Evidence of Effectiveness: How Much Can We Extrapolate From Existing Studies?

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ABSTRACT

Drug development can be a science of extrapolation if the use of a drug exposure-response relationship is embraced and implemented through mechanistically oriented pharmacokinetic (PK)-pharmacodynamic (PD) modeling analysis and clinical trial simulation. The traditional requirement of at least 2 adequate and well-controlled phase III studies by the US Food and Drug Administration for drug approval can be waived in certain situations, substantially reducing the resources and time. In this article, the authors introduce a real drug development case where the chance for this exemption was maximized by actively using PK-PD modeling followed by clinical trial simulation, resulting in faster and more economical introduction of a new dosage regimen to patients.

KEYWORDS: extrapolation, drug development science, pharmacokinetic-pharmacodynamic modeling, exposure-response relationship, etanercept

INTRODUCTION

Contemporary clinical drug development uses much extrapolation. Drug developers rely on the information and knowledge obtained from a relatively small number of subjects to plan their next steps based on the implicit assumption that the behavior of a drug is predictable in similar circumstances. Even in the case of little similarity, drug developers assume that the behavior of a drug may vary within a certain range, which can be reasonably predicted based on the understanding drawn from the existing studies. For example, a phase III clinical study is designed to maximize its power to reject the null hypothesis of no difference between an active drug and a placebo. To accomplish this objective, the exposure-response, or pharmacokinetic (PK) - pharmacodynamic (PD), relationship of

the drug can be elucidated from appropriate analysis of the phase I or II data, which, in turn, enables the sponsor to select the optimal dose, dosage regimen, or even the patient population most likely to respond to the drug.^{1,2} In other words, the knowledge gained from existing studies is used to improve the understanding of the pharmacology of the drug, enabling informed and more predictable drug development.

However, this is not the end of the story. In the above example, the results from the phase III study, coupled with the data from the phase I and II studies, can be used to confirm or modify the expected exposure-response relationship of the drug. It is clear that the knowledge and information that has been newly gained can be used in formulating new drug development objectives. For example, the sponsor may become interested in developing different doses, regimens, or dosage forms of the drug. They may even want to develop the drug for different populations (eg, from adult to pediatric uses) or indications. Thus, the drug development objective once again becomes the issue of extrapolation, that is, how much can we extrapolate from existing studies?

Sheiner³ conceptualized the epistemology of the process of drug development using the famous learning-confirming cycle. Briefly, a confirming step has the goal of falsifying the claim that there is no efficacy; however, estimating the shape of the response surface is the main interest of a learning study. Extrapolation can be viewed as the link between the 2 opposing, but related, drug development objectives, and it becomes critical when transitioning from a learning step to a confirming step.

The use of extrapolation in drug development dramatically increases as more data become available from a number of studies of a drug in closely related indications that are pertinent to the assessment of its effectiveness for a new use.⁴ Likewise, more drugs have been tested in different populations, different doses, and dosage forms, alone or in combination with other drug(s). This results from the fact that many clinical studies have been conducted in more narrowly defined or focused settings, for example, on a more specific disease stage or in a clinically distinct subpopulation. This is the natural consequence of the

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advancement of our understanding in the pathogenesis, staging, and prognostic classification of a disease, along with the effects of the pharmacologic intervention. Collectively, these studies can support a particular new use of a drug, and extrapolation plays a key role in this process.

The US Food and Drug Administration (FDA) has historically requested that the sponsor submit the results of at least 2 adequate and well-controlled phase III clinical studies for any drugs seeking regulatory approval. The legal basis of this effectiveness requirement was the language adopted in the Kefauver-Harris Amendment of the Federal Food, Drug, and Cosmetic Act of 1962 (the FDC Act).⁵ Specifically, section 505(d) in the FDC Act defined substantial evidence as “evidence consisting of adequate and well-controlled investigations [note, plural] to evaluate the effectiveness of the drug involved,” and this has been interpreted by the FDA to require at least 2 such trials.

