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ARTICLE

Dose Finding in the Clinical Development of 60 US Food and Drug Administration–Approved Drugs Compared With Learning vs. Confirming Recommendations

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This review characterizes clinical development that supported the label dose in 60 drug indications recently approved by the US Food and Drug Administration. With Lewis B. Sheiner's *Learning vs. Confirming* clinical drug development paradigm as a reference point, the clinical development paths, the design of dose-ranging trials, and the dose–exposure–response characterization were examined using US Food and Drug Administration approval packages. It was found that 89% of clinical development programs included several doses in the first-in-patient trial, 43% proceeded directly to confirmatory trials after the first-in-patient trial, and 52% included multiple doses in confirmatory development. A low number of doses and narrow dose ranges were generally included in dose-ranging trials, with only 20% including at least four doses over an at least 10-fold dose range. In a third of approval packages, no dose–response or exposure–response evaluation was identified, and model-based dose–exposure–response characterization was rarely alluded to, as only 2 of 60 approval packages mentioned the use of a model-based approach. The findings suggest that confirmatory development may often be guided more toward learning than confirming, and furthermore that dose exposure response is robustly assessed in only a minority of clinical drug development programs, indicating that there may be room left for optimizing the benefit/risk profile of confirmatory/marketed dose(s). Significant deviation from *Learning vs. Confirming* may exist in clinical development practice on several levels, and the reasons for why this may be the case are discussed in light of contemporary literature.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The *Learning vs. Confirming* paradigm entails sequential clinical development stages, appropriate dose-ranging trial design, and model-based dose–exposure–response characterization for identifying the optimal drug dose.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ In practice, how is sequential clinical development performed, and how many doses are included in each stage? What is the number of doses and dose range in dose-ranging trials? To what extent is dose exposure response assessed, and how is it characterized?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Multiple doses are often included in confirmatory clinical development. Dose-ranging trials commonly include a low number of doses spanning narrow dose ranges. In approval packages, model-based dose–exposure–response characterization is rarely mentioned and dose response/exposure response not consistently assessed. There may remain considerable room for improving the efficiency and robustness of dose finding by way of appropriate trial design and model-based analysis.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This work may inspire thinking on optimizing dose finding in clinical drug development.

Recent reports from regulatory authorities have pointed toward the importance of dose finding in clinical drug development for achieving regulatory approval. Uncertainty pertaining to the adequacy of the proposed marketing dose(s) was the highest prevailing reason (15.9%) for denials of new molecular entity applications by the US Food and Drug Administration (FDA) between 2000 and 2012.[1] Beyond regulatory approval, postmarketing changes to the label dosage occur frequently as a result of emerging benefit/risk information: 21% and 18.2% of FDA-approved drugs in the periods of 1980–1999 and 2000–2014, respectively, have required postmarketing changes of the label dose.[2,3] These are strong incentives for drug developers to take dose finding seriously.

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With the aim of increasing the efficiency and informativity of clinical drug development, Lewis B. Sheiner's seminal *Learning vs. Confirming* paradigm[4] described the premise for scientifically sound clinical development cycles, clinical trial design, and interpretation of resulting data to inform dose finding. It emphasized the need for a balance between learning and confirming in clinical development and is structured around two sequential cycles. The first cycle entails learning what dose is tolerated in healthy volunteers (phase I maximum tolerated dose identification) and subsequently confirming that this dose shows promise of efficacy in patients (phase IIa first-in-patient (FIP) trial/proof-of-concept establishment). The second cycle aims to make acceptable drug benefit/risk likely by testing "many" doses in patients (phase IIb dose ranging) followed by confirmation that acceptable drug benefit/risk is achieved with the most promising dose in a large patient population (phase III). In Sheiner's view, the intellectual focus of sponsors is predominantly on obtaining regulatory approval (confirming) based on confirmatory trials and to a lesser extent on obtaining an in-depth understanding of the drug benefit/risk (learning) based on exploratory trials. Consequently, he underlined the importance of adequately designed dose-ranging trials, which should include a large number of doses over a wide range, allowing for dose–exposure–response characterization through a model-based approach, crucial for informing optimal dose selection. Model-based analysis has been shown to significantly reduce the required clinical trial sample size[5,6] and increase accuracy in dose selection[7,8] when compared with pairwise testing. Despite occurring almost 2 decades apart, Sheiner's points are very similar in nature to those agreed on at the 2014 dose-finding workshop hosted by the European Medicines Agency.[9] Here it was pinpointed that dose selection in drug development is "rarely scientifically sound," and the need for appropriate design of dose-ranging trials, which generally should include a minimum of four doses over an at least 10-fold dose range, was emphasized. Moreover, the recent joint regulatory and industrial Model-Informed Drug Discovery and Development initiative has built its quantitative framework around "learning and confirming," with the assessment of benefit/risk to support dose selection being one of several applications of modeling and simulation in clinical development.[10]

Motivated by the continued high relevance of clinical development concepts brought forth in the *Learning vs. Confirming* paradigm, we set out to examine to which extent these concepts are implemented in the clinical development of drugs that ultimately received regulatory approval. *Learning vs. Confirming* may not be ideally suited for all clinical development programs; however, it is of interest to see how its concepts are overall adhered to in practice. Although detailed information on clinical development programs has long been available at the drugs@FDA website,[11] to our knowledge no work has to date been published evaluating the totality of clinical evidence supporting the label dose. Focusing on drugs that have recently been granted FDA approval, this article reviews the clinical development paths, the design of dose-ranging trials, and the characterization of dose exposure response used for identifying the label dose and for obtaining regulatory approval.

