PERSPECTIVE

Precision Dosing: An Industry Perspective

Richard W. Peck[1,*]

Drug development usually delivers a single recommended dose level providing good efficacy relative to safety for the patient population. This is sufficient for health authority approval and simple to use. But advances in technology are making it easier to tailor dosing for each patient to overcome the response variability inevitable with fixed doses. Changing patient, prescriber, and payer expectations will require this. Drug developers must change their approach to deliver precision dosing for new medicines.

Precision dosing is individually tailoring the dose of a drug to ensure the greatest benefit and least risk for each patient. With the exception of the accepted requirement to adjust doses for well-recognized factors such as age, ethnicity, organ failure, or the use of interacting drugs, most drugs today are not developed for precision dosing but with the intent to identify a single dose level that will be used in all patients. Such a "one dose fits all" approach has served drug development and medicine well for many decades with the benefits of simplicity of development, manufacturing, and clinical use. It is an effective way to develop and use drugs with relatively wide therapeutic windows because response variability is overcome by giving all patients doses that are higher than many might need but that are still well tolerated (**Figure 1a**). At the other extreme there are some drugs, for example insulin, warfarin, and anaesthesia, for which there is no single dose level that will provide acceptable efficacy and safety for all. There is a therapeutic window for each patient, but it is narrow compared with the variability between patients, such that, for the whole population, there is no therapeutic window (**Figure 1b**). In such cases precision dosing is the only way to ensure safe use of these effective drugs.

Precision dosing adds some complexity and costs to clinical use with a requirement for additional tests, the need to interpret the tests, and additional clinic visits for monitoring and dose adjustment. For drug developers this raises concerns about commercial attractiveness, despite the increased benefit to patients and the growing number of examples where precision dosing has been shown to be cost-effective despite the additional costs.[1] Perhaps an even more important reason why most drugs are not developed to support precision dosing is that there is no requirement to do so. If an acceptable level of efficacy and safety can be shown with a single population-level dose, then health authorities will grant approval, so why do anything more? Precision dosing is only considered in situations where it is impossible to identify a single dose level that is adequately safe and effective in all patients. Even then, many drug developers would decide instead to stop development of that molecule and develop one with different properties that make it more likely there will be a single population dose level with adequate safety and efficacy. Only if the need for precision dosing is intrinsic to the drug class, and the benefits of that class are thought large enough, will continued development using precision dosing be considered.

In determining the need or opportunity for precision dosing, the critical factors are the size of the individual therapeutic window compared with the variability between patients and the consequences of using a suboptimal dose. There are not simply two groups of drugs with either a wide or no population level therapeutic window; instead there is a continuum from drugs for which one-size-fits-all dosing is feasible to those where it is impossible. Towards the "impossible" end of the continuum are drugs where it is possible to identify a single dose level with acceptable efficacy and safety but for which an individualized precision dosing approach would deliver significantly greater efficacy and/or safety, albeit at the cost of some added complexity (**Figure 1c**). An elegant mathematical approach to describe this uses utility functions to demonstrate the variation of optimal individual doses compared with the optimal population dose.[2] Today such drugs are still developed using the familiar one-dose-for-all approach that meets health authority needs. They remain separated in our minds from the small group of drugs where precision dosing is an absolute requirement. The questions for drug developers are is this the right thing to do and will the dividing line change in future use?

It is becoming easier and therefore more necessary to consider precision dosing in the

[1]Clinical Pharmacology, Pharma Research & Early Development, Roche Innovation Center, Basel, Switzerland. *Correspondence: Richard W. Peck (richard.peck@roche.com)