However, the Food and Drug Modernization Act of 1997 (FDAMA) provides for a new route of drug approval that relies on “data from one adequate and well-controlled investigation and confirmatory evidence (see section 115a).”⁶ Under this provision, the FDA may consider the data from a single adequate and well-controlled phase III study and scientifically sound, supportive evidence to constitute substantial evidence. One of the authors has explored possible drug development cases where a single clinical trial, coupled with causal evidence of effectiveness, is sufficient for drug approval.⁷

The FDA responded promptly to the passage of FDAMA, releasing the *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (the Effectiveness Guidance) in 1998.⁴ Many forward-thinking drug-development ideas were included in the Effectiveness Guidance, but section II.C (“The Quantity of Evidence to Support Effectiveness”) is a particularly important directive from the perspective of drug development. This shift in the required evidence of effectiveness reflects substantial progress in the science of drug development and regulation, notably acknowledging the value of a mechanistic or causal interpretation of drug action, an approach that clinical pharmacologists have long encouraged.

Objectives

This article is comprised of 3 parts. First, the authors summarize the main extrapolation ideas identified in section II.C. of the Effectiveness Guidance that specifically pertain to the development of different doses or regimens. This is followed by a real drug development case where the active adoption of the extrapolation strategy, based on PK-PD modeling analysis and clinical trial simulation, successfully helped the sponsor achieve the drug development

objectives. The authors finally conclude that more frequent and creative applications of mechanistically oriented drug development using the extrapolation strategy are strongly recommended to bring better medicines to patients in a faster and more efficient way.

Extrapolation Is Possible

What is most striking in the Effectiveness Guidance is that the FDA agrees, in certain cases, that effectiveness of an already approved drug product for a new indication or the effectiveness of a new product may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials (see section II.C.1 “Extrapolation From Existing Studies”). This is mainly based on the well-regarded axiom in clinical pharmacology that dose-exposure-response relationships are generally continuous, so information about the effectiveness of a dose, dosage regimen, or dosage form is informative about the effectiveness of other doses, regimens, or dosage forms.

In order for this no-additional-efficacy-trial requirement to be met, blood levels and exposure patterns of a new dose, regimen, or dosage form are to be “not very different from those of the already approved dose, regimen, or dosage form.” To show that blood levels are not very different, comparative pharmacokinetic data may be sufficient. However, the FDA goes further:

Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective based on pharmacokinetic data without an additional clinical efficacy trial (section II.C.1.d).

Thus, a well-defined PK-PD relationship, coupled with pharmacokinetic data, serves as the key link for extrapolating controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form.

In certain cases, the relationship between blood concentration and response may not be clearly defined or not-so-well understood. At the same time, the pharmacokinetics of a new dose, regimen, or dosage form may differ from those of the already approved one. Even in these situations, the traditional requirement of at least 2 adequate and well-controlled efficacy trials is not likely to be necessary. To support this notion, the FDA clearly indicated that, “a single additional efficacy study should ordinarily be sufficient (section II.C.2.a).”

Figure 1 summarizes the regulatory framework for the development of a new dose, dosage regimen, or dosage formulation according to the Effectiveness Guidance. This reflects the current thinking of the FDA that has become

Is Extrapolation Possible?

Figure 1. Flow chart for the development of a new dose, dosage regimen, or dosage form using existing studies based on the Effectiveness Guidance by the FDA.

more and more open to scientifically sound, abbreviated approval pathways.

Etanercept: Drug Development Objectives

Etanercept is a soluble, dimeric fusion protein consisting of 2 copies of the extracellular ligand-binding protein of the human p75 tumor necrosis factor receptor linked to the constant portion of the human IgG1.⁸ The efficacy of etanercept has been demonstrated in adult patients with refractory rheumatoid arthritis (RA),⁹ as well as RA of early onset (≤ 3 years).¹⁰ Etanercept was also shown to be superior to methotrexate in delaying bone erosion and joint space narrowing in a randomized, double-blind clinical trial of patients with early RA.¹⁰ Current indications of etanercept in the United States include RA, polyarticular course of juvenile RA (JRA), psoriatic arthritis, and ankylosing spondylitis. Etanercept is also indicated for the treatment of adult patients (≥ 18 years) with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.¹¹

