ADDPLAN® DF
AN ADVANCED TOOL FOR
OPTIMIZING DOSE SELECTION IN
EXPLORATORY DRUG DEVELOPMENT

An Aptiv Solutions White Paper
Executive Summary

Driven by high attrition rates in Phase 2 and Phase 3, the pharmaceutical industry has set itself the major objective of dramatically improving R&D efficiency and productivity. A key determinant of this high level of failure is poor dose selection in exploratory development. Two key processes underpin Pharma’s ability to reduce product attrition. The first is the accurate assessment of Proof of Concept and the second is robust determination of the target dose to be taken forward into confirmatory Phase 3 trials.

Determining an optimal dose level for a drug and characterizing its dose response relationship are key objectives for any new medicine. Drug developers are concerned with safety and tolerability when the dose is too high and inadequate efficacy if the dose is too low. Accurately defining this risk/benefit ratio is a key step in the clinical development process and failure to achieve this can lead to patients missing out on groundbreaking medications and the pharmaceutical industry failing to achieve key product approvals. Thus, selection of the dose to be taken forward into confirmatory studies is a critical decision which has important ethical and financial consequences.

Proof of Concept and dose selection can be achieved through use of a Multiple Comparison Procedure and a modeling approach. When used alone both techniques have limitations. The Multiple Comparison Procedure can be used to determine Proof of Concept using few assumptions on the underlying dose-response relationship and taking the dose as a qualitative factor. In the modeling approach, assumptions on functional relationships are used for estimating the target dose. The dose is taken as a quantitative factor allowing greater flexibility and accuracy in the dose selection process.

More recently a hybrid methodology (MCP-Mod) has been described that combines the approaches of the Multiple Comparison Procedure (MCP) with modeling (Mod) enabling a much more robust determination of the optimal dose for a drug, and its dose-response relationship. In collaboration with the authors of the hybrid methodology, Apriv Solutions has developed a fully-validated software package ADDPLAN® DF, that implements the MCP-Mod dose-finding methodology. This methodology will enable drug developers to determine more accurately the effective dose to take forward into confirmatory Phase 3 studies.

The Critical Importance of Dose Finding Trials

The pharmaceutical industry is facing unprecedented challenges to increase R&D efficiency and effectiveness. The average cost to bring a new molecular entity to market is now estimated to be approximately $1.8 billion. Both the FDA and Industry acknowledge that the processes used to define dose and dosing regimen in Phase 2 are not robust however, are a major contributing factor to late phase attrition. Thus, the consequences of improving dose selection in Phase 2 should be measured in terms of the success rate of subsequent confirmatory trials. In this case, the business value of improving dose selection can amount to billions of dollars across a product portfolio and perhaps more importantly, deliver an increased number of novel medicines to patients.

The objectives of Phase 2 trials have been succinctly described:

- Detect dose response and establish Proof of Concept: evaluate if there is evidence of activity associated with the drug, represented by a change in clinical response resulting from a change in dose
- Identify clinical relevance: if Proof of Concept is established, determine if a pre-defined clinically relevant response (compared to placebo) can be obtained within the observed dose range
- Estimate the dose-response profile within the observed dose range
- Select the target dose: when the previous goal is met, select the target dose to be studied in confirmatory trials

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CONCLUSION

This white paper discusses the important role that MCP-Mod has to play in dose selection and describes the embodiment of this methodology in a fully validated software tool called ADDPLAN® DF. The software has been designed to address the critical need for establishing Proof of Concept and determining the optimum target dose to select for Phase 3 trials. This tool will enable drug developers to remove a number of the uncertainties inherent in Phase 2 dose-finding trials and improve critical decisions on dose-selection, which will directly impact the probability of success in Phase 3.

The Aptiv Solutions Innovation Center is working closely with international academic and industrial methodology specialists to further enhance and extend innovative and adaptive approaches to dose-finding. Future versions of ADDPLAN® DF will include adaptive design components for Multiple Comparison Procedures, Modeling and MCP-Mod, as well as standard approaches like 3+3 dose escalation and continuous reassessment methods (CRM). These will allow simulation of the adaptive aspects of trial design and demonstrate the benefits of this approach compared to standard fixed design and analysis techniques.

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MCP-MOD APPROACH

TO DOSE-FINDING

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A combination of the Multiple Comparison Procedure and the modelling approach is called MCP-Mod. The steps for defining the MCP-Mod methodology are as follows and described further in the flow chart below:

- Define several plausible candidate dose-response models
- For each candidate model, derive an optimal contrast against a flat dose response
- Test Proof of Concept

• Model-dose-response and estimate the target dose with one (or a weighted average) of the significant models

The MCP-Mod approach circumvents the use of pairwise comparisons for proving a dose-response effect. Optimal contrasts based on assumptions of likely dose-response shapes provide weighted scores for the different dose-levels. This allows the determination of true dose-response effects with a higher probability, compared to pairwise comparisons. Moreover, model-based optimal contrasts do not suffer from multiplicity issues. Dose-levels can therefore be added to test Proof of Concept without an additional penalty for multiplicity. These additional dose-levels then support the detection of a reliable working model for the dose-estimation.