METHODS

Investigational points

We reviewed FDA approval packages to assess to which extent clinical development programs hold up against several key elements of the *Learning vs. Confirming* paradigm.

Clinical development paths. We characterized clinical drug-development paths by examining the number of doses in the FIP trial, in subsequent exploratory development (if conducted), and in confirmatory development while highlighting the number of doses ultimately approved by the FDA. We compared our findings with the sequential clinical development stages described in *Learning vs. Confirming* using Sheiner's definition of a "pure" confirmatory trial (test and control, i.e., one active dose). Next, we investigated the ratio of the number of doses included in exploratory to confirmatory clinical development, as *Learning vs. Confirming* states that acceptable drug benefit/risk should be made likely by exploring "many" doses followed by confirmatory testing of a "few" doses.

Dose-ranging trial design. We quantified the number of doses, dose range, and sample size in dose-ranging trials and compared our findings with the general recommendation from the European Medicines Agency dose-finding workshop (minimum of four active doses over an at least 10-fold range).

Dose–exposure–response characterization. We inspected the use of model-based analyses as well as the apparent assessment and characterization of dose response and exposure response, respectively, in FDA approval packages, while noting the number of doses and dose range of the assessment data.

Identification of drug approvals

Original new drug approvals (type 1 and type 9/10 new drug applications as well as biologics license applications) between February 2015 and February 2017[11] were included in the review. Locally acting drugs (e.g., topical, ophthalmic, inhalation treatments), diagnostic/contrast agents, medical gases, fixed-dose combinations, biosimilars, drugs developed under the Animal Efficacy Rule,[12] drugs approved with no specified starting dose or titration dose range in the label, and new formulations of previously approved compounds were excluded from the review.

Data extraction

Clinical trials were added to the review database using a two-stage approach. In the first stage, all clinical trials listed in the FDA Medical/Clinical review sections *Sources of Clinical Data and Review Strategy, Review of Efficacy, Review of Relevant Trials to Support Efficacy, and Integrated Review of Effectiveness were considered.* Clinical trials were excluded if they were deemed irrelevant toward identifying the label dose in the general US patient population, e.g., clinical trials for indications other than the one(s) approved and not supportive of the efficacy evaluation. All exclusion criteria are listed in the **Supplemental Material**.

In the second stage, additional clinical trials relevant to the identification of the label dose were identified by searching across all documents (including the Medical/Clinical review, Clinical Pharmacology and Biopharmaceuticals review, Statistical review, etc.) in individual approval packages using Pharmapendium[13] (details of search terms in the **Supplemental Material**). In cases in which clinical trial characteristics were not reported in FDA approval packages, these were retrieved from clinicaltrials.gov,[14] assessment reports from other international/national regulatory agencies, and scientific publications. The start and end date of each clinical trial was noted using the reported study start date and study completion date as listed on clinicaltrials.gov.[14]

Classification

Clinical trials. All included clinical trials were classified as *exploratory* or *confirmatory*. Phase I clinical trials were classified as *exploratory,* whereas phase III trials were considered *confirmatory*. Phase II trials were considered exploratory in drug approvals in which clinical development was initiated in healthy subjects (IIHV), as these trials traditionally pertain to proof-of-concept demonstration and/or dose ranging. For drug approvals in which clinical development was initiated in patients (IIP), it was considered whether the therapeutic area was oncology. In traditional oncology clinical development, the maximum tolerated dose is identified in phase I, and based on this the recommended phase II dose is brought forward for efficacy evaluation in the subsequent phase(s) to support approval.[15,16] Thus, for oncology drug approvals, phase II trials were classified as *confirmatory*. Clinical trials consisting of a dose-finding component followed by an activity-estimation/dose-expansion part (i.e., oncology phase I/II trials in which additional patients are enrolled in the dose expansion) were considered as separate trials, the first part being exploratory and the latter confirmatory. Further information regarding exploratory/confirmatory trial classification is presented in the **Supplemental Material**. In addition to the exploratory or confirmatory classification, specific clinical trials were classified as dose-ranging trials. Classification was based on information in approval packages, namely, trial description, trial objectives, FDA comments, or if mentioned in the context of the label-dose justification. As specified by Sheiner in the *Learning vs. Confirming* paradigm, several assumptions must hold true for dose-escalation trials to be valid for dose ranging, namely, that a full response on each dose level is observed and no carryover of response from the previous dose level is present. Hence, dose-escalation and dose-ranging trials were considered separately in the current review. Only trials including multiple doses of the investigational drug were considered dose ranging. Additional information regarding dose-ranging trial identification is presented in the **Supplemental Material**.