At the time of its initial approval, the recommended regimen of etanercept was 25 mg twice weekly by subcutaneous (SC) injection for adult patients and 0.4 mg/kg (up to 25 mg) twice weekly by SC injection for JRA patients, aged 4 to 17 years. As is commonly seen with large molecular weight proteins that are administered SC, etanercept has a very flat PK profile, that is, it is slowly absorbed after SC injection reaching the peak serum concentration approximately 50 hours after injection¹² and cleared from the body with a reported mean half-life of 102 hours.¹¹

To improve the convenience to patients, the sponsor (then Immunex) became interested in developing a new dosage regimen for etanercept. Based on the long half-life of etanercept, a once-per-week dosing regimen was considered, for example, a doubled dose with half frequency, such as a 50-mg, once-weekly SC injection in adult patients with RA.

There were supportive data that made the proposed new dosage regimen seem reasonable. For example, the absolute bioavailability of SC-injected etanercept is relatively high, reaching approximately 60% in adults,¹³ and the pharmacokinetics were linear at doses up to 50 mg of twice-weekly SC injection.¹⁴ Additionally, in a small pilot study, the new dosage regimen had a comparable safety profile with the already approved regimen. Furthermore, the steady-state trough concentrations of both regimens were 1 to 2 mg/L, well above the concentration yielding 50% of the maximal effect for biomarkers, such as swollen joints, painful joints, erythrocyte sedimentation rate, and interleukin 6 and matrix metalloproteinase-3 with a range from 0.1 to 0.6 mg/L.¹⁵ Therefore, a 50-mg, once-weekly

regimen was expected to have a PK profile not very different from a 25-mg, twice-weekly regimen, while promoting better patient adherence because of a less frequent injection and fewer injection-site reactions.

The Center for Drug Development Science (CDDS) was asked to assist the sponsor with this drug development objective for a new dosage regimen, and it soon became clear that the Effectiveness Guidance was the most important regulatory document to take into account. Consequently, as summarized in Figure 1, the following 2 questions were asked: (1) is the PK of the 50-mg, once-weekly SC regimen very different from that of the 25-mg, twice-weekly regimen; and (2) is the exposure-response relationship of etanercept including its time course well understood?

Based on these regulatory questions, CDDS proposed the following drug development strategies and practical recommendations (Table 1). First, because formal pharmacokinetic evaluations had not been conducted for the new dosage regimen, although there were some preliminary PK observations, a full, short-term, repeated-dose PK study was recommended to compare the steady-state PK profiles of the 2 regimens. Second, a population PK-PD modeling analysis was proposed to characterize the exposure-response relationship of etanercept and its time course in adult patients with RA. Population PK-PD analysis using a nonlinear, mixed-effects modeling approach was recommended, because it enables the quantification of the population means of the PK and PD parameters (ie, fixed effect) and of their variability between subjects (ie, random effect). Additionally, the influence of covariates can be incorporated into the model to explain the variability between the different individuals. Collectively, these characteristics of the population approach have been shown to be especially useful in elucidating the exposure-response relationship, and the flexibility and high utility of population PK-PD modeling, coupled with stochastic clinical trial simulation, has been well documented.^{1,16,17} Third, a clinical trial simulation experiment was recommended to compare the PK profiles of the new and already approved dosage regimens using the population PK model developed in the previous step. Finally, for a possible safety concern by the FDA, a single safety-oriented clinical trial was to be considered as a contingency plan.

