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Proceedings of a Workshop: Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting

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Introduction

Defining and predicting drug dosing has improved substantially over the past 20 years. However, dosing for newly approved drugs by the U.S. Food and Drug Administration (FDA) often does not include individualized recommendations for many in the real-world patient population. This summary captures viewpoints from the August 12, 2019 workshop *Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting* co-hosted by the FDA and University of North Carolina.[1]

Challenges and Opportunities for Drug Dosing in the Real World

Precision dosing refers to the identification of a drug dosing regimen that accounts for patient factors to maximize effectiveness while minimizing toxicity for an individual patient.[2] Issam Zineh (FDA) noted that while some approaches that enable precision dosing are currently incorporated into drug development; in general, the goal of individualized patient

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Conflicts of Interest

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dosing remains aspirational. As such, uncertainty regarding the optimal dosing regimen is a common reason for delayed or denied drug approval by the FDA.[3] Furthermore, a recent FDA study determined that 78 percent of 181 drugs approved from 2013-2017 had only one approved dosing regimen, and of the drugs considered to be amenable to response-guided treatment, only 39 percent provided response-guided dosing instructions in the labeling.[4]

Technologies to enable precision dosing, including modeling and simulation approaches during drug development and analysis of real-world data, are identifying more accurate dosing regimens for specific populations. However, challenges such as increased clinical trial complexity, perceived patient inconvenience, and a continued focus on population-based dosing, still need to be addressed, Zineh noted. This workshop assembled multiple stakeholders, including industry, regulators, patients, clinicians, academicians, and device/software developers to: (1) explore the need to further leverage approaches for precision dosing in drug development and patient care; (2) investigate opportunities in drug development and in real-world settings to generate the information needed to support precision dosing approaches; and (3) discuss the translation of dosing information to state-of-the-art drug dosing tools to enable precision dosing in clinical practice.

Current Landscape and Barriers to Precision Dosing Implementation

To fully understand the potential of precision dosing, it is important to understand the current state of precision dosing in healthcare and challenges in implementation from the perspectives of all stakeholders, including regulators, industry, patients, and clinicians. The FDA encourages the study of variations in dose-response relationships through subgroup analyses on age, sex, and race, and more recently, on disease severity, and concomitant diseases and medications, noted Robert Temple (FDA). However, the problem of multiplicity in subset analysis means that the FDA must proceed with caution in making dosing recommendations from such analyses. The study of the effects of age, race, gender, metabolism, and drug-drug interactions has increased in most drug development programs, and Temple encouraged continued efforts to expand relevant subgroup analyses to improve individualized drug dosing.

Providing an industry perspective, Jack Cook (Pfizer) noted significant improvements to dosing instructions in labeling in the last 50 years due to increased understanding of individual pharmacodynamic differences, identifying drug-drug interactions, and studying dosing in pediatric populations. However, differences in pharmacodynamic effects are still not as well studied for some subgroups, such as patients with more severe forms of renal and hepatic impairment, women who are pregnant or breast-feeding, patients with common co-morbidities, and pediatric patients.[5] Cook also highlighted several challenges in the labeling language itself that hinders individualized dosing. For example, the absence or presence of information in labeling is not necessarily related to its importance for dosing, and ambiguous language such as ‘use with caution’ can lead to variable interpretations. Cook offered several opportunities to increase the diversity of patients in clinical trials, including using innovative clinical trial designs, pooling data across compounds to generate predictive models, and developing technology to bring personalized dosing to patient point-of-care.

Representing a patient advocacy perspective, Cynthia Bens (Personalized Medicine Coalition (PMC)) noted that a patient's history, circumstances, and values are also critical components for individualized medical care. A record number of personalized medicines[6] were approved by the FDA in 2018;[7] however, for many patients, the pace of progress is still too slow, Bens noted. Barriers to personalized medicine include minimal innovation in therapeutic areas outside of oncology, challenges with insurance coverage and reimbursement, and slow clinical adoption. Patients can facilitate the translation of research in precision dosing approaches to clinical application by advocating for research and increased insurance coverage.