Clinical trial design characteristics and dose–exposure–response characterization. The number of investigational drug doses and the dose range were noted for each included clinical trial. To do so, the doses were normalized to a common administration frequency (active regimen normalized doses ($active_{RN}$)). For example, 2 mg given once daily and 1 mg given twice daily counted as one $active_{RN}$ dose. Dose range was calculated as the highest $active_{RN}$ dose divided by the lowest $active_{RN}$ dose. For clinical trials including dose titration ranges, each treatment arm comprising a different dose titration range was considered to be a separate dose, and the dose range was calculated using the highest and lowest allowed titration dose.

Using all documents available in individual drug approval packages, predominantly the Clinical Pharmacology and Biopharmaceuticals review, it was assessed whether dose exposure response was characterized for efficacy and/or safety and which clinical trial(s) this was based on. To assess whether a dose–response or exposure–response relationship was identified, comments such as, e.g., "a relationship was observed/demonstrated/established" or "a dose/exposure-dependent increase in response was observed" in relevant sections were retrieved. Comments such as, e.g., "no relationship was observed between doses/exposure," "the curve was relatively flat," "no clinically significant difference in between doses/exposures was observed" were used to assess whether a dose–response or exposure–response relationship was not identified. If no information regarding dose response or exposure response was identified in the approval packages, these evaluations were classified as missing. In the latter case, the reasons for not assessing dose response and/or exposure response were identified. Lastly, the FDA comments regarding dose exposure response and dose selection in individual approval packages were noted.

Statistical analysis

Fisher's exact test, Wilcoxon's rank sum test, and a Poisson rate ratio test were used for statistical comparisons of categorical, continuous, and count variables, respectively.

RESULTS

A total of 57 new drug applications approved by the FDA between February 2015 and February 2017 comprise the current review (**Figure 1**). An overview of included and excluded approval packages is shown in **Tables S1 and S2**, respectively. Three approval packages covered two approved indications with separate clinical development programs for each indication; these were regarded as separate, resulting in 60 included development programs. This allowed for the inclusion of 303 clinical trials (**Figure 1**), and an overview of their phase number and exploratory/confirmatory classification is shown in **Table S3**. Following classification, the median number of clinical trials per clinical development program was four, and the median duration from the start of the first to the start of the last included clinical trial was 4 years. An overview of the excluded clinical trials can be found in **Table S4**.

Clinical development paths toward label-dose approval

The employed development paths in 56 clinical programs are depicted in **Figure 2**. Four approval packages only