MCP-Mod is adaptive in analysis. Based on the optimized contrast tests, a set of models will be fitted to the data and a working model is selected for estimating the targeted dose. Adaptive modelling accounts in this way for model uncertainty in dose estimation. Although relatively new, the MCP-Mod approach has already been implemented in a range of studies by large pharmaceutical companies and there is growing interest in applying this novel approach to dose-finding more widely.
ADDPLAN® DF has been developed to enable easy deployment of the MCP-Mod methodology and address the growing demand for designing and conducting Phase 2 studies that accurately determine true dose response.

ADDPLAN® DF - A TOOL TO DESIGN, SIMULATE AND ANALYZE INNOVATIVE DOSE-FINDING STUDIES

Using the design engine of ADDPLAN® DF, the optimal allocation rates for a robust dose-estimation can be calculated. Weighted sets of dose-response assumptions can be considered in the design engine to address the uncertainty about the true dose-response relationship when optimizing the allocation rates with respect to the generalized variance of parameter estimates (D-optimality), the asymptotic variance of dose-estimates (TD-optimality) or a combination of both criteria (D&T-optimality).

The required sample size for rejecting a “no-dose-response-effect” can be calculated with the computed allocation rates. Model-based contrasts optimize the power of the statistical testing procedure under the assumption of the specified candidate dose-response shapes. Different scenarios on the true dose-response relationship can be taken into account in the sample size calculation in order to claim the existence of a dose-response effect with high probability.

The simulation engine of ADDPLAN® DF allows the verification of characteristics of the chosen design. The reliability of the dose-estimates can be verified by simulating dose-finding trials with the considered designs, different working model selection rules, as well as sets of contrasts and scenarios for the underlying true dose-response. Verifying the study design with the help of simulations is crucial for the final design selection. Ineffective designs and assumptions on models can be excluded by analyzing the simulation results. This will provide the evidence that an effective and efficient dose-finding design has been chosen.

The modeling facilities of ADDPLAN® DF allow the fitting of typical dose-response models to the data using least squares techniques, Bootstraping and Bayesian approaches. The doses delivering a targeted effect above placebo can be estimated and the dose-response can be characterized over the whole dose-range.

The MCP-Mod approach combines model-based multiple comparison techniques and modeling in a single system. ADDPLAN® DF provides parameter and dose estimates for all significant models, and the target dose can be selected based on the computed decision criterion for the model selection.

The whole design, simulation and analysis functionality of ADDPLAN® DF is available for normal, binary and count data.

ASTHMA TRIAL EXAMPLE

The primary objective of this study was the selection of a dose for a Phase 3 trial on an anti-asthmatic drug. Four active dose levels and placebo were considered for administration in the Phase 2 trial. A placebo effect of 60mL and a maximum increase over placebo of 280 mL of the change from baseline for the forced expiratory volume was assumed. The clinically relevant benefit over placebo was set at 200 mL and 5 different dose-response shapes where taken into account for addressing the uncertainty on the true underlying dose-response relationship in the design optimization step (Figure 1).

With the computed allocation rates and the selected dose-response shapes, the required sample size for Proof of Concept can be calculated based on different contrast types. Taking information on likely dose-response-shapes into account reduces the required sample size to establish Proof of Concept. The model based contrasts need a total of 149 subjects for the assumed allocation rates. Williams-contrasts use monotonicity assumptions on the dose-response, and the sample size is slightly increased to 166. Pairwise comparisons against control (Dunnett-contrasts) do not use any assumptions on the dose-response and require the largest sample size to establish Proof of Concept (Table 1).

The design and simulation process can be repeated to take these findings into account. Additional models can be added to the candidate set of models, assumptions on the true dose-response can be included in the simulation, or the allocation rates and sample sizes might be changed and additional dose-levels included, to examine the impact on the statistical power of Proof of Concept, and to increase the accuracy of dose estimation. ADDPLAN® DF provides the functionality to assess these different design, simulation and analysis options for dose-finding trials in a clear and validated environment.

The blue line represents the mean dose estimate of 10,000 simulations. The Akaike information criterion (AIC) penalizes additional parameters in the models. In the example provided, the model selection procedure tends to select the linear dose-response shape which leads in both scenarios to an overestimation of the Minimum Effective Dose (left-hand side). The criterion wAIC estimates the dose based on a weighted average of the dose-estimates of different models. These weights are calculated according to the AIC. The model with the maximum contrast will be selected using the maxT criterion (maximum t-statistic).

### Table 1: Sample size for 90% power for different contrast tests

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Simulation of the design under various scenarios provides insight into the working model selection for dose estimation. The impact of model mis-specifications can be easily studied via simulations. Figure 2 displays the effect of model selection criteria in different scenarios for the given design and candidate models.

**FIGURE 1:** Candidate shapes and allocation weights

**FIGURE 2:** Dose-estimates and dependence on model selection

**Left side:** Linear candidate included

**Right side:** No Linear candidate

**Logistic scenario (1)**

**Logistic scenario (2)**
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