

## PERSPECTIVE

# Pharmacometrics: Focus on the Patient

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Pharmacometrics, whether using simple or complex models, has contributed to rational and efficient drug development,<sup>1–3</sup> with the main focus on early drug development.<sup>4</sup> This article describes why opportunities more directly focused on the patient abound in late stage development, illustrating the concept with three innovative examples which focus on benefits to patients, enabling drugs that are truly efficacious to reach the market faster in diseases with high unmet medical needs, while maintaining adequate safety.

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Model-based approaches offer unique opportunities in phase IIb-III (**Figure 1**), where demonstrating efficacy superior to the standard of care may be difficult due to variability in the symptoms of a disease and/or the efficacy end point itself, the presence of numerous subtypes of heterogeneous diseases, and practical aspects of study design in patients with urgent medical needs.

While the use of innovative models describing data and using evolving pharmacostatistical methodology is important, more focus should be given to how pharmacometrics affects patients, and communicating resulting effects on benefit:risk decisions, not on the models themselves. These concepts are illustrated in three innovative case studies, in which pharmacometrics has been used to understand phase III failures, expand indication statement through bridging of data, and balance the needs of patients with the needs for information on dose response.

### CASE #1: UNDERSTANDING PHASE III FAILURES

In addition to inefficiencies, when phase III trials fail for study design reasons (not a true lack of efficacy), patients do not receive medication that could meet an unmet medical need. Phase III studies can fail due to inappropriate doses or too few subject numbers.<sup>4</sup> This example shows how the end point itself can lead to failure of a phase III trial and illustrates the need to be conservative, yet not introduce hurdles that unintentionally misclassify responders and inhibit the ability to demonstrate efficacy in a disease with a high unmet medical need.

To understand failure of clinical studies in irritable bowel syndrome, a population model was developed to describe placebo-time data from four clinical irritable bowel syndrome trials, using an efficacy end point of whether or not each subject reported adequate relief from his irritable bowel syndrome symptoms.<sup>5</sup> Clinical trials were simulated for a hypothetical irritable bowel syndrome drug, assuming an average maximum effect ( $E_{max}$ ) of 15% over placebo with an average time to maximum effect ( $T_{max}$ ) of 4 weeks and between-subject variability in  $E_{max}$  and  $T_{max}$  of 50%.

For each simulated trial, the following end points were evaluated:

- Fraction of responders 4 out of last 4 treatment weeks (“4 of 4”)
- Fraction of weeks responding out of all on-treatment weeks (“all weeks”)
- Fraction of weeks responding out of the last 4 weeks of treatment (“last 4 weeks”)

Results showed that the “all weeks” end point required the smallest sample size to achieve 80% trial success rate, while the “4 of 4” end point, the end point used in failed clinical trials, had the poorest performance (**Figure 2a**). **Figure 2b** shows the reason for this poor performance is that a subject with 90% day-to-day probability of adequate relief has only a 66% chance of being classified a responder based on the “4 of 4” end point. Therefore, in making the analysis conservative, patients with appropriate efficacy (90% day-to-day probability) were misclassified.

This analysis showed that:

- If the end point is too conservative (unintentionally losing its clinical relevance), an efficacious drug fails to meet a regulatory end point and would not be available to patients with unmet medical needs.
- Pharmacometrics can provide the optimal way to evaluate an end point, balancing the need to be conservative but not excluding a drug with appropriate efficacy.

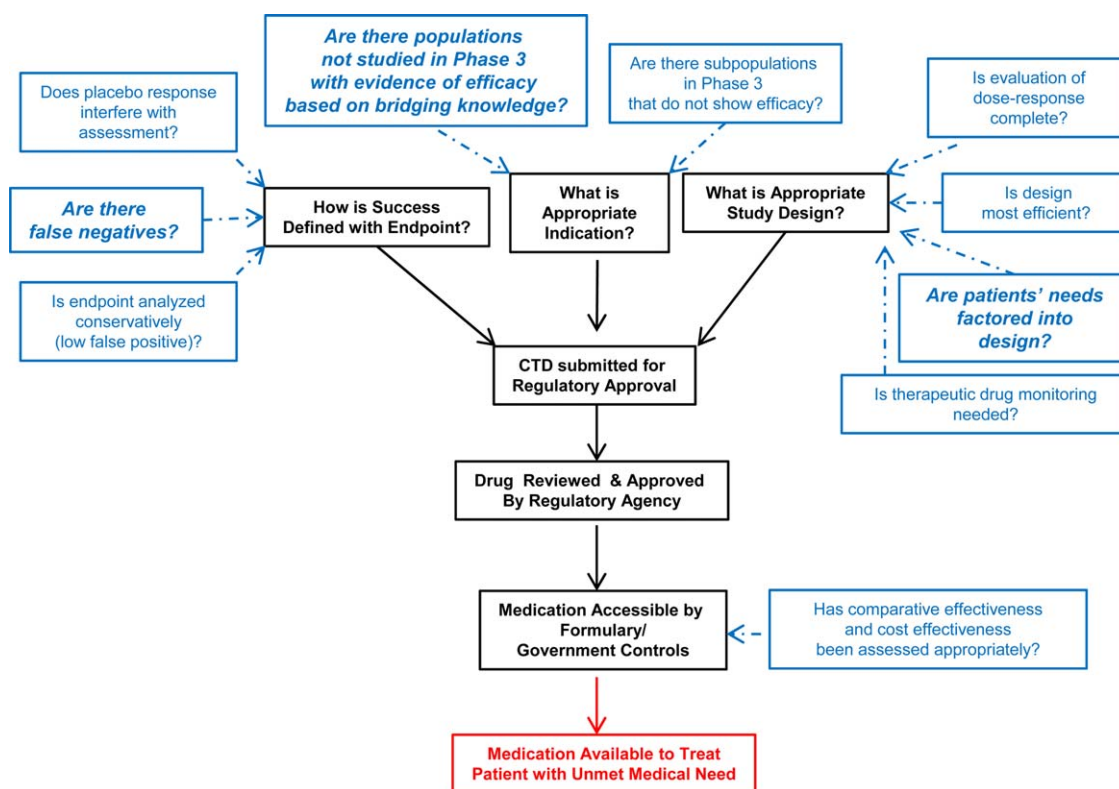
The current challenge is that most regulatory end points, many of which are dual end points, have not been studied using this model-based approach and need evaluation to ensure that truly efficacious drugs are not being turned down because of pharmacostatistical issues.