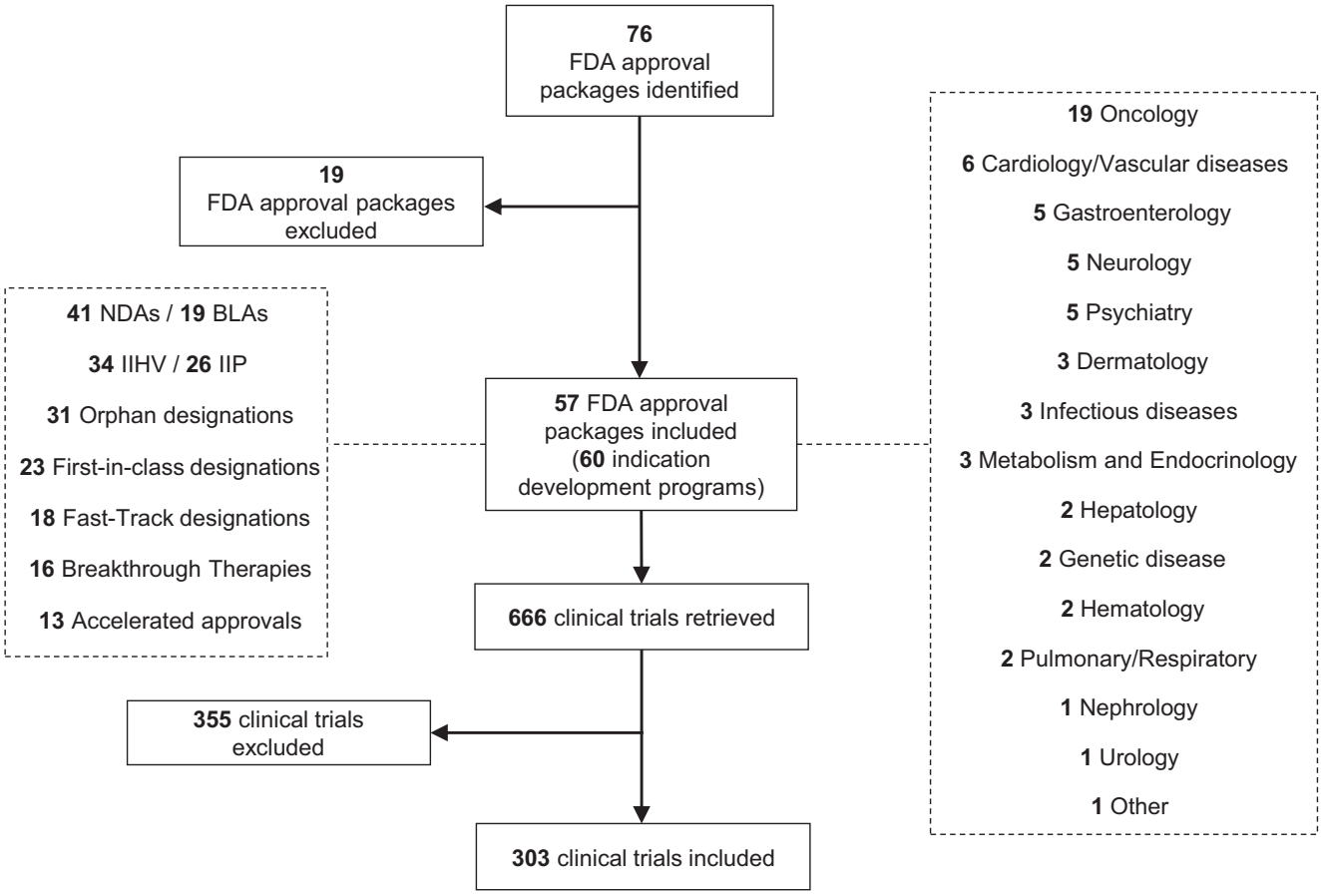

Figure 1 Flow chart for the inclusion of US Food and Drug Administration (FDA) approval packages and clinical trials. Dashed boxes indicate the characteristics of included FDA drug approvals. BLA, biologics license application; IIHV, clinical development initiated in healthy volunteers; IIP, clinical development initiated in patients; NDA, new drug application.

contained confirmatory trials and therefore could not contribute information. The vast majority (89%, 50 of 56) of FIP trials included multiple active$_{RN}$ doses (**Figure 2**, first column from the left). These included a median of three active$_{RN}$ doses in programs IIHV, whereas programs IIP included a median of six active$_{RN}$ doses (**Figure 2**, first column from the left). A substantial part of the programs (43%, 24 of 56) did not perform any exploratory post-FIP trials, instead proceeding directly to confirmatory development after the FIP trial (**Figure 2**, second column from the left). In confirmatory development, the majority of programs IIHV (71%, 22 of 31) and a smaller portion of programs IIP (28%, 7 of 25) included multiple active$_{RN}$ doses (**Figure 2**, third column from the left). Ultimately, less than a quarter of programs (24%, 7 of 29) that had included multiple active$_{RN}$ doses in confirmatory development received FDA approval for multiple label doses (**Figure 2**, last column from the left). The two most common reasons for having more than one active$_{RN}$ dose approved were titration-based dosing involving fixed up-titration and/or down-titration doses contingent on response/tolerability and subindications requiring different doses. No significant difference in clinical development paths could be discerned between approvals based on FDA drug/pathway designations (orphan, accelerated approval, fast track, breakthrough, first-in-class, new drug application/biologics license application).

The median ratio of the number of active$_{RN}$ doses in exploratory (considering both FIP and post-FIP exploratory trials) to confirmatory development was 2:1 for programs IIHV and 5:1 for programs IIP. The number of active$_{RN}$ doses in exploratory development was found to be significantly higher for development programs with a single active$_{RN}$ dose in confirmatory development when compared with programs with multiple active$_{RN}$ doses (median 6 vs. 4, $P = 0.004$). Additional results pertaining to the ratio of number of active$_{RN}$ doses in exploratory to confirmatory development and the introduction of new active$_{RN}$ dose levels in confirmatory development are presented in the **Supplemental Material**. **Table S5** presents an overview of the number post-FIP exploratory and confirmatory trials as well as the number of active$_{RN}$ doses and dose ranges in exploratory and confirmatory clinical development.

Dose-ranging trials

A total of 84 exploratory clinical trials relevant to label-dose finding were identified in 48 of 60 development programs, whereas in the remaining no such trials were identified. A total of 38 trials were dose-escalation trials and were