Received July 20, 2020; accepted September 19, 2020. doi:10.1002/cpt.2064

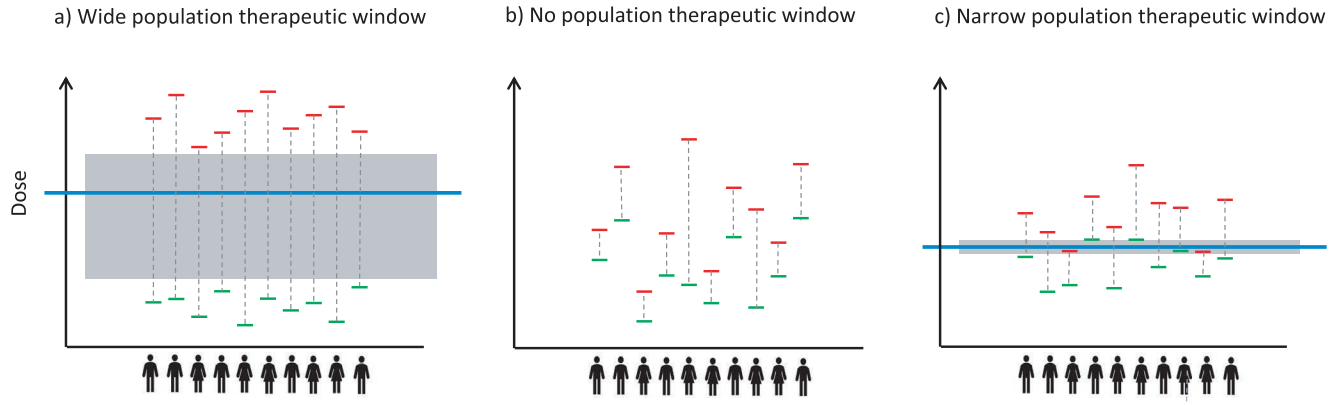

Figure 1 The relationship of individual and population therapeutic windows for drugs with (**a**) a wide population-level therapeutic window, (**b**) no population-level therapeutic window, and (**c**) a narrow population-level therapeutic window. In each panel the therapeutic windows for 10 representative patients on the x-axis are illustrated with minimum effective dose (green bar), maximum tolerated dose (red bar), the population therapeutic window (gray box), and a population dose (blue line). There is no population dose or therapeutic window in **b**. In **c** even the narrow dose window considered acceptable for the whole population is below the minimum effective dose or above the maximum tolerated dose for some patients.

future for drugs that today are developed, approved, and used as one dose for all.[1] From the industry perspective it is important to note that prescribers and payers are exploring ways to reduce drug expenditure by individualized dosing, which should encourage a better understanding of dosing at the time of approval and pricing. The growth of outcomes-based pricing will further encourage understanding of dose individualization. Precision dosing will increase efficacy and/or decrease unacceptable adverse events and thereby improve development success rates and competitiveness in clinical use. Precision dosing is already included successfully in some clinical development today. Seventeen percent of drugs approved by the US Food and Drug Administration (FDA) between 2013 and 2017 have a response-guided dose titration component in their label. In almost all of these cases the pivotal trials included the precision dosing approach or multiple separate dose levels from which a subsequent dose titration could be developed.[3] Omalizumab was developed with a dosing algorithm taking account of disease variability, specifically immunoglobulin E concentration,[4] and replacement therapies for immunoglobulin[5] or factor VIII protein / von Willebrand factor protein[6] included relatively complex precision dosing algorithms in at least one pivotal trial.

Precision dosing will not be required for all drugs; however, there are several categories where it should be considered. Firstly, drugs with a narrow therapeutic window offer significant opportunity for improved utility with precision dosing, especially when adverse effects are due to excessive pharmacology. Drugs for diseases with serious or irreversible consequences of undertreatment, for example progression of a cancer or neurodegeneration, or those with serious or irreversible adverse effects from too high a dose should also be considered. Drugs with invasive routes of administration, including intravitreal or intrathecal, represent additional opportunities where increasing the interval between injections in suitable patients, without risking treatment failure, will have high patient and healthcare system benefit. Treatments for serious, rare diseases are also good opportunities; patients and caregivers are highly knowledgeable about the disease and motivated to ensure effective treatment.

Ideally precision dosing should be included in the pivotal preapproval trials (**Figure 2**). Analogous to the development and use of a companion diagnostic, this will validate the algorithm. Clinical decision support tools delivering the algorithm at the point of care will need to be approved. The recently released guideline on software as a medical device[7] provides a framework to enable this. Potential precision dosing algorithms need to be developed before or during exploratory (phase I and II) development. Population pharmacokinetic/pharmacodynamic (PKPD) modeling will be an effective way to identify some of the important covariates of response variability, especially when plasma drug concentration is a useful predictor of effects. In such cases plasma concentration would be the biomarker to include to guide dose adjustment over time after the model has estimated the best starting dose for that patient. In other cases, perhaps the majority, biomarkers of drug effect will be required; insulin doses are guided by glucose and HbA1c, rather than insulin concentration. For drugs with rapid effects, clinical response can be used to guide dosing, but, for drugs with delayed responses, identifying suitable biomarkers will be more challenging. At a minimum, a marker of pharmacological effect or disease activity should be included in the early trials even if there are no established biomarkers of clinical outcome. Effective Population PKPD models must take account of covariates of disease variability in addition to the usual covariates of variability that tend to be chosen for potential impact on drug concentrations. Prior to pivotal trials, disease and population PKPD models should be used to simulate and compare phase III trial designs of one-dose-for-all and individualized dosing (of starting dose and titration to effect as relevant) in virtual patients. The decision to include individualized dosing in pivotal trials will be based on these simulations. If the benefit of individualized dosing is large enough, then it should be included in the pivotal trials. The precision dosing development paradigm (**Figure 2**) may be more complex and perhaps more resource demanding than conventional development but should not be longer, and the extra investment is justified by the higher benefit of the drug to patients and prescribers. Other practical considerations

