A question based approach to drug development

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The value of timing additional studies

In this section, four studies were presented that investigated what the improved profile of a new sustained release formulation would be and what its effects are in patients with hypertension. Using blood pressure and the most sensitive marker for the side-effect sedation (saccadic peak velocity), the therapeutic window of the new formulation was improved. Furthermore, it was possible to correlate the *in vivo* with the *in vitro* dissolution of a new formulation. Combined, these studies helped in designing an improved sustained release formulation for an existing drug with adequate clinical effects at tolerated levels. Because the drug has been on the market for quite some time, the development of the original formulation apparently did not optimally answer these questions. Now additional studies had to be performed at a post-registration stage. In this chapter it is investigated what the value of these additional studies have if they are performed at an early stage versus later on in the development.

TABLE 1 **Input parameters of the retrospective question-based approach for the development of rilmenidine**

Parameter	Input
Success action site	85.00%
Success pharmacological effect	85.00%
Success clinical efficacy	75.00%
Success therapeutic window	70.00%
Success population	80.00%
Estimated market value	400
Costs action site	30
Costs pharmacological effect	35
Costs clinical effect	40
Costs clinical window	35
Costs population	35

The first step in the analysis consists of estimation of the success probabilities and the accompanying costs. Obviously, this is done retrospectively since both the original and the new formulations have already been developed. The set of input parameters used in the QBD tree is shown in table 1. The overall probability of

success, the cumulative costs and the final payoff equal the values in the previous section and are based on historical data. It can be argued that for this compound the window question will have the relatively lowest probability of success with this compound. The clinical question would also be relatively difficult to answer and would introduce substantial costs since this would involve large patient studies. The penetration to the site of action, and the pharmacological effects the drug would exert, could have higher probabilities of success.
The optimal priority list of this question-based approach for the development of rilmenidine yields the optimal sequence of questions represented in table 2.

TABLE 2 **Optimal question sequence in the development of rilmenidine**

Priority ranking	Question
1	Window
2	Clinical
3	Population
4	Site
5	Pharmacology

However, the actual development of rilmenidine apparently did not fully answer the "window" and "clinical" question. This deficiency is reflected in the fact that in the actual development of rilmenidine, a sustained release formulation was developed after registration of the original rilmenidine formulation. Rilmenidine is currently available in several European countries, but was not registered in, for instance, the USA and the Netherlands. The development of a formulation with sustained release properties could allow introduction of the drug in these countries. In this section, a comparison of the optimal development plan with the actual development sequence was made. The studies presented here all address the "window" and "clinical" question and were performed late in the development (assuming that worldwide registration is the endpoint). This approach yields the sequence represented in table 3.
The project value of the question-based development of rilmenidine is (as demonstrated in the previous sction) the sum of all possible outcomes weighted for the probability that a particular outcome will happen. Calculation of the project value of the optimal sequence with the input parameters presented in table 2 yields an estimated value of M€ 14.9. However, the project value of the actual development

program (with the same overall success probability and costs) is only M€ 2.2.
In order to investigate how this substantial drop in value is created, risk analyses were performed that show all possible outcomes and the probability this will happen. The results of these analyses are represented in figure 1.

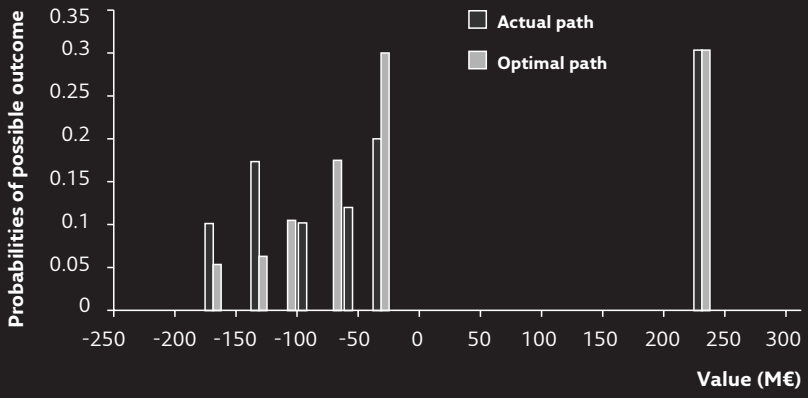
TABLE 3 **Actual question sequence in the development of rilmenidine**

Priority ranking	Question
1	Population
2	Site
3	Pharmacology
4	Window
5	Clinical

This analysis shows substantial differences in the two different priority sequences. Obviously, if all questions are answered successfully, no difference exists between the two options; both have a payoff of M€ 225 and a probability of 30% this will happen. However, if the product is abandoned somewhere in the process, the probabilities of the subsequent negative outcomes differ. In the optimal path, the higher the negative outcome is, the lower the corresponding probability is. The actual situation shows relatively high probabilities the outcome will be M€ -137.5 (17,3% vs. 6,3%) or even M€ -175 (10,1% vs. 5.4%). M€ -137.5 will be the outcome if the product is abandoned after answering "window" in the sequence presented in table 3 and M€ -175 if the product is abandoned after the last question ("clinical"). By moving these questions to early in the development, the risk of late abandonment is reduced in the optimal sequence.
The analysis shows that without reducing the probability of failure, the project value can be increased simply by rearranging the sequence of studies. The increased value allows additional studies to be performed that, in the NPV approach, would only introduce additional costs and development time. The studies presented in this section are an example of additional studies that combined solves the "window" and "clinical" question. While the NPV would decrease, the question-based approach adequately describes the impact of these studies.
The impact could have been even more valuable if the studies were performed at an early stage in the original development of rilmenidine. The inclusion of these studies at an early stage in the original development of rilmenidine would have

allowed the introduction of the improved formulation for this compound and thereby reducing the additional costs of having to introduce a new formulation. Remarkably, the NPV of this hypothetical development plan would be lower than the one actually used due to additional costs and development time. However, the result would be a formulation that would potentially meet a larger market demand (e.g. registration in the USA and other countries where rilmenidine is currently not registered) and the revenues could therefore have been even higher.

FIGURE 1 **Risk profiles of the QBD programs of rilmenidine**



From a business perspective, there is quite another view, which basically says 'introduce the product into the market, if it is basically satisfactory, as soon as possible. Additional useful information will be obtained from market experience and then consider what might be accomplished with an improved formulation'. This approach has been adopted in the nifedipine case, where after introduction of the original product, an improved formulation was successfully developed based on the discovery of a novel pharmacodynamic property of the drug. The improved product after the launch of the original product is sometimes referred to as a 2nd-cycle product. Clearly, critical evaluation of emerging new post-launch data is always necessary and additional investigations sometimes lead to highly successful new products, as proven by the nifedipine case. However, the starting point for the first cycle of development should be to develop the best possible treatment.