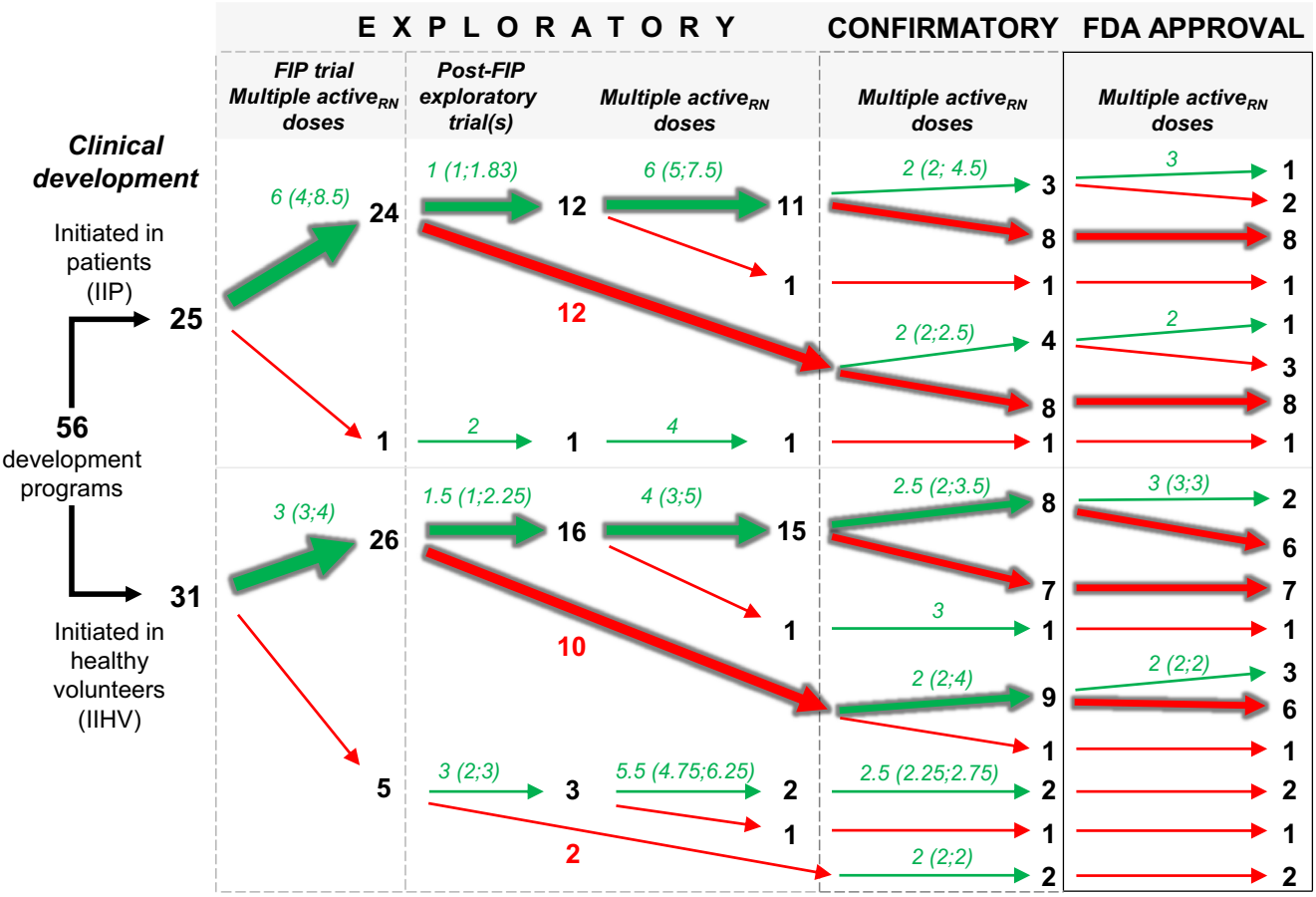

Figure 2 Clinical development paths to label-dose identification and approval for 56 US Food and Drug Administration (FDA)–approved drugs. The most common clinical development paths are highlighted. Green arrows signify "yes," whereas red arrows signify "no" regarding whether multiple active$_{RN}$ doses were included in the respective stages (FIP trial, post-FIP trial(s), confirmatory development, and FDA approval) and whether post-FIP trials were conducted, respectively. If multiple active$_{RN}$ doses were included or post-FIP trial(s) were conducted, the median (first quartile; third quartile) number of active$_{RN}$ doses/number of post-FIP trials is specified in green above the green arrow. The red numbers indicate the number of development programs that did not conduct any post-FIP exploratory trial(s). A total of 56 of 60 included development programs contributed with information, as three programs (ID 6, ID 27, ID 40 in **Table S1**) only reported confirmatory trials, whereas it was not possible to characterize the chronological order of listed clinical trials for one development program (ID 37 in **Table S1**). If multiple trials were conducted in the respective stages, the number of unique active$_{RN}$ doses across trials was considered. Four programs IIHV and one program IIP initiated several first-in-patient (FIP) trials simultaneously. active$_{RN}$, active regimen-normalized doses; FIP, first-in-patient.

reviewed separately (**Supplemental Material**). The remaining 46 trials were exploratory dose-ranging trials of which 42 implemented a parallel group, three a single group, and one a crossover intervention model. Of the exploratory dose-ranging trials, 52% (24 of 46) included two or three active$_{RN}$ doses over a ≤ 5-fold dose range, 30% (14 of 46) included at least three active$_{RN}$ doses over a ≥ 10-fold dose range, and only 20% (9 of 46) included at least four active$_{RN}$ doses over a ≥ 10-fold dose range. Substantial variation in sample size was observed across dose-ranging trials, and this was seemingly unrelated to the number of included active$_{RN}$ doses as well as dose range. **Figure S1** illustrates the relationship between the number of active$_{RN}$ doses, dose range, and sample size in individual dose-ranging trials. Regarding the timing of dose ranging, it is to be noted that 58% and 72% of development programs IIHV and IIP, respectively, performed dose ranging in FIP trials. Additional results describing dose spacing in dose-ranging trials (Figure S2) and the change in the number of doses and dose range when multiple exploratory trials relevant to dose finding were conducted sequentially (Figure S3) are presented in the **Supplemental Material**.

