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Synergistic effects—Is it possible to make 'the devil an angel'?

H.G Schweim[a,b,*]

[a] Regulatory Sciences & Services, Köln, Germany
[b] Department of Drug Regulatory Affairs, Pharmaceutical Institute, Rheinische Friedrich-Wilhelms-University of Bonn, Bonn, Germany

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ABSTRACT

At the conclusion of all drug research is the 'approval of the (new) drug'. Therefore, for scientists, it's unavoidable to think about the process of regulation. First, keep in mind that all regulators are (very) conservative. All regulators have learned the lesson: avoid pharmacovigilance cases. Don't take risks; it will infringe on your career. Non-approval is the best way to avoid failures. To be frank, there were and are several unacceptable combinations on the market. If new ideas like '*synergy*' come up, 'slow motion' is the *state-of-the-art* response among regulators. But, maybe there's light at the end of the tunnel.

The Book of Revelation describes a war in heaven between angels led by the archangel Michael against those led by Lucifer, 'the devil', who are defeated and thrown down to the earth. Watch out! The 'devil' prior to this must have been an "angel".

Comparing this picture with the treatment of diseases, the "devil" can be regarded as the negative effects of medicines in a combination treatment. The main task of classical pharmacovigilance is to identify such 'devils' and avoid them. Textbooks are consistently filled with the same negative interactions and due to a lack of ethics or no obligation to undertake randomized controlled trials (RCTs). The examples are limited and are mainly discovered by chance. Over the years, this has resulted in the conclusion which is generally accepted as common knowledge in classical pharmacology: 'Avoid combination!'

In the past, we have often ignored the fact that the 'devil-angel' picture can also be switched to convey the positive effects of interactions.

One example is analgesics which result in pain relief, but which have different modes of action in the human body than non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. They differ in their influence on the perception of pain because they have different targets; e.g., different receptors located peripheral or centrally and eventually different bioavailabilities. For example, a combination of morphine and ibuprofen can increase the overall pain relief of severe pain and/or reduce the side effects of single substances.

There are major arguments against combinations, however, including – to name just a few – different ingredients of a fixed combination could have different courses or durations of action and there may be problems with the synchronization of the bioavailability, or interacting with the (same) receptors. However, these arguments are only convincing in cases when the mode of action is needed simultaneously, but not if there are different targets (with an ultimately similar outcome) and/or there is an overlapping longer period of 'steady state' for both. Perhaps 'synergy' can demonstrate that this is not a real problem if the synergism is sophisticated enough. I am entirely convinced the circumstances of the upcoming treatments of actual diseases will force us to deal with this topic.

First: It has been known for a long time that there are serious diseases that can't be sufficiently influenced (or cured) with one drug alone [1]. Over the last years, the number of diseases which require combination-therapies have increased.

Second: Our ageing society raises the issue more and more of 'multi-morbidity' patients, who are treated with several drugs where the influences of different drugs upon each other are mainly unknown. Nevertheless, a certain level of 'polypharmacy' is often unavoidable due to the severity of the diseases. The present knowledge about multifactorial causes of diseases and the necessity of multi-medications, especially in elderly patients, shows the growing challenge of demographic change. 'Normal' parameters, such as renal and heart functions, decline with advancing age for biological reasons. Therefore, a 'basic (combi-) medication' of an ageing person is quite common. If this is accompanied by 'acute medications' (which means often changing to multi-medication) in cases of (severe) illness, aspects of interactions are often unknown. The methods used to measure synergy might be a key to understanding interactions of multi-

* Corresponding author at: Department of Drug Regulatory Affairs, Pharmaceutical Institute, Rheinische Friedrich-Wilhelms-University of Bonn, Bonn, Germany.
E-mail address: schweim@web.de (H.G. Schweim).

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drug combination [2]. Perhaps a new scientific approach is required (or: Perhaps 'synergy' represents a new scientific approach).

Thirdly: With regard to the fight against bacterial infections, we are close to reaching the end of effective antibiotics. We urgently need new substances (WHO [3] or new ideas for treatment). Therefore, we have to strengthen our efforts in the area of interaction-research. For example, if it was possible to simultaneously attack a germ with all different modes of action (e.g., cell-wall, – membrane, RNA, DNA, etc.), it would be possible to eradicate the germ with lower dosages of single substances, resulting in less side effects and the eradication should result in less resistance. However, right now this is only a dream.

