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PERSPECTIVE

A framework to guide dose & regimen strategy for clinical drug development

Optimizing new drug therapies remains a challenge for clinical development, despite the use of ever more sophisticated quantitative methodologies. Although conceptually simple, the idea of finding the right treatment at the right dose for the right patient to ensure an appropriate balance of risks and benefits is challenging and requires a multidisciplinary approach. In this paper, we present a framework developed as a tool for organizing knowledge and facilitating collaboration in development teams.

INTRODUCTION

Determining the appropriate dose and regimen is one of the hardest and most important tasks during the development of new drugs.

Incomplete or inaccurate understanding of the dose- or exposure-response relationships can lead to study design errors, erroneous strategic decisions, general clinical development inefficiency, concerns from regulators on dose selection rationale, and ultimately suboptimal drugs.

Approximately 16% of drugs (~1 of 6) that failed the first US Food and Drug Administration (FDA) review cycle were rejected because of uncertainties in the dose selection rationale. Furthermore, poorly selected doses in the confirmatory studies may have resulted in a substantial fraction of deficiencies regarding efficacy and/or safety in the remaining dossiers.[1] About 20% of FDA-approved new molecular entities required label changes regarding dosing after approval.[2]

The challenge of dose and regimen finding is not new, with the International Conference on Harmonization (ICH) E4 guidance originally written in 1994. The need to understand how the benefit/risk balance for individual therapies can be quantified and optimized sparked pioneering conceptual work decades ago.[3,4] Today, with the development of sophisticated novel therapies (e.g., therapies affecting gene transcription/translation, bispecific antibodies, or antibody-drug conjugates), the depth and breadth of this task is growing.

Advances in the methodology for clinical dose finding (e.g., the development of model-based dose finding designs) have been instrumental in meeting the challenge.[5–7] However, finding the right treatment at the right dose for the right patient at the right time remains difficult due to a multitude of practical, scientific, and/or financial constraints. In this paper, we present a framework developed as a tool to organize knowledge and facilitate collaboration to define dose finding strategies in multidisciplinary development teams.

THE DOSE FINDING FRAMEWORK

The process of finding and justifying doses and regimens is iterative and spans all phases of drug development. The need to identify an appropriate set of doses typically starts before preclinical studies, continues with determining the starting dose and dose range for first-in-human and the dose for proof-of-concept studies. Dose finding studies characterize the dose-exposure-response relationships for efficacy and possibly safety, before moving into confirmatory studies. Even confirmatory studies sometimes continue evaluating multiple doses due to remaining uncertainties in dose selection.

Under high medical need, for rare diseases or often in pediatric drug development, conduct of the full sequence of studies might be unethical or infeasible. Consequently, strategies that yield only partial knowledge of dose-exposure-response may be inevitable. In such cases, the demand to optimize data generation toward increased inferential value for best-possible therapy is greatest, because unresolved uncertainties can have an even bigger impact.

Successful dose finding requires multidisciplinary expertise from the basic and applied/clinical sciences, including biology, statistics, pharmacology, pharmacokinetics, pharmaceutics, pharmacometrics, translational

medicine, and drug safety. Regulatory affairs and market access perspectives should also be taken into account when defining dose finding strategies.

The dose finding framework is a simple tool to help teams establish a common ground of knowns and unknowns about a drug, the disease and target population(s) and the wider development context, and for mapping this knowledge onto viable strategies. The intent is to start early (i.e., before the first-in-human investigation), revise often (i.e., as new knowledge is acquired or the program focus shifts), and ensure involvement of all relevant disciplines.

COMPONENTS OF THE FRAMEWORK

The framework consists of two main components (i.e., knowledge collection [part 1] and strategy building [part 2]; see Figures 1 and 2, and the supplementary material for details).

Part 1 provides a list of "trigger" topics that can be used as a checklist to establish common understanding and agreement on constraints and assumptions. Although the relevance of each topic may vary between projects and development stages, it is advisable for teams to discuss each item to ensure nothing is missed. Teams are also encouraged to agree on a rating of the relevance and criticality of all items. Once completed, part 1 will represent a transparent "snapshot" of the current knowledge and can serve as an informal documentation of the team's current thinking, including references to relevant source material.