Dose–exposure–response characterization in clinical development

The evaluation of dose response and exposure response was reported in 62% and 66% of approval packages, respectively. In nearly all approvals that stated whether there was evidence for a dose–response/exposure–response relationship, the analysis method that led to this conclusion (i.e., whether through statistical analysis or by visual assessment) was not specified. Model-based dose response and exposure response were rarely alluded to in the reviewed approvals, as only 2 of 60 approval packages

Table 1 Dose–response and exposure–response evaluations and characterization in 60 development programs

	Exploratory		Confirmatory		Pooled exploratory & confirmatory	
Evaluation/data	**Relationship identified**	**Relationship not identified**	**Relationship identified**	**Relationship not identified**	**Relationship identified**	**Relationship not identified**
D-R efficacy						
Number of development programs, n (%)	13 (22)	5 (8)	12 (20)	5 (8)	0	2 (3)
Median number of active$_{RN}$ doses, n (IQR)	4 (4–10)*	3 (2–3)*	2 (2–2)	2 (2–3)	—	4 (4–4)
Median dose range, n (IQR)	15 (8–32)*	4 (3–4)*	2 (2–9)	1.7 (1–2)	—	4.5 (4–5)
E-R efficacy						
Number of development programs, n (%)	4 (6)	0	14 (23)	12 (20)	5 (8)	5 (8)
Median number of active$_{RN}$ doses, n (IQR)	4 (3–5)	—	2 (1–3)*	1 (1–1)*	8 (6–10)*	3 (2–5)*
Median dose range, n (IQR)	7.5 (3–34)	—	2 (1–4)	1 (1–2)	40 (8–42)	3.8 (2–10)
D-R safety						
Number of development programs, n (%)	8 (13)	2 (3)	12 (20)	9 (15)	3 (5)	1 (2)
Median number of active$_{RN}$ doses, n (IQR)	4 (4–4)	3 (2–4)	2.5 (2–3)	2 (2–2)	4 (4–4)	3 (3–3)
Median dose range, n (IQR)	9 (5–32)	11 (6–16)	2.1 (2–6)	2 (2–4)	3 (3–6)	10 (10–10)
E-R safety						
Number of development programs, n (%)	2 (3)	1 (2)	10 (17)	11 (18)	6 (10)	6 (10)
Median number of active$_{RN}$ doses, n (IQR)	6.5 (6–7)	5	2 (1–3)	1 (1–2)	5 (3–6)	5.5 (3–8)
Median dose range, n (IQR)	21 (16–26)	100	1.8 (1–4)	1 (1–3)	10 (4–33)	5.9 (2–11)

Poisson rate ratio test and Wilcoxon's rank sum test, respectively, were used for hypothesis testing.
D-R, dose response; E-R, exposure response; IQR, interquartile range.
*Statistically significant difference in median number of active regiment-normalized (active$_{RN}$) doses and median dose range, respectively, between "relationship identified" and "relationship not identified."

reported model-based dose–response evaluation (IDs 4 and 16 in **Table S1**, respectively).

Table 1 shows the number of approval packages that evaluated dose response and/or exposure response for efficacy and/or safety, respectively, while specifying the data on which these evaluations were based. For the assessment of dose response for efficacy based on exploratory data, evaluating across a higher number of active$_{RN}$ doses was associated with a higher rate of identifying a relationship (median of 4 vs. 3), and the same was observed in terms of dose range (median of 15 vs. 4). Furthermore, **Table 1** shows that for the evaluation of exposure response for efficacy based on confirmatory and pooled exploratory/confirmatory data, respectively, the number of included active$_{RN}$ doses was higher when a relationship was identified (median of 2 vs. 1 and median of 8 vs. 3, respectively). No significant associations could be discerned for safety relationships. Among the 28 approval packages that did not report a dose–response evaluation for safety, 17 did not report a reason for not doing so, whereas the remaining included only one dose in mentioned clinical trials or had implemented individual dose titration. In the 27 approval packages that did not evaluate exposure response for safety, only one specified a reason, namely, the benign safety profile of the drug. Further results and highlights of the FDA perspectives on the dose finding and dose–exposure–response characterization retrieved from approval packages are presented in the **Supplemental Material**.

DISCUSSION

Summary

Motivated by the recent focus on dose finding in clinical drug development,[6] this review aimed to evaluate its current practice in the pharmaceutical industry and to assess the totality of clinical evidence supporting the optimality of the label dose. To our knowledge, previous work has focused on dose-ranging trial design,[17,18] whereas clinical development paths and dose–exposure–response characterization for label-dose identification have not been reviewed. The current work has shown that, in practice, dose finding is not confined to a single trial, phase, or development stage. Furthermore, significant discrepancy appears to exist between drug development theory rooted in *Learning vs. Confirming* and current clinical drug development practice. This was most evidently supported by (i) the frequent inclusion of multiple active$_{RN}$ doses in FIP trials; (ii) the common inclusion of multiple active$_{RN}$ doses in confirmatory development, indicating that this stage may often

be guided toward learning as opposed to confirming and, in these instances, questioning the sponsors' certainty of drug benefit/risk when initiating confirmatory development; (iii) the low number of active$_{RN}$ doses and narrow dose ranges in dose-ranging trials, presumably affecting the extent of learning in these trials, the extent to which model-based analysis can be meaningfully applied, and the extent to which dose exposure response can be accurately and/or precisely characterized; and (iv) the lack of formal dose–exposure–response characterization by statistical models to inform dose selection, leaving questions surrounding the benefit/risk optimality of confirmatory/marketed dose(s).

