Dose Finding in Clinical Development of 60 FDA-approved Drugs Compared to the Learning versus Confirming paradigm

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Objectives
To investigate the clinical development paths, dose-ranging trial design, and dose-exposure-response characterization, which formed the basis for label identification in drug development programs.

In many cases, confirmatory development leans more towards learning than confirming as multiple doses are commonly included in this stage, questioning sponsors’ certainty of drug benefit/risk when initiating confirmatory development.

Conclusions

Dose-exposure-response appears to be robustly assessed in only a minority of clinical development programs, suggesting there may be room left for optimizing the benefit-risk profile of confirmatory marketed dose(s).

Methods

All information available in individual FDA approval packages on the Drugs@FDA website [7] was used to identify clinical trials relevant to dose finding and dose-exposure-response characterization. Clinical development programs were categorized based on initiation in healthy volunteers (IHV) or in patients (IP).

The highest prevailing reason for non-approval of new molecular entity applications by the US Food and Drug Administration (FDA) between 2000 and 2012 was uncertainty regarding the adequacy of clinical development programs (%)

In 46 exploratory dose-ranging trials that did not implement dose-escalation:
- Only 20% included at least four investigational drug doses over an at least 10-fold dose range (Figure 4, left), as suggested at the Dose Finding Workshop hosted by the European Medicines Agency [4];
- No predominant dose spacing/allocation designs could be discerned (Figure 4, right).

Background

The driving highest reason for non-approval of new molecular entity applications by the US Food and Drug Administration (FDA) between 2000 and 2012 was uncertainty regarding the adequacy of clinical development programs (%)

In many cases, confirmatory development leans more towards learning than confirming as multiple doses are commonly included in this stage, questioning sponsors’ certainty of drug benefit/risk when initiating confirmatory development.

Figure 1: Clinical drug development as described by Shiner [6], consisting of two Learning-Confirm sequences. Each clinical stage has a specific objective, resulting in the need for a differing number of doses and analysis methods.

Clinical Development Paths

The clinical development paths in the included programs are illustrated in Figure 3.

Conclusions

Dose-exposure-response appears to be robustly assessed in only a minority of clinical development programs, suggesting there may be room left for optimizing the benefit-risk profile of confirmatory marketed dose(s).

Table 1: Evaluation of dose-exposure-response for efficacy in 60 development programs. * indicates a statistically significant association.

References