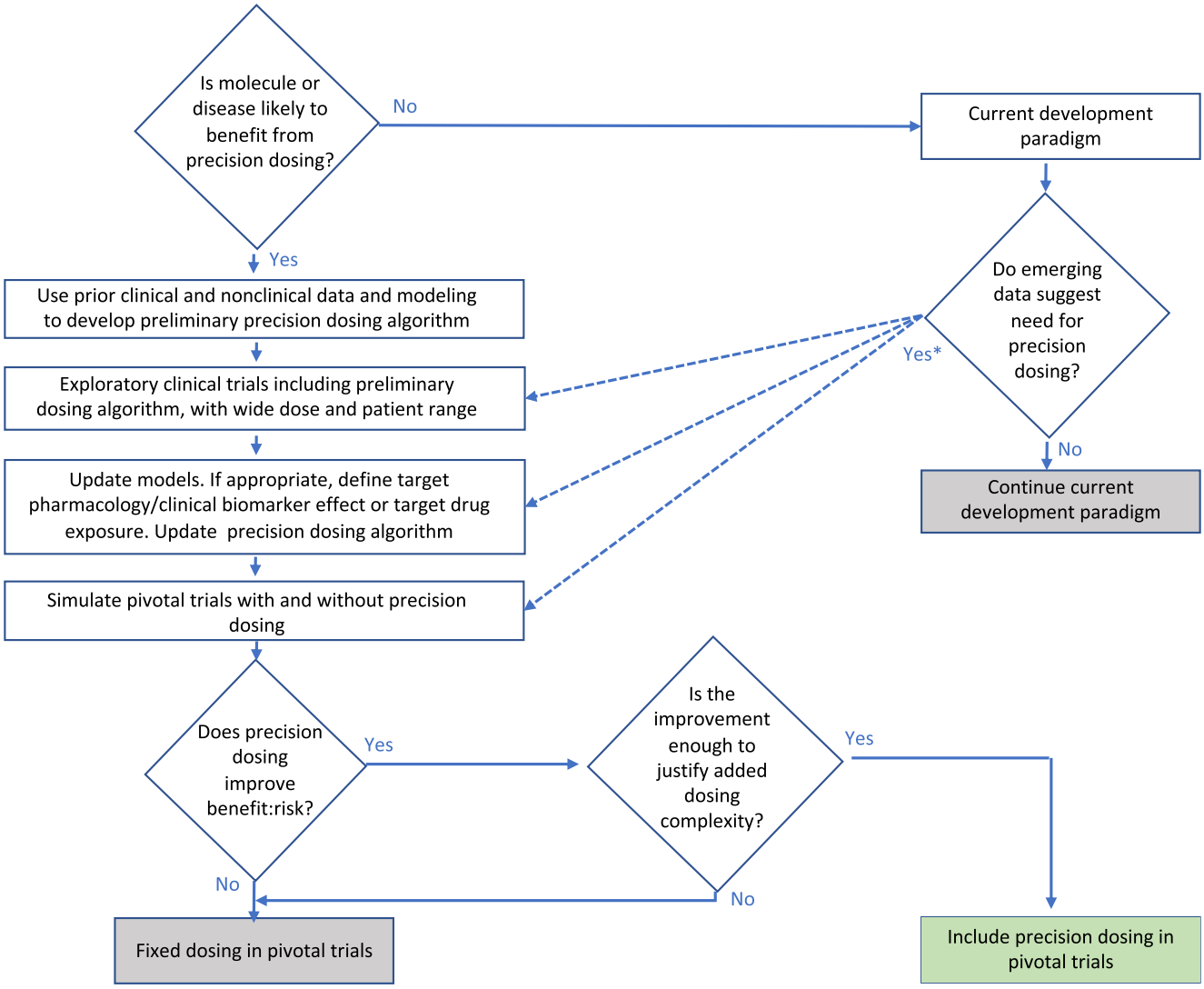

Figure 2 Decision tree and flow chart for implementation of a precision dosing paradigm in drug development. *When emerging data suggest the need to switch from the current "one-dose-for-all" to precision dosing development the exact point of entry to the precision dosing paradigm is dependent on the extent of prior clinical development and available data.

