a NSAID and a PPI for patients with high gastrointestinal risks for whom a treatment with low-dose NSAIDs and/or PPI is insufficient. Risk factors for the development of NSAID-associated gastrointestinal complications are, among others, high age, parallel use of anticoagulants, corticosteroids, other NSAIDs — including low-dose acetylsalicylic acid —, significant cardiovascular diseases and a medical history of gastric and/or duodenal ulcera. Those patients concerned may be treated with a fixed combination, but for all other patients a therapy either with a free combination of a NSAID and a PPI or simply a NSAID shall be more appropriate in the view of the G-BA. No exception is made for the approved and marketed fixed combination of Diclofenac and Misoprostol due to the poor tolerance of Misoprostol compared to PPIs.

A restriction for prescription of medicinal products according to § 92 (1) 1 HS. 3 SGB V and § 16 (1), (2) AM-RL can be found for ''analgesics in fixed combination with non-analgesic active substances — apart from combinations with Naloxone'' in Annex III No. 6. For justification, it is stated that the use of analgesics in fixed combination with non-analgesic active substances does not meet the current state of medical knowledge, as pain and other disease conditions shall each be treated with specific targeting of mono-preparations. The fixed combinations of an analgesic with Naloxone, which are approved and can be reimbursed, are Targin® (Oxycodone/Naloxone), Andolor®/Celldolor®/Valoron N® (Tilidin/Naloxone) und Suboxone® (Buprenorphine/Naloxone).

It can be regarded as a general principle that the G-BA rejects the reimbursement of fixed combinations of medicinal products in most cases. The amendment of Annex III to the AM-RL does not represent a deviation from this principle with further exceptions. There is a clear limitation for the use of a fixed combination of a NSAID with a PPI — the product Vimovo® (Naproxen with Esomeprazole) — in Annex III No. 18 for patients with a high gastrointestinal risk. A precondition for the reimbursement is always the careful diagnosis of the physician who has to identify the risk factors for the development of NSAID-associated gastrointestinal complications. Only in this case, a prescription financed by the statutory health insurance may be justified. Another limitation is made by the statement that a fixed combination of Diclofenac with Misoprostol shall not be reimbursed due to its poor tolerance compared to PPIs.

Nevertheless, in order to achieve the prescription of a *combination medicinal product* to be financed by the statutory health insurance, the reasons of the G-BA against fixed combinations of active substances need to be factually debilitated. It has to be proven that the fixed combination offers an equivalent or improved side-effect profile compared to the mono-preparation, nearly equivalent pharmacokinetics — which means the same duration of action of both active substances due to their half-life periods — and an improvement of therapy and compliance compared to the separate intake of several medicinal products. Also, the argument of the G-BA needs to be disproved that the treatment goal can be reached more medically appropriate and/or cost-efficient when using therapeutically equivalent mono-preparations instead of fixed combinations of active substances.

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