Fourthly: We have a lot of problems with (tropical) diseases; e.g., malaria in Africa. Of course, we have a number of effective medicines against malaria, but poorer countries can often not afford them and we need (cheaper) alternatives; e.g., plants like *Artemisia annua* L. (Fig. 1).

Plants 'protect' vulnerable substances within a matrix which stabilizes them – e.g., by reductones – and makes them more easily soluble. Therefore, plants have for decades used the principle of synergy to protect themselves in the evolutionary process to survive.

Artemisia annua possesses the capacity to produce a high number of phenolic compounds, which results in high antioxidant activity. Five major groups (coumarins, flavones, flavonols, phenolic acids, and miscellaneous) containing over 50 different phenolic compounds have been identified. *Further research into the* ***synergistic effects of artemisinin and flavonoids*** *and their biological interaction with malaria and cancer is needed* [4].

Therefore, our first conclusion is that more synergistic combination-treatments are required to 'make the devil an angel'. We can thereby profit from this evolutionary concept of plants. Nevertheless, we have to learn our lessons well. Our efforts in research should be strengthened to detect the many vulnerable sides of 'enemies' such as cancer cells or deranged biological pathways or germs. The regulatory framework of the future must make provisions for this concept, if such evidence is forthcoming; this is irrespective of whether the medicines are chemically defined or from natural origins.

Since ancient times, creatures have used 'self-synergistic' therapeutic agents in the form of naturally occurring plants and their derived pharmaceuticals. These were the first treatment attempts in history and were even used by animals; e.g., elephants, birds, and apes.

Perhaps the most famous example of an animal herbalist is the common chimpanzee. Those living in Tanzania's Gombe National Park are often seen pulling leaves off of Aspilia Africana ssp. a genus of bushy plants related to the sunflower (*Helianthus annuus* L.) [5] and which are claimed to be anti-hemorrhagic, anti-infective, and which support wound healing [6]. Sick animals pick these leaves and instead of simply chewing the leaves, the apes roll them around their mouths for a while, rather like humans sucking medicinal pills, before swallowing them.

A good example from the 'ape' Homo sapien is his use of willow bark (*Salix spec.* L). The plant has been mentioned in ancient texts as a remedy for aches, fever, and pain relief and was mentioned for the first time in the Edwin Smith Surgical Papyrus [7], dating back to the seventeenth century B.C. The papyrus is one of the oldest of all known medical papyri. The mode of action of willow bark is stronger, as would be expected from the salicin content [8], therefore synergistic effects of the other ingredients are suspected [9–11].

The main reason for the use of plants is the so-called phytochemicals, the secondary metabolites'.They are produced by the plants not for energy purposes or in the anabolic or catabolic pathways. At first glance, it seems that they are not essential for the life of the plant. However, given a closer look, it appears that they are important, especially for the survival of plants. This is the basis of our interest in and use of plant secondary metabolites. Often