### CASE #2: EXPANDING THE INDICATION STATEMENT THROUGH BRIDGING OF DATA

Clinical studies exclude many comorbidities or factors that may suggest nonresponse in order to reduce variability, resulting in indication statements narrowed to the exact

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**Figure 1** Questions related to efficacy that pharmacometrics can address and help focus on getting medications to patients with an unmet medical need. The article will give three innovative examples (bolded) with perspectives that have not been focused on previously.

population studied in phase III. Model-based bridging of data from different sources can be used to expand the indication statement to other population subtypes, allowing appropriate use in those with a large unmet medical need. For example,<sup>6</sup> the sponsor conducted two pivotal phase III trials of boceprevir in patients with chronic hepatitis C virus (HCV):

1. Treatment-naïve patients (SPRINT-II), who never received the standard of care treatment, which at the time was pegylated interferon and ribavirin (PR)
2. PR-experienced subjects who were partial responders ( $\geq 2 \log_{10}$  IU/ml drop in HCV-RNA, but never RNA negative) or relapsers (HCV-RNA negative at the end of treatment but quantifiable HCV-RNA off treatment) (RESPOND-II)

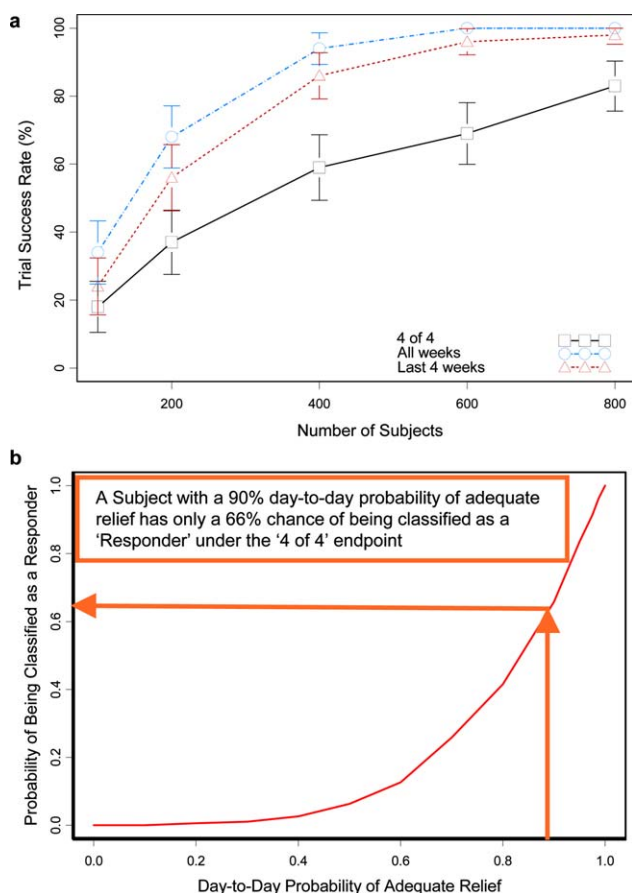
Null responders ( $<2 \log_{10}$  decline from baseline in HCV-RNA after 12 weeks of PR treatment) were excluded from the PR-experienced study. Using traditional approaches, null responders would not be included in the indication statement for boceprevir and would not have access to therapy, even though they have a very high unmet medical need. Instead, a model-based bridging strategy was used to show that null responders experienced benefit from boceprevir and can be included in the indication statement. This was accomplished because:

1. Data from studies of PR treatment alone<sup>7</sup> showed that:
  - a. PR responsiveness was similar between the first and subsequent treatment courses (allowing bridging of data between

treatment-naïve and PR-experienced patients in boceprevir trials).