Part 2 guides through a three-step process to translate the knowledge into a path forward. The first step is to condense the most critical aspects identified in part 1, including knowledge to build upon, knowledge gaps to be filled (or accepted), constraints that limit options, and assumptions on which further planning should be based. Step 2, the evaluation of different program and study design options should be specific on how each study contributes to the execution of the overall strategy, how knowledge gaps are addressed, and how the critical assumptions or constraints influence or limit the program and study design. Finally, the team can summarize their preferred end-to-end strategy for learning

DOSE FINDING FRAMEWORK (PAGE 1)

PROJECT _____

Project characteristics - context *(What is the wider context and the constraints of the project? List key knowns, unknowns, and assumptions.)*

Patient population / indication	Competitive landscape	External factors
- Target population - Population comparable between clinical studies? (inclusion/exclusion criteria, disease stage, etc.) - Orphan / rare disease? - High unmet medical need? - Life-threatening disease? - Populations w/unique requirements (e.g. pediatric, elderly, ...)? - Bridging across indications / populations?	- Approved drugs in same indication? Standard of care? - Drugs under development? Competitive race? - Benchmarking - Data on mechanism / surrogate markers from competitors?	- Evaluation of sub-therapeutic doses possible in this indication? - Regulatory guidance / requirements / precedence in this indication? - Low recruitment rate (e.g. due to rare disease? Due to high competition?) – consider feasibility of study size

Drug characteristics - causal chain

(What is known & unknown about the causal chain? Receptor occupancy → mechanistic marker → efficacy marker → clinical endpoint / registration endpoint?)

D → E → R

Drug substance	Drug input / dosing	PK (dose-exposure)	Target	Response (efficacy) *(and relation between markers)*	Response (safety)
- Modality (small molecule vs. biologic) - Manufacturable doses - Formulation - Same as final market image (FMI)? - Formulation considerations for vulnerable populations?	- Routes of administration - Considered dose range Limiting factors? - Regimen (frequency, loading / induction, drug holiday, ...) - Drug combination - Intended as add-on therapy? - Concomitant therapy – background therapy (PK or PD interactions? Additive / synergistic?)	- **A** bsorption - bioavailability - **D** istribution Elimination - Paths characterized? - **M** etabolism metabol. characterized? - **E** xcretion Half-life (terminal / effective) - Variability - PK non-linear in dose? - Drug-drug interactions? - Food effect - Concomitant medications	- Target - Mechanism Novel? - Does drug reach target? - Does drug bind target?	- Endpoints – Registration endpoint - Endpoint continuous, categorical, event-driven? - Variability of endpoint compared to relevant effect size - PD marker / surrogate endpoint for dose finding? - Practicality of measuring the endpoint (Easy? Non-invasive? Cheap? Sensitivity?) - PD dynamics – long vs short duration of action - Time of onset, plateauing, return, progression - Disease process (acute, chronic-progressive, chronic-stable, ...) - Underlying fluctuations (e.g. seasonal, circadian rhythm, ...) - Predictive variable to define differently responding patient subgroups?	- Acute and long-term toxicities (observed or anticipated) - On-target / off-target toxicities - Therapeutic window - Benefit-risk tradeoff - Rare AEs - Toxicity-driven dose reductions / interruptions - Chronic vs. acute use *(see also relevant points in "Response (efficacy)")*

FIGURE 1 The dose finding framework – page 1 (project characteristics and drug characteristics). AE, adverse event; PD, pharmacodynamic; PK, pharmacokinetic

DOSE FINDING FRAMEWORK (PAGE 2)

Critical characteristics

List the assumptions, constraints, knowns and unknowns that were identified as critical for dose-regimen strategy on page 1

Program design

Discovery/Research and Nonclinical Development	Early Clinical Development	Late Clinical Development	Submission and beyond	Other

Use this section to brainstorm viable dose-regimen program designs. Columns are only for guidance – consider merging or skipping columns if appropriate.

Describe the sequence of studies that contribute to achieving the dose-regimen strategy. Note: this space is not intended for detailed description of study designs/results, focus on the key contribution of each study to the overall strategy, e.g.:

- *Be specific about how each study contributes to the execution/implementation of the overall strategy (including any applicable bridging across indications/populations)*
- *Clarify which questions, gaps each study addresses*
- *How do constraints and assumptions influence the study design?*
- *Describe risks associated with study design*

Dose-regimen strategy

What is the end-to-end strategy for dose-regimen finding/selection/justification? Describe the planned approach for

- *Learning about the dose-exposure-causal chain including analysis methods.*
- *Selecting a dose and regimen*
- *Justifying that selection*

Consider pros and cons/risks (and risk mitigation strategy) of the chosen strategy. How do constraints and assumptions influence the overall strategy?

