Impact of Dose Selection Strategies on the Success of Drug Development Programmes

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Abstract
A number of parameters need to be considered when designing dose-ranging (phase IIb) trials. These are: the number of doses to be studied; the choice of design/statistical methodology; dose selection criteria for phase III; the number of doses to be taken into phase III; and the size of phase IIb. When assessing the impact of dose selection strategies, efficacy and safety need to be addressed simultaneously. Product development scenarios can then be compared based on the associated probability of success in phase III and/or the expected net present value. Assessing the impact of dose selection strategies with the consideration of multiple parameters is best carried out using simulations, due to their complexity.

Keywords
Dose selection criteria, adaptive design, probability of success (PoS), net present value (NPV), simulations

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Let us begin by specifying the main objectives of phase IIb studies. First and foremost, dose-ranging studies need to address regulatory requirements to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen.1 Another key objective is to select the dose(s) to be studied in phase III that would give the best chance for regulatory approval of the product. A well selected dose would have a desirable risk–benefit profile and would thus provide the most benefit to future patients. This would result in a better market value for the product and improved market share. To address these objectives one has to study not only the product’s efficacy characteristics but also the product’s safety profile early on. There are a number of characteristics that one has to consider for the design of phase IIb trials.2 These are: the number of doses to be studied; the choice of design/statistical methodology; dose selection criteria for phase III; the number of doses to be taken into phase III; and the size of phase IIb.

Number of Doses to Study in Phase IIb
Traditionally, phase IIb trials have studied a handful of doses. At the time that phase IIb is reached, however, sponsors usually have very limited information on the safety profile of the drug, as well as limited efficacy information on the clinical endpoints. Consequently, doses that are evaluated in phase IIb may not be the ones that would achieve maximum efficacy. They may be in a region of the dose–response curve where the efficacy has already reached a plateau, or may be at the level where the risk of patients experiencing treatment-limiting toxicities is too high. Occasionally, a dose with an optimal combination of safety and efficacy can be somewhere in between two doses included in the phase IIb trial if the spacing between doses is too wide. Clearly, then, there should be an advantage in including a larger number of doses in clinical trials at this stage of development. However, a large number of doses would require very large studies if each dose were to be compared with the control independently. To avoid this, one could instead assess the observed dose–response profile as a whole. This could be achieved by fitting an appropriate model that best describes the relationship between dose and outcome. A number of different modelling approaches for phase IIb dose-ranging studies have been described in the literature.3

Phase IIb Adaptive Design
Studying a large number of doses inevitably means that most likely not all of them are safe, or that not all of them are efficacious, and most definitely that not all of them are the best ones to be selected for phase III. Thus, randomising patients to all available doses until the end of the trial would not be very efficient and arguably raises ethical concerns.

Adaptive design allows for key design parameters to be changed during the trial based on the data observed during that trial, and as such is a natural fit for the exploratory stages of development. For example, in phase IIb trials ineffective doses can be discontinued, new doses added or the randomisation allocation ratio adjusted in favour of doses that demonstrate better safety/efficacy during the trial. As a result, over the course of a trial a larger and larger proportion of patients would be randomised to doses with better safety and efficacy characteristics. Numerous phase IIb adaptive designs have recently been developed and described by PhRMA’s Adaptive Dose-Ranging Studies Working Group.4,5

Criteria for Phase III Dose Selection
Defining dose selection criteria is a key strategic decision in the planning and design of dose-ranging studies. The effect of dose
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Selection criteria is illustrated in Figure 1. In the referenced study, the minimum clinically significant dose was used as the target for dose selection. Simulations were applied to select doses to progress into phase III based on the pre-selected safety and efficacy dose-response profiles; that is, the ‘true’ efficacy as well as the ‘true’ risk of experiencing a dose-limiting toxicity was known for each dose.

The x-axis in Figure 1 shows the eight doses included in this simulation study. The minimum clinically significant dose was dose number 3. The purple bar represents the dose with the best chance of success based on a combination of pre-selected safety and efficacy dose responses. Doses above dose 4 are associated with higher safety risks, while doses below dose 3 have insufficient efficacy. The y-axis on this graph shows the proportion of times each dose has been selected to advance into phase III. Naturally, given the dose selection criteria, dose 3 has been selected most often. As one can see from the graph, the next dose above actually has a more promising combination of safety and efficacy. Optimal dose selection criteria would shift the distribution of selected doses so that the optimal ‘purple’ dose is selected with the highest frequency.

A number of dose selection criteria can be applied to any given study. The selection of criteria depends on indication, specific regulatory requirements, the development strategy and the amount of efficacy and safety data available. In any case, an attempt should always be made to implicitly or explicitly address both safety and efficacy in dose selection criteria. Below are some suggested approaches, but this is not an exhaustive list:

- selecting the maximum dose beyond which no further beneficial effect is seen;
- choosing the highest dose that still appears to be safe and shows a clinically relevant effect;
- selecting the dose that yields the largest probability of success (PoS) based on both its observed efficacy and safety profiles;
- choosing a dose that maximises a pre-specified ‘utility’ function (the utility function is defined so that efficacy and safety are combined and weighted according to their respective clinical and commercial significance); and
- selecting the minimum dose that delivers a pre-defined percentage of the maximum efficacy.

Number of Doses to Select for Phase III

The observed differences in efficacy between two doses in phase IIb may not always allow a clear choice for the phase III trial, or the safety data observed during phase IIb may be insufficient or inconclusive. In some cases there may be a dilemma as to whether lower doses are sufficiently good to warrant an approval, while there may be existing safety concerns associated with the higher doses. Selection of more than one dose to be studied in phase III should then improve the PoS of the phase III programme. Looking back at Figure 1, if two doses are selected for phase III it is much more likely that the optimal ‘purple’ dose will be included in phase III. However, one needs to keep in mind that in phase III a penalty will be imposed on the type I error level to control for multiplicity if more than one dose is studied.