In clinical practice, precision dosing can be encouraged through innovations at the patient, process, and regulatory levels, noted Michael Neely (University of Southern California, Children's Hospital of Los Angeles). At the patient level, applying clinical pharmacometrics, or real-time quantitative modeling and simulation, can increase precision of the timing of sample collection, patient adherence, and prediction accuracy of individual patient drug concentrations. In health care delivery, novel formulations prepared from 3-D printing, wearable devices that measure drug concentrations, and increased training in clinical pharmacometrics can facilitate precision dosing in real-world situations. Regulatory challenges such as software device regulation and restrictive labeling language could be addressed by broader dosing recommendations and changing requirements to include more comprehensive pharmacokinetic data in FDA labeling to enable independent modeling and analysis. Additionally, maintaining de-identified subject-level pharmacokinetic data in an FDA repository would allow analyses to inform individualized dosing. Neely noted that fully realizing precision dosing in the clinic will require collaboration and innovation among multiple stakeholders and proposed the formation of a Precision Dosing Advisory Group to move the field forward, for example, to create and revise FDA guidance and package insert content.[8]

Key Considerations for Successful Development and Use of Precision Dosing

Precision dosing approaches have been successfully applied during drug development as well as in the post-marketing space when it significantly improved the benefit/risk profile of the drug. Therefore, drugs that are most likely to benefit from precision dosing include those with a narrow therapeutic index, mechanism-based or severe adverse events, or are used in vulnerable populations, highlighted Richard Peck (Hoffman La Roche). During pre-market drug development, Peck recommended that evaluating exposure-response early during phase 1 or 2 trials, designing adaptive clinical trials to explore multiple doses, including a wider range of patients, and publishing trials and models to crowdsource data would allow for full exploration of the utility of precision dosing approaches. Incentives that could further encourage the incorporation of precision dosing approaches into premarket drug development include demonstrating a higher drug development success rate and outcomes-based pricing.

Post-marketing, there are significant opportunities for modeling and simulation-based approaches to address the gap between doses recommended from phase 3 clinical trials and those needed in real-world clinical settings, noted Daniel Gonzalez (University of North Carolina Eshelman School of Pharmacy). Considerations for using modeling and simulation to enable precision dosing approaches throughout a product's life cycle include choosing an appropriate model, qualifying the model, and handling model bias and inter-occasion variability. Gonzalez further emphasized the importance of clinical decision support (CDS) tools that align to electronic health records (EHRs) and wearable electronic devices that provide efficacy and safety feedback for use in modeling and simulation to enable precision dosing post approval.

Additionally, real-world data have the potential to fill the data gaps needed to individualize dosing under conditions not previously studied. Sara Van Driest (Vanderbilt Children's Hospital) presented several retrospective case studies using Vanderbilt's de-identified clinical record database, Synthetic Derivative, and DNA repository, BioVu, to collect real world data and explore drug-drug or drug-patient interactions that historically have not been well studied. Van Driest provided several case studies from her research, including: (1) the combination of vancomycin and piperacillin-tazobactam had a higher incidence of acute kidney injury versus vancomycin and cefepime; and (2) pediatric patients who were poor or intermediate metabolizers of risperidone had a higher rate of adverse drug events.

Translating Real-World Dosing to Patient Drug Dosing Tools

CDS tools that recognize exposure differences and recommend optimum dosing regimens should be capable of identifying exposure differences at the individual patient level, function efficiently within the clinical workflow, and provide value over the standard of care, noted Roger Jelliffe (University of Southern California). To this end, Jelliffe discussed the method of a multiple model dosage design, which uses non-parametric modeling, a statistical approach that requires the population data to meet fewer assumptions than other modeling approaches. He emphasized that a multiple model approach best reproduces the pharmacokinetics of the drug as well as the response of each patient and can account for the unknown parameters to inform the optimal dose. Jelliffe highlighted how a multiple model design can be applied in the clinic and called on the FDA and industry to publish their non-parametric population pharmacokinetic models and promote its use in clinical practice.