Clinical development paths

In programs IIHV, the practice of including multiple active$_{RN}$ doses and performing dose ranging in the FIP trial may be explained by a wish to obtain dose–exposure–response information to inform anticipated clinical development. The go/no-go decision-making capability of FIP trials with a single or several active doses has been found to be comparable, the advantage of the latter being the obtainment of dose–exposure–response information to better inform forthcoming exploratory dose-ranging trials.[19] However, in the reviewed development programs, a large number of sponsors did not perform any post-FIP exploratory trials, and hence a wish to accelerate clinical development by combining multiple objectives may also be a reason. It has further been suggested that the rare occurrence of the confirming FIP trial in clinical development practice can indeed be attributed to time restraints in clinical development but also difficulty in objectively establishing proof of concept.[20] The same author suggests that the omission of the confirming-oriented FIP trial renders implementation of learn–confirm "subjective and quite challenging" in ensuing clinical development,[20] which may further explain the substantial number of clinical development programs that did not include any post-FIP exploratory trials in the current work.

A significantly higher number of active$_{RN}$ doses in exploratory development were observed for development programs that did not include multiple active$_{RN}$ doses in confirmatory development, and this may suggest that the need to include multiple active doses in confirmatory development is reduced when a larger number of active doses is studied in exploratory development and vice versa. Limiting exploratory development efforts and incorporating dose finding into confirmatory development may be viewed by sponsors as a time-efficient way to reduce clinical development duration and time to approval. In the authors' view, the downsides of performing dose finding in confirmatory development may be costliness considering the larger number of patients included in this stage and the ethicality of exposing a larger number of patients to dose levels that potentially lack efficacy and/or safety. However, irrespective of the number of active doses in exploratory development, in some cases including several active doses in confirmatory development may be thought to increase the chances of ultimately receiving regulatory approval based on the favorable assessment of at least one of the doses. This is supported by simulation studies showing greater probability of success when including two active doses in phase III compared with one dose.[21,22] In addition, the inclusion of multiple active doses may also be a precautionary measure against unforeseeable efficacy and/or safety outcomes in the larger and longer confirmatory trials, which reflect a more accurate depiction of benefit/risk when compared with that observed in exploratory trials. Such unpredictable outcomes are supported by a recent report by the FDA, highlighting 22 drug candidates where promising phase II (exploratory) clinical trial results were not confirmed in phase III, leading to drug-development termination.[23] This was seen even when phase II was "relatively large,"[23] suggesting that these outcomes may have been independent of the extent of exploratory learnings.

Dose-ranging trials

Slightly more than half of the exploratory dose-ranging trials included two or three active$_{RN}$ doses over a ≤ 5-fold dose range. This suggests that the majority of dose-ranging trials may be designed and powered for testing-based analysis as opposed to model-based analysis. This finding is consistent with research spanning an earlier time period (2009–2014) focusing on 66 FDA-approved small-molecule drug indications. Here, 66% of the dose–response trials included three or less active doses, and moreover, a ≤4-fold dose range was studied in "most" trials.[17] In addition, 45% of the dose–response trials reported on clinicaltrials.gov (1999–2013) included three or fewer dosage groups.[18] The authors of the aforementioned study did not, however, specify whether placebo treatment was considered as a dosage group; hence, the number of dose–response trials with three or less active doses may be as high as 72%.[15] The similarity of the observed trial design characteristics between the current and previous time periods may be indicative of a long-standing trend of not prioritizing model-based dose finding in clinical development practice. The very low number of development programs that reported model-based dose response/exposure response in the current approval packages further supports this notion. It is, however, important to note that within certain therapeutic areas it may not be possible to study doses over a wide range, as ethical considerations may hinder the study of low and likely ineffective doses while toxicity concerns may limit the study of high doses. Patients may be more hesitant to participate in clinical trials in which they are unlikely to receive adequate medication, and investigational review boards are less likely to approve protocols with doses that may be discontinued as a result of poor response, which can be viewed as a necessary evil of dose–exposure–response characterization. Although the use of modeling and simulation could potentially help identify low doses with adequate efficacy for trial inclusion to circumvent this issue, it can be argued that the data must first be available to develop such models with robust predictive ability in the patient population. These reasons may partly explain the design of some of the currently reviewed dose-ranging trials.

Dose–exposure–response characterization

Dose–response/exposure–response evaluation was not consistently reported in approval packages, with large variation in whether exploratory, confirmatory, or pooled data were

used as well as whether the end point was efficacy or safety (**Table 1**). Although dose–response/exposure–response evaluations were reported in approval packages, questions can be raised regarding the validity of these conclusions, as in most cases the analysis method was not specified, and the relationships may have been assessed only visually.