Extrapolation From Existing Studies

Following the recommendations by CDDS, a population PK-PD model of etanercept was developed, and the details of the model were reported elsewhere.¹⁴ In summary, a 1-compartment, first-order absorption and elimination PK model with interindividual and interoccasion variability on the apparent clearance (CL/F), apparent volume of distribution, and absorption rate constant, with covariates of sex

Table 1. Strategies to Develop a New Dosage Regimen for Etanercept

Drug Development Question	Answer	Strategy	Recommendation
PK of the new regimen not very different from that of the approved regimen?	Expected so, but more data needed	To compare the PK profiles between the 2 regimens	<ul style="list-style-type: none"> • Conduct a short-term, repeated-dose PK study to compare the regimens • Conduct a simulation experiment to compare the regimens using a population PK model
Exposure-response relationship and its time course well understood?	No	To develop the exposure-response relationship	<ul style="list-style-type: none"> • Conduct a population PK-PD modeling analysis of etanercept in adult patients with RA
Contingency on possible safety concern	50-mg once weekly will yield a higher peak concentration profile	To address safety concern	<ul style="list-style-type: none"> • A single safety-oriented clinical trial may be conducted

and race on CL/F, and standardized body weight on CL/F and apparent volume of distribution, adequately described the time course of the concentration profiles of etanercept after SC administration in adult patients with RA. Additionally, a mixed-effects logistic regression model that links the cumulative area under the curve of etanercept with the probability of attaining the American College of Rheumatology 20% response criterion (ACR20) adequately characterized the time course of clinical improvement in adult RA patients who were receiving etanercept. A separate placebo response model was also developed. As a result, the model-predicted percentage of patients achieving ACR20 at 6 months after receiving 25-mg SC twice-weekly dosing was 54.9% compared with the observed 52.9%.

Encouraged by the model performance, a simulation experiment was conducted to compare the time courses of steady-state concentrations of etanercept between the 25-mg twice-weekly and 50-mg once-weekly SC regimens in adult RA patients using the population PK model.¹⁸ As expected from the flat PK characteristics of etanercept SC administration, the 5th and 95th percentile concentrations for the 50-mg once-weekly regimen overlapped with those for 25-mg twice-weekly regimen over the postdose period. The mean peak concentration of the 50-mg once-weekly regimen was only 15% higher than that of the 25-mg twice-weekly regimen. Figure 2 summarizes the simulation results, and it is clear that the 50-mg once-weekly SC regimen yields an overlapping steady-state PK profile with 25-mg twice-weekly SC dosing.

Based on the PK-PD modeling and PK simulation experiment, the sponsor became confident that etanercept 50-mg once weekly will yield a similar clinical outcome

(ie, ACR20) to etanercept 25-mg twice weekly in adult patients with RA. The remaining step is to confirm that the PK profiles are not much different between the 2 regimens. Therefore, the sponsor used the results of the modeling and simulation analyses to plan a short-term, repeated-dose PK study to compare the new and already approved regimens.

The FDA responded positively to the approach of the sponsor. In fact, the FDA initially required the sponsor to conduct large, pivotal clinical trials using hundreds of patients to compare the safety and efficacy of the 2 doses and placebo for at least 6 months. With the modeling and simulation analyses of etanercept, however, the FDA accepted a shorter study period (ie, 4 months) and agreed that the placebo patients could then roll over to one of the etanercept arms after 8 weeks of treatment.

At the same time, the FDA was concerned that the PK of the revised dosing schedule may differ, that is, whether the peak concentration of the 50-mg once-weekly regimen can be high enough to cause increased adverse drug reactions. This safety concern by the FDA was relevant given that there had been postmarketing reports of serious infection or sepsis with the use of etanercept.¹¹ Therefore, the FDA requested the safety concern be addressed in a single safety and efficacy trial instead of at least 2 adequate and well-controlled studies, which coincided with the plan proposed by CDDS (Table 1).

The Utility of PK-PD Modeling and Clinical Trial Simulation

According to the request by the FDA, the sponsor conducted a 16-week, placebo-controlled, randomized clinical trial to compare 50-mg etanercept administered SC once

Figure 2. Simulated concentrations for 25-mg, twice-weekly SC and 50-mg, once-weekly SC regimens at steady-state in adult patients with rheumatoid arthritis. The mean, 5th and 95th percentiles are represented. Hatched areas denote 5th to 95th percentile for 25-mg twice-weekly regimen. As external validation, observed concentrations from the 2 regimens (○, 50-mg once weekly; △, 25-mg twice weekly) but not used for the model development are also plotted against simulated concentrations. An overlapping PK profile of 50-mg, once-weekly SC regimen with that of 25-mg, twice-weekly SC regimen is clearly shown.

weekly with a 25-mg, twice-weekly SC regimen in terms of the safety, efficacy, and PK using 420 adult patients with active RA. When evaluated by ACR20, 50% and 49% of the patients receiving 50 mg of etanercept once weekly and 25 mg of etanercept twice weekly, respectively, responded to the treatments, and these were both statistically significant relative to the 19% response in the placebo group ($p < 0.0001$ for each etanercept group versus placebo).¹⁹ The safety profiles were also comparable between the 2 etanercept regimens.