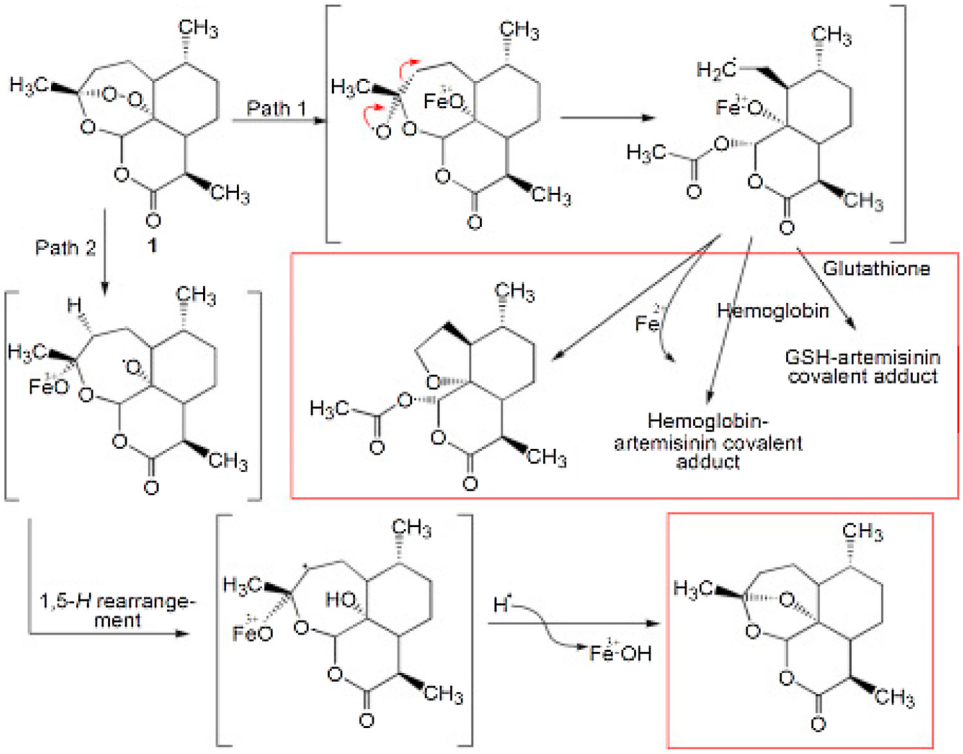

Fig. 1. The products and biochemical mechanism of artemisinins' action.
Zongru Guo, Artemisinin anti-malarial drugs in China Acta Pharmaceutica Sinica B, Volume 6, Issue 2, 2016, 115–124.

they are 'poison' to the 'enemies' of the plant and are toxic for 'human enemies' like germs.

Nevertheless, what is special about these substances and different to chemically defined and synthesized substances? Normally the plant produces them in 'clusters' or 'families' of related substances in special biological pathways. Very often – in view of the therapeutic action – we have 'naturally occurring prodrug systems' with synergistic actions. A common example is *Papaver somniferum*, a species of flowering plant in the Papaveraceae family. It is the species of plant from which opium is derived. Opium contains approximately 12 percent of the analgesic alkaloid morphine. It also contains the closely related opiates codeine and thebaine, and non-analgesic alkaloids such as papaverine and noscapine.

However, why do plants produce phytochemicals/secondary metabolites? Most believe that it is one part of the evolutionary 'battle' between plants and herbivores [12,13]. Moreover, if one is attacked by clusters of related toxic agents, it is much more difficult to 'escape'; e.g., by a chemical detoxification of the 'poison'. Let us remember, some very strong drugs are derived from plants (e.g., digitalis, colchicin), as are some very toxic poisons (e.g., cicutoxin from *Cicuta virosa* L.).

During the evolution of pharmaceutical chemistry, we searched for THE active principle in plants, isolated the same (if possible), and made chemical modifications to increase its power. Up to now, this is ONE way (and not an inefficient one; e.g., Taxol [14]) to discover new medicines. But sometimes the plants are 'the better chemists'.

The biosynthetic pathway to paclitaxel has been investigated and consists of approximately 20 enzymatic steps. The complete scheme is still unavailable. The two main reasons why this type of synthesis is not feasible in the laboratory is that nature does a much better job of controlling stereochemistry and a much better job of activating a hydrocarbon skeleton with oxygen substituents in which cytochrome P450 is responsible for some of the oxygenations.

On the other hand, plants produce their ingredients at low temperatures (e.g., by using deep eutectic solvents) [15] and 'protect' vulnerable substances within a matrix, which stabilizes them (e.g., by reductones). Therefore, plants have for decades used the principle of synergy to protect themselves in the evolutionary process to survive.

A good example is *Artemisia annua* L., which is used in the therapy of malaria. The proposed mechanism of action of artemisinin involves the cleavage of endoperoxide bridges by iron, producing free radicals which damage biological macromolecules, causing oxidative stress in the cells of the parasite. The main advantage of a living organism compared with a chemical reaction carried out in a reaction vessel is the differentiation of – sometimes running *vice versa* – biological reactions through the principle of compartment-separation. Thus, we can benefit from this evolutionary concept of plants, if we learn this lesson. Our efforts in research should be strengthened to detect several vulnerable sides of our 'enemies'; e.g., cancer cells or deranged biological pathways or germs. If evidence is shown, combinatory treatment regimens should be established and the regulatory framework of the future needs to follow this concept; this should be the case irrespective of whether the medicines are chemically defined or of natural origin.