- b. The 4-week HCV-RNA change from baseline following treatment with PR predicts sustained viral response and null response (HCV-RNA drop  $\leq 1.0 \log_{10}$  at week 4) to PR at the end of treatment<sup>7</sup> (allowing the use of run-in period in boceprevir trials to identify null responders early and conduct a subanalysis of those patients).
2. Data from the 4-week run-in period (those with an HCV-RNA drop  $\leq 1.0 \log_{10}$ ) with PR treatment within the boceprevir treatment-naïve trial demonstrated the presence of null responders who were exposed to boceprevir or PR treatment.<sup>6</sup>
  3. A subgroup analysis from the treatment-naïve trial showed that patients with a drop  $\leq 1.0 \log_{10}$  at week 4 had a 28% or 38% sustained viral response rate following 24 or 44 weeks of PR + boceprevir, respectively, compared to 4% for PR treatment alone.<sup>6</sup>

This model-based bridging strategy provided critical evidence for the US Food and Drug Administration to include null-responders in the indication statement for boceprevir, even though this population had been excluded from the PR-experienced phase III trial. This unique application is a model example, where data across compounds and trials established efficacy in a subpopulation and allowed patients with a high unmet medical need to receive an approved drug >2 years earlier than the traditional need for a double-blind, placebo controlled study prior to approval.



**Figure 2** Choice of end point and the probability of success. (a) The trial success rate (whether  $P < 0.05$ ) expressed as a percentage is shown vs. the number of subjects for the following end points: the fraction of responders who achieved adequate relief 4 out of last 4 treatment weeks (“4 of 4”) (black squares); fraction of weeks responding out of all on-treatment weeks (“all weeks”) (blue circles); and fraction of weeks responding out of the last 4 weeks of treatment (“last 4 weeks”) (red triangles). (b) Probability of being classified as a “Responder” under the “4 of 4” end point.

### CASE #3: CONSIDERING PATIENTS’ NEEDS IN TRIAL DESIGN

An ideal dose–response trial is placebo controlled, uses multiple doses or a controlled dose-escalation schedule, consists of repeated visits with collection of numerous end points over time and controls for all potential sources of variability. Realistically, patients have comorbidities, have limited time for visits, or may require rescue treatment (which does not provide information about efficacy). This example shows that pharmacometric approaches are useful to balance the need for information on dose–response with the patients’ needs.

Retosiban is a competitive oxytocin receptor antagonist that is being developed for the treatment of spontaneous preterm labor, with a goal to prolong pregnancy by  $\geq 7$  days compared to placebo, with the ultimate goal to reduce neonatal morbidities and mortality.

A phase II study was conducted to determine the safety and efficacy of retosiban in spontaneous preterm labor.<sup>8</sup> Parts A and B had a forced titration design (gold standard) where spontaneous preterm labor women were randomized to receive an infusion of active or placebo, the rate of which was increased every 3 h to achieve response (a  $\geq 50\%$  reduction in the number of contractions  $>30$  s/h and change in cervical dilation  $<1$  cm). The recruitment in Parts A/B was extremely slow (29 patients in 2.5 years) and subject dropout was high because physicians rescued patients who did not respond quickly.

A preliminary analysis determined a target steady-state concentration and target infusion rate (DOSE) which helped design a reasonable study to evaluate the efficacy of retosiban in spontaneous preterm labor. Clinical trial simulations showed that if one DOSE was selected for confirmation of efficacy, there could be an 80% probability of response if the  $IC_{50}$  from 29 patients was representative of a larger population, but only a 60% probability of response if the  $IC_{50}$  was underestimated by five-fold. If one DOSE was chosen alone, the dropout rate could be too high to evaluate the efficacy of retosiban. Clinical trial simulations allowing the ability to increase the DOSE at 1 h (as a rescue) increased the probability of response from 60% to 75% and gave physicians the ability to treat the condition and keep the patient in the study. Therefore, Part C of the study was conducted using an infusion of active or placebo with one DOSE and the ability to increase the DOSE at 1 h.<sup>8</sup> While clinical trial simulations suggested that 20% of subjects would not respond to the target DOSE and require a DOSE increase, the actual study showed that  $\sim 30\%$  of the subjects had a DOSE increase after 1 h. Thus, this model-based design allowed individualized therapy, increased subject retention, balanced patients’ needs, and facilitated gaining important dose–response information in a difficult therapeutic area.

### DISCUSSION

These case studies illustrate the unique opportunities to use pharmacometrics to address key questions that directly benefit patients, with the obvious impact of decreasing development timelines and costs. The keys to the successful implementation of these examples are:

- Definition and creative/proactive management of the right drug development questions
- Perseverance in communicating complex models in a simplistic manner to decision makers
- The availability of the 2013 EMEA concept paper on extrapolation of efficacy and safety across studies and populations to avoid unnecessary studies and the US Food and Drug Administration exposure–response guidance that describes the regulatory applications of exposure–response analysis to improve efficiency, address questions, and help get important medicines to patients<sup>9,10</sup>
- Follow-through in the ever changing scientific and regulatory environment

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