In the same study, the PK was evaluated in a subset of the patients (ie, 26 patients in the etanercept 50-mg once-weekly group and 18 patients in the 25-mg twice-weekly group). The mean concentration-time profiles for the 2 etanercept groups were very similar; the mean trough con-

centrations at week 8 were 1.2 mg/L for both regimens with the 95% confidence intervals being entirely overlapped. These values were comparable with the mean trough concentrations of 1.51 mg/L for the 50-mg once-weekly regimen and 1.99 mg/L for the 25-mg twice-weekly regimen predicted in the simulation experiment. The small but systematic difference between the observed and simulated concentrations can be partly explained by the difference in the covariate distribution, that is, the patients in the study weighed more than the simulated patients (ie, the mean body weight was 80 kg compared with 75 kg in the simulation), leading to a higher clearance and lower trough concentrations.

Likewise, the peak concentrations at steady state (ie, week 8) were similar in the 2 etanercept groups: 2.4 ± 1.5 mg/L

(mean $\pm$ SD) and 2.6 ± 1.2 mg/L for the etanercept 50-mg once-weekly and 25-mg twice-weekly groups, respectively. Additionally, the mean weekly partial areas under the time-concentration curves were similar (ie, 297 ± 166 mg $\times$ h/L and 317 ± 136 mg $\times$ h/L for the etanercept 50-mg once-weekly and 25-mg twice-weekly groups, respectively).

Based on the confirmation of the comparable efficacy, safety, and PK profile between the 50-mg once-weekly and 25-mg twice-weekly regimens in adult RA patients, the FDA initiated communication with the sponsor for a possible extrapolation of the new regimen in JRA patients (ie, 0.4 mg/kg twice weekly to 0.8 mg/kg once weekly) using population PK analysis and PK simulation in this population without conducting additional clinical trials. CDDS and the sponsor performed the requested analysis and confirmed again that the PK profiles overlap between the 2 regimens.²⁰ This additional analysis, coupled with the PK-PD model development and PK simulation in adult RA patients with its subsequent confirmation of similar clinical outcome, safety, and PK profile in a real clinical trial, comprised the basis for the new once-weekly dosage regimen for not only RA and JRA but psoriatic arthritis and ankylosing spondylitis by the FDA in October 2003.²¹

CONCLUSION

Drug development is a science of extrapolation to the extent that the use of the exposure-response relationship of a drug is fully recognized by the FDA and put into practice through advanced analysis including PK-PD modeling and clinical trial simulation. The traditional requirement of at least 2 adequate and well-controlled phase III studies by the FDA for drug approval can be waived in certain situations. As a result, resource savings resulting from this waiver can be large, enabling faster and more economic introduction of new drugs to patients. The likelihood of this exemption increases as the understanding of the exposure-response relationship of a drug is gained.

However, current drug development practice in the pharmaceutical industry makes the use of extrapolation relatively infrequent because the next studies have already started in many cases before data from the prior studies have become available. At present, the extrapolation strategy seems best suited for line extensions (ie, different populations, dosages, or regimens), new formulations, or new indications in closely related diseases.

It must be also recognized that the FDA is equally concerned about safety and efficacy. Not only has the etanercept case exemplified how PK-PD modeling and clinical trial simulation can be used for the development of a new dosage regimen, but it reminds us that the FDA tends to respond conservatively when safety matters. Nevertheless,

the FDA is more and more open to innovative approaches. This should invite more frequent and creative applications of extrapolation strategies using the exposure-response relationship.

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