1. Regulatory consequences

The EMA states: 'The proposed combination should always be based on valid therapeutic principles. Fixed combination medicinal products have been increasingly used in order to benefit from the added effects of medicinal products given together. In addition, it is necessary to assess the potential advantages (e.g., product is more rapidly effective, has higher efficacy, or has equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g., cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product. Potential advantages of fixed combination products may also include the counteraction by one substance of an adverse reaction produced by another one and the simplification of therapy.

Fixed combinations are commonly found for many different indications. Cardiovascular diseases often require multiple active substances and for patient convenience many fixed combinations are on the market in this area (e.g., candesartan and hydrochlorothiazide). To cover the individual needs of the patients, a wide range of different combinations with different contents of active substances needs to be marketed. Even though these combinations are easy to use for the patient as they only need to take one rather than two or more pills a day, fixed combinations are inflexible (as their name already indicates). A change in the dosage of one active substance, for example, is quite complex to implement. There are also certain restrictions and limits to fixed combinations. They can only be developed under certain conditions; for example, if the active ingredients can be taken concurrently. Furthermore, the duration of action of each active substance should correspond with the administration interval.

The FDA acknowledges the need for combination therapy in certain conditions and encourages the co-development of drugs. They released draft guidance in December 2010 concerning the co-development of novel un-marketed drugs for use in combination and published finalized guidelines for industry on this topic in June 2013. Before the FDA released this guidance, co-development of drugs for a combination regimen was rather challenging as no further assistance in this matter existed. The concept of combination treatment is, of course, not new, but the FDA guidance gives precise requirements and recommendations on how the development should proceed. Regulatory, scientific, and medical aspects are addressed. Having guidance that highlights the importance of drug combinations helps to speed up drug development and reduce costs. It also helps patients gain earlier access to treatment (Table 1).

The guidance states that for many serious diseases such as cancer, infections, and cardiovascular diseases "combination therapy is an important treatment modality".

Table 1
FDA-Guidance on combination therapies.

The combination is intended to treat a serious disease or condition.
There is a strong biological rationale for the use of the combination (e.g., inhibition of different pathways, lower doses of drug can be administered to decrease toxicity, resistances are reduced)
A full, non-clinical characterization of the activity of both the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents.
A non-clinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.
There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., risk of resistance, limited activity when used as monotherapy).

Growing understanding of pathophysiological mechanisms helps to improve treatment responses using drug combinations. New therapeutic approaches based on this knowledge can be used to our advantage. Due to a higher risk of those combinations compared to single drug use alone, combinations should only be developed for serious diseases. Knowledge of the individual active compounds in the combination is lower than that of only one active ingredient developed for the treatment. Therefore, the data concerning the safety profile, effectiveness, and dose-response are less informative. The FDA therefore specifies the conditions under which co-development is reasonable.

Furthermore, the procedure for clinical development is described in the guidance. The main objective of Phase 1 studies is to determine the safety and pharmacokinetics of both the individual drugs and the combination. Whenever feasible, all pharmacokinetic parameters of the individual drugs should be investigated. If it is not possible to characterize the drugs individually in humans, non-clinical studies should be conducted. Phase 2 should further demonstrate the contribution of each individual new investigational drug in the combination, provide evidence of the combination's effectiveness, and adjust the dose(s). When possible, a factorial study design is desirable to obtain as much information about the drugs and their combination as possible. Three scenarios are conceivable for Phase 2 studies:

1. Alone, each new investigational drug has activity and they can be administered separately.

To obtain the maximum of information about safety and effectiveness, the individual drugs should individually be compared to the combination and standard of care (SOC).

2. The individual new investigational drugs in the combination cannot be administered separately.

In cases where the individual drug cannot be administered separately for pharmacological or ethical reasons (e.g., ineffectiveness of the individual drug or rapid development of drug resistance), only the combination should be studied.

3. When administered separately, one new investigational drug in the combination is active and one is inactive.

The minimally active compound requires Phase 1 safety studies but not a further individual drug Phase 2 study. The study designs suggested by the FDA for each scenario are given in Table 2.

The guidance, however, only concerns **novel un-marketed drugs**. Nevertheless, it can also be expected that drugs that are already marketed can be beneficial in certain combination therapies for specific indications. Therefore, the FDA has requested the major pharmaceutical companies to consider drug combinations of known drugs for drug development in addition to newly developed drugs [16], but this is not reflected in the regulatory framework.