for precision dosing development have been reviewed recently.[1,8]

Machine learning is generally considered to require "big data" from thousands or even hundreds of thousands of patients, much larger data sets than available prior to pivotal trials. However, some machine learning methods such as reinforcement learning[9] and causal inference[10] offer the potential to identify precision dosing strategies from smaller data sets. Used alone or combined with population PKPD modeling, these could be powerful techniques for identifying precision dosing algorithms to study in confirmatory trials. A wide dose range should be studied in the exploratory clinical trials and also a wide range of patients in order to be representative of the whole population who will take the drug and to allow study of the potential range of response. The usual reason to exclude patients who may be subject to extreme responses is no longer valid since their doses are adjusted to minimize the risks. Health authorities can play an important role to encourage precision dosing, ultimately by changes in legislation that require developers to identify how to obtain the maximal benefit:risk from a new drug. More immediately, a simple change of regulatory language such as changing the statement "recommended phase II or III dose" to "recommended phase II or III dose range" would help promote the idea that there should not be one dose for all and that greater dosing flexibility to improve response is encouraged.

In conclusion, it is time to move away from the current treatment paradigm of one dose for all. Precision dosing-based development will lead to higher clinical utility for more and more drugs as advances in technology and data science make it increasingly feasible to adjust both starting and on-treatment doses to maximize the chances of individual benefit. For many drugs the increased benefit will outweigh the ever-smaller added complexity and should become the expectation for how these drugs are developed. For these drugs, it should no longer be acceptable to use a one-dose-for-all approach to their development just because we can.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST

Richard Peck is an employee and stockholder of the pharmaceutical company F. Hoffman-La Roche.

DISCLAIMER

As an Associate Editor of *Clinical Pharmacology and Therapeutics*, Richard W. Peck was not involved in the review or decision process for this paper.

1. Vinks, A.A., Peck, R.W., Neely, M. & Mould, D.R. Development and implementation of electronic health record-integrated model-informed clinical decision support tools for the precision dosing of drugs. *Clin. Pharmacol. Ther.* **107**, 129–135 (2020).
2. Maloney, A. A new paradigm. "Learn—learn more"; Dose-exposure-response at the center of drug development and regulatory approval. *Clin. Pharmacol. Ther.* **102**, 942–950 (2017).
3. Schuck, R.N., Pacanowski, M., Kim, S., Madabushi, R. & Zineh, I. Use of titration as a therapeutic individualization strategy: an analysis of Food and Drug Administration-approved drugs. *Clin. Transl. Sci.* **12**, 236–239 (2019).
4. Xolair [prescribing information]. (Novartis, East Hanover, NJ, 07936-1080) <https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf> Accessed July 8, 2020.
5. Gammagard liquid [prescribing information]. (Baxter Healthcare Corporation, Westlake Village, CA, 2012) <https://www.fda.gov/media/70812/download> Accessed July 8, 2020.
6. Wilate [prescribing information]. (Octapharma, Vienna, Austria, 2019) <https://www.fda.gov/media/77812/download> Accessed July 8, 2020.
7. US Food and Drug Administration. Guidance for industry and FDA staff: software as a medical device (SAMD): Clinical evaluation (2017) <https://www.fda.gov/media/100714/download> Accessed July 8, 2020.
8. Peck, R.W. Precision medicine is not just genomics: the right dose for every patient. *Annu. Rev. Pharmacol. Toxicol.* **58**, 105–122 (2018).
9. Ribba, B., Dudal, S., Lavé, T. & Peck, R.W. Model-informed artificial intelligence: reinforcement learning for precision dosing. *Clin. Pharmacol. Ther.* **107**, 853–857 (2020).
10. Bica, I., Alaa, A.M., Lambert, C. & van der Schaar, M. From real-world patient data to individualized treatment effects using machine learning: current and future methods to address underlying treatment challenges. *Clin. Pharmacol. Ther.* **109**, 87–100 (2021).