Sander Vinks (Cincinnati Children's Hospital Medical Center) presented their decision-support EHR-aligned platform which integrates pharmacogenetics with model-based pharmacokinetic and pharmacodynamic algorithms for individualized precision dosing in real-time. Their CDS tool is a 'learning system' with real-time monitoring that feeds into a centralized cloud-based portal to leverage Bayesian estimations for dosing recommendations. This and other examples of CDS tools demonstrate that model-informed therapeutic drug management is feasible through learning health systems. Vinks called for further development of CDS tools that incorporate pharmacokinetic, pharmacodynamic, and disease progression measures.

Several factors have thwarted the wide-spread utility of model-informed precision dosing tools in the clinic, said Srijib Goswami (InsightRX), including decentralized dosing calculators coupled with manual data entry, a lack of data standardization, and limited interoperability within the clinical work flow. However, the increasing adoption of EHR systems, transitions to cloud-based healthcare systems, and a movement toward value-based care payment models reveals new opportunities to develop CDS tools that integrate into the clinical workflow. To that end, Goswami highlighted that the optimal CDS tool is useful, intuitive, simple, high quality, and incorporates input from both experts and users. For widespread implementation, scalable integration approaches are needed to more readily apply CDS tools across multiple clinical settings. Goswami also emphasized the importance of including data analytics to evaluate the clinical benefit and value of drug dosing CDS tools.

Conclusion

Through work to understand clinically actionable genotypes, phenotypes and target drug concentrations, clinical pharmacology at the FDA has laid the groundwork for quantitative clinical and regulatory decision-making, said Bob Powell (University of North Carolina). This foundation facilitated the identification of the phase III trial/real-world gap between clinical study subjects and real-world patients and is driving innovative precision dosing approaches. Powell highlighted that precision dosing approaches have immense potential to assist clinicians, promote value-based and efficient care, and improve patient outcomes. In particular, panel discussions at this workshop identified diverse and innovative opportunities to enable precision dosing in drug development and real-world use (summarized in Table 1 below). Through a concerted effort among all relevant stakeholders, including regulators, clinicians, industry, academicians, educators, insurers, software and device companies, and patients, it is possible to overcome the barriers to precision dosing and realize the future of individualized patient care.

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[6]. PMC defines a personalized medicine as “those therapeutic products for which the label includes reference to specific biological markers, identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.”

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Table 1:

Challenges and solutions discussed in the panel sessions for precision dosing in the real-world setting

Challenge identified	Solution offered
Current drug labeling practices discourage individualized dosing in the clinic	• Use broader labeling language to encourage the use of exposure-response data within the studied range of safe and effective doses in the clinic
There is a lack of data to inform precision dosing approaches	• Create an FDA repository of de-identified subject-level data to help develop precision dosing tools
	• Encourage the use of multiple drug doses or titration-based dosing during clinical trials
Clinical trial populations do not represent real-world patients	• Enroll understudied and more diverse populations to inform dosing in real-world settings
	• Use innovative clinical trial designs to enable the enrollment of subpopulations
There is a lack of predictive models for major drug clearance mechanisms	• Create a process for agreeing that a model is useful for predicting a clinical dose
There is a lack of real-world data to inform and confirm precision dosing	• Identify real-world data sources capable of providing adequate information regarding efficacy and safety to help predict precise doses for certain clinical patient subgroups (e.g., children, pregnant women, obese subjects)
Drug labeling lags behind advances in science and knowledge from real-world use	• Create more dynamic drug labels that can be modified and disseminated in reaction to real-world data post marketing
There is a lack of clarity on regulatory pathways for clinical decision support tools	• Create and improve FDA guidance regarding the appropriate regulatory approval pathways for clinical decision support tools and devices
The culture of the healthcare industry does not broadly support precision dosing approaches	• Increase training on quantitative modeling and simulation for clinicians and pharmacists to champion this approach to patient care
	• Increase the understanding of how precision dosing increases the value of health care encounters and improves patient outcomes
	• Incentivize precision dosing approaches at the bedside by providing increased reimbursement for these value-based approaches
	• Encourage patient activism to increase awareness of the benefits of precision dosing and barriers to access
There is a lack of efficient and user-friendly CDS tools	• Develop precision dosing tools that integrate into clinical work flows and add value over the standard of care