The FDA guidance takes a step in the right direction, but does not yet go far enough. It will be necessary to enlarge the concept to include new combinations of well-known drugs. From my perspective, the most promising new approach is the inclusion of free combinations of different drugs if they have proven their potency in synergy experiments.

The introduction of the **Adaptive Pathway** shows that the regulatory framework for drug authorization needs constant development and changes to adapt to new challenges. There are several other aspects in drug authorization that are reflected unsatisfactorily in the regulatory framework. In the current status of drug development and drug approval, only one agent at a time is reviewed and approved by authorities. Yet, it is common knowledge that for certain diseases a variety of drugs and medical devices are used in combination to treat a condition. Combinations of medicinal products are very frequently used in medical practice, but the legislation for combinations lags behind when compared to single drug authorization. Combinations of medicinal products have a long history and it is likely that with the current research, the use of medical combinations will extend. With the evolution of personalized medicine, research is just beginning to recognize the many different biological and genetic aspects of diseases. This knowledge can be used in drug development and therapy. Having a more detailed understanding of the cellular pathways provides better chances to target drug therapy. Because the body is a complex biological system, in many diseases it is not enough to inhibit only one cellular pathway, as alternative routes can be activated as a response to such inhibition leading to therapy resistance. In order to develop a targeted therapy, a complete understanding of the biochemical response to drugs and disease is needed. Then, drug combinations can be designed to address multiple cellular pathways and resistance mechanisms. Personalized medicine and genomic research are an important part of the development towards targeted drug combination therapy. Today, some of the most serious diseases require a combination of drugs for treatment. Other treatments rely on the outcome of a diagnostic test. The diagnostic test should hence be considered to be part of the treatment regime.

2. Conclusion

There exists a gap between treatment reality, including the approval practice, and research. The limits of single drug authorizations have been reached. New pathways for the authorization of combinations need to be introduced. The next logical step in the regulatory framework is the co-approval of combination therapies based on targeted approaches, which so far does not exist. The approach introduced in this paper recommends this additional new way of drug approval to overcome this gap. The development and approval of novel therapeutic concepts would be a consistent step towards better health care. A clear regulatory pathway towards an approval of drug combinations could help agencies, health care professionals, and patients to obtain safer therapies and clear recommendations for medical practice.

To distinguish between an approved combination regimen and the frequently used term 'combination therapy' that refers to a general therapy consisting of a therapy with multiple medicinal products or other treatment options, a new term is introduced for approved combination therapy: 'Therapeutic concept'.

Our definition for a therapeutic concept [17,18] as it is introduced and used, is the following (Table 3):

Therapeutic concepts could be one of the next steps and would also cover combinations, including free ones, containing

Table 2
Study design as suggested by the FDA for scenarios 1 to 3 (for details see text).

Scenario	Study design	Remarks
1	A v. B v. AB v. SOC or placebo	SOC can be added to each arm, when it is a known effective, not palliative, therapy
2	AB v. SOC	SOC can be added to AB, when it is a known effective, not palliative, therapy, comparing to placebo + SOC
3	A^* v. AB^+ v. SOC or placebo	

Abbreviations: SOC (standard of care), A: drug A; B: drug B, v: versus.Source: FDA

Table 3
Definition for a Therapeutic concept [17,18].

Therapeutic concept:
A therapeutic concept is the approval of a treatment regimen, consisting of two or more, marketed or not yet marketed, medicinal products or one or more medicinal products and a companion diagnostic/medical device, if it is required for a safe and effective use of the regimen, that have been developed and studied together for a specific condition and patient population.

compounds that are already marketed to improve the safety of combinatory use of these compounds.

In order to tackle the challenge of one of the most pressing health phenomena – the development of drug resistance (e.g., cancer, antibiotics) – using combinatory drug regimes which harbour the risk of therapeutic problems (e.g., interaction in a multi-drug-environment, therapy of complex diseases, dose reduction, reduction of adverse drug events, improved efficacy), in practice the introduction on a regulatory level of an 'approval of therapeutic concepts' and on a research level of the 'search and use of synergistic effects' may be the answer.

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