FIGURE 2 The dose finding framework – page 2 (critical characteristics, program design, and dose-regimen strategy)

about the dose-exposure-response causal chain, selecting a dose and regimen, and justifying that selection. Risks of the chosen approach should be addressed, and mitigation strategies outlined. This summary may be used to populate relevant sections of other documents (e.g., development plans).

EXPERIENCES FROM USING THE DOSE FINDING FRAMEWORK

The dose finding framework is a recent initiative and its longer-term impact is yet unknown. Nevertheless, at the time of writing, it has been implemented in more than 25 projects at various stages of drug development, ranging from candidate selection to submission. A survey was conducted among users, to seek feedback on (i) which team members team were involved, (ii) when, (iii) how teams worked with the framework, and (iv) examples of perceived added value.

Who? Frequently, the work was initiated in dedicated meetings of the project clinician, statistician, clinical pharmacologist, and pharmacometrician(s), with other functions contributing as needed. It was noted that such multidisciplinary discussions often required dealing with different perspectives, including moderating and reconciling contrasting opinions.

When? A recommendation when rolling out the framework was to apply it as early as possible in the development process. This was reflected in feedback like "we wish we had done this earlier." Reaching collective understanding of knowledge and strategies early benefits projects early on and can avoid the need to rationalize in hindsight.

How? Users highlighted the importance of keeping the format of the framework flexible and adjustable to the team's preferences. Extending and refining the framework as needed was the design intent. Several respondents mentioned that structuring the process with the framework resulted in higher quality discussions.

A common concern among project teams was that yet another "check-box" activity was being added to an already documentation-heavy workflow, despite the rollout-communication emphasizing that its use was optional. The concern highlights the realities of working in large organizations and related challenges of

introducing any new tool or process. Nonetheless, the early adopters saw benefits and value while working with the framework.

Added value? Users also shared examples how programs benefitted from the dose finding framework, for example:

- For one compound investigated in two different indications in parallel, the framework made differences in critical characteristics between indications transparent, facilitating distinct dose finding strategies for those two indications.
- When applied during a phase I dose escalation, the framework helped identify opportunities to generate additional biomarker data to strengthen the exposure-response assessment.
- In a late phase project, the framework helped the team focus on forward-looking dose justification, rather than retrospectively discuss dose selection decisions of past studies. Acknowledging the limited data availability due to the rarity of the indication and anticipating potential challenges by health authorities allowed the team to gain clarity on what would constitute an acceptable dose.

Encouraged by the positive feedback, the ambition now is to share these early experiences and systematically implement use of the dose finding framework across the whole project portfolio.

CONCLUSION/PERSPECTIVES

Getting the dose and regimen "right" continues to be paramount for both the success of drug development and an optimal benefit/risk for the clinical use of medicines. Although several approaches have been suggested, used, and published,[8] the systematic implementation on a broad basis remains a challenge, in part because of our limited understanding of complex diseases that require novel treatments.

Simple frameworks or checklists are widely used for complex routine tasks, for example, by pilots or surgical teams.[9] Despite a natural resistance to checklists "because they insult our intelligence," there is consistent evidence that they "greatly reduce errors," because the most difficult parts of a complex task can distract from the overall goal or lead to errors in the simpler parts.[10] Drug development is a complex task that is prone to errors and misjudgments, thus one that may indeed benefit from a simple tool that helps teams organize their knowledge and thinking.

The dose finding framework is an easy-to-use tool that helps development teams establish a comprehensive working plan for dose and regimen selection. A survey of users' experiences suggests an overall positive impact. The tool has the potential to minimize risks by facilitating alignment across the multiple contributing disciplines and tailoring of strategies to the specific demands of projects. Additional awareness and experience will determine its long-term impact.

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CONFLICT OF INTEREST

O.S., B.M., I.L., A.J., C.M., D.L., B.B., M.H., S.J.K., and M.L. are employees of Novartis and may hold Novartis stock.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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