Size of Dose-ranging Studies

Calculating the sample size required for a phase IIb trial is much more complex than calculating the sample size required for a confirmatory trial, particularly if an adaptive design is implemented. The primary objective of a phase IIb trial is to select the ‘best’ dose(s) for a confirmatory trial. Therefore, the objective at the end of the study is to have a satisfactory level of evidence that the selected dose differentiates from other doses included. How to define the satisfactory level of evidence will be discussed later in this article.

First, refer back to Figure 1. While the optimal decision criteria would centre the distribution of selected doses close to the optimal dose, a larger sample size would make that distribution narrower and increase the percentage of times the optimal dose is selected. Even with decision criteria that are right on target, the best dose will not always be selected due to the variability in response. The smaller
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the sample size, the larger that variability will be. However, for a selected dose to always be on target, massive phase IIb studies would have to be conducted. The art then is to determine an optimal study size.

Figure 2A shows a theoretical relationship between the size of a phase IIb study and the PoS in phase III. Usually there would be a sharp initial increase in the PoS up to the point where it starts levelling off as the ceiling is approached. A common approach in phase IIb is to fix the maximum sample size or to pre-determine the desired target PoS. In either case, that may be at the point on the y-axis where much can still be gained by small increases in sample size (x-axis), or at the other extreme at the point where the curve has levelled off and very little information is gained per unit invested. One may instead decide to select the sample size in the region of the curve where the PoS starts levelling off. However, the decision as to where to place the ‘optimal’ sample size would still be an arbitrary one. One would not know where the point on the curve is up to which an increase in sample size ‘pays-off’ financially. To answer this question, the approach described in the next section has to be taken.

Expected Net Present Value

In general, any given design or development strategy collecting more information results in a higher PoS. Selecting more than one dose to be studied in phase III improves the probability of a positive study. Likewise, a larger phase IIb study would improve the chance of selecting the best dose for phase III, provided that decision criteria are not significantly off target. This would, again, result in a better PoS of phase III programme. The question then is: how much to invest in any given phase of development, and at which stages of development does investing more result in higher returns on investment? To address this, one has to compare different programmes not only on the basis of their resulting PoS but also on financial criteria. The financial analysis needs to contemplate three parameters:  

• the PoS associated with various development strategies;  
• the direct cost of a development programme; and  
• the length of patent time remaining after the drug approval.

As already discussed, larger studies would generally result in improvements in the PoS, but would increase the programme cost and delay time to approval. The improved PoS would, of course, have a positive impact on the expected net present value (NPV), while increased costs and delays in approval would have negative impacts. In most cases, particularly for products that would result in large revenues, a balance has to be struck between the PoS and the length of patent time. Increased costs do balance against improvements in the PoS, but usually to a lesser extent. Rather, cost should be seen as a limiting factor, particularly if investment decisions are made at the portfolio level.

In Figure 2B, a theoretical relationship between the size of a dose-ranging study and the expected NPV is presented, with an assumption that it would have a quadratical shape with a peak most likely in the region where the PoS is levelling off. The optimal size of phase IIb would then be at the point where the expected NPV starts going downwards. A similar approach can be taken when other design parameters are considered. For inclusion of an additional dose in phase III, for example, one can compare the financial benefits associated with increased PoS versus the negative impact of delayed time to regulatory submission and additional costs.

Simulations for Scenario Comparisons

The above makes it clear that methods and processes for calculating the PoS and expected NPV involve a very high level of complexity. Assessing the impact of dose selection strategies on phase III trials – particularly with the inclusion of multiple doses, adaptive design and simultaneous consideration of safety and efficacy – is best achieved by using simulations.

The use of simulations has the additional advantage that pre-clinical and early clinical findings can be incorporated in ‘prior distributions’ for the assumed efficacy and safety profile of the treatment. This prior knowledge can then be combined with the observed data into the posterior information, using the Bayesian paradigm.

Conclusion

We are coming to an era with increased pressure on sponsors to improve the cost-effectiveness, productivity and quality of their product development. There is less reliance on the ‘gut feeling’ at decision points, with much more focus on quantitative decision-making based on the PoS and expected NPV. It is then to be expected that simulations for comparisons of different development scenarios will become an integral and necessary part of product development programmes.

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Welcome to Drug Delivery

The moment man started to treat disease with oral potions and skin liniments, the art of drug delivery began. Since then, we have made enormous strides in the complexity and diversity of drug delivery systems that can be administered using the varied routes available in the body. However, as many novel molecules face the challenge of adequate membrane transport and of therapeutically effective levels in the body, we are still seeking enhanced performance through innovation in the drug delivery systems arena.

In this year’s edition of Drug Delivery, we have brought together articles addressing key issues and industrial challenges from opinion leaders in the field along with representatives from governing and regulatory bodies. Jared Hahn looks at the biopharmaceuticals market and its context as part of the broader challenges facing the drug delivery industry. Other authors examine various routes of drug delivery: transdermal (Weiyong Li), nasal/inhaled (Mark Everard, James Fink and Michael Benninger), oral (Andrea Gazzaniga), molecular imaging (Xiaoyuan Chen) and nanotechnology (Mark Bünger and Raj Bawa).

May this edition stimulate our thoughts and provide good reading for all of us who work in and are passionate about innovation in drug delivery.

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