Only a third of the approval packages reported dose response based on exploratory data. The lack of dose–response evaluation is in contrast to International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E4 guideline from 1994, which reads "assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug."[24] A third of the reviewed development programs did not report any exposure–response evaluation. This is in steep contrast to recommendations from the FDA, which highlights the importance of exposure response in clinical development in the FDA guidance, which reads "Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs."[25] Furthermore, when performed, exposure–response evaluation was predominantly based on confirmatory trial data (**Table 1**). This is not in accordance with the *Learning vs. Confirming* paradigm, where exposure response is regarded as a learning-oriented analysis based on exploratory data. The inclusion of multiple active$_{RN}$ doses in confirmatory development may partly explain the observed imbalance in data used for exposure–response evaluation in approval packages.

The recent FDA establishment of a public comment docket in April 2018 for the enhanced incorporation of exposure response in drug development and decision making[26] clearly indicates the interest of the FDA in dose–exposure–response characterization. Questions raised by the FDA included the following: "What attributes of an exposure–response analysis are critical to effectively inform a drug development or regulatory decision?" "What are the main obstacles preventing widespread acceptance of exposure–response analyses?" Knowledge obtained from initiatives such as this might facilitate the understanding, acceptance, implementation, and impact of dose exposure response in future clinical drug development.

Limitations

Model-based dose–exposure–response analyses may have informed sponsors' dose-finding efforts yet did not appear in FDA approval packages or in the literature. However, the design of dose-ranging trials and the very low number of reported dose–response/exposure–response models in the approval packages clearly point toward a lack of attention to model-based methods. A total of 33 dose–response/exposure–response models for the currently reviewed drugs were identified in the literature, 27 of these being analyses of confirmatory or pooled exploratory/confirmatory data (data not shown). Models based on confirmatory trials are unlikely to have influenced decision making during clinical development, whereas the remaining six models may have contributed to dose selection without being included in the file submission.

Many of the reviewed drugs had special regulatory designations (**Figure 1**), which may have explained the inclusion of several active doses in FIP trials, the omission of post-FIP exploratory trials, or the inclusion of several active doses in confirmatory development as these designations generally aim to help reduce time to approval. However, other than accelerated approvals and breakthrough designations being less likely to include multiple active doses in confirmatory development, no significant association was found in the current data (data not shown).

Our data set was characterized by approximately half of the included drugs having an orphan drug designation, reflecting that orphan drugs are becoming increasingly common in current drug development.[27–31] This may have affected the available patient sample size for clinical trials and, consequently, dose finding. However, for both IIHV and IIP orphan drug–development programs, no significant difference was found in the number of included active$_{RN}$ doses in exploratory clinical development. This suggests that orphan drugs, similar to nonorphan drugs, are not exempted from identifying a dose with suitable benefit/risk.

Four development programs included pediatric patients in addition to the adult population. This may have affected the number of active$_{RN}$ doses in various stages of development as well as the number of approved active$_{RN}$ doses because different doses are commonly required for such different age populations. However, different doses in different age populations were only approved in one approval package, and hence the impact of including drugs approved for different patient populations on current findings can be assumed to be limited.

Perspectives

As described by Sheiner more than 2 decades ago and again highlighted by regulators at the 2014 European Medicines Agency dose-finding workshop, clinical drug development may be much more result oriented (confirming) than performance oriented (learning), the ultimately desired result being marketing approval. Because of this result-driven approach to drug development, approved drugs may set precedents and notably inspire sponsors in terms of the reported dose-finding efforts that led to label-dose approval (e.g., clinical development paths, dose-ranging trial design, and/or extent of dose–exposure–response characterization). The asymmetry in available detailed knowledge of the consequences of clinical development decisions may be an important contributing factor in this regard, with the approval information being readily available contrasted with the confidentiality of reasons for FDA denial often not accurately translated in sponsor press releases.[32] The work by Sacks *et al.*[1] revealing hitherto confidential reasons for FDA new drug application denial may have been a step in the right direction toward achieving a more balanced perspective. A discussion of what may be done to spawn a change in dose-finding practice is presented in the **Supplemental Material**.

The current work reviewed approvals from February 2015 to February 2017. Considering the recent focus on dose finding, model-informed drug development, and dose–exposure–response characterization by regulators,[9,10,26,33,34]

it is of interest to review the clinical development programs of future approved drugs to investigate the perceived impact of these initiatives on dose-ranging clinical trial design and utilization of model-based dose–exposure–response characterization to support dose selection.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Number of doses, dose range, and sample size in dose-ranging trials.
Figure S2. Dose spacing in dose-ranging trials.
Figure S3. Changes in dose range and median dose when sequential dose-ranging trials were conducted.
Table S1. Included US Food and Drug Administration approval packages.
Table S2. Excluded US Food and Drug Administration approval packages.
Table S3. Number of included clinical trials and classification by development phase.
Table S4. Number of excluded clinical trials and exclusion reason.
Table S5. Summary of clinical development characteristics of reviewed clinical drug development programs.
Supplemental Material.

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