Personalized reproductive medicine: regulatory considerations

Jonathan P. Jarow, M.D.

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland

Personalized medicine has many definitions. This term is often used synonymously with precision medicine, which is defined as the classifying patients with a disease or condition based on their phenotypic findings, such as biomarkers or genomics, into subpopulations that differ in their response to a specific treatment. Personalized medicine, however, can also mean the treatment of individual patients based on many contextual factors, such as response to therapy and patient preferences, in addition to predefined phenotypic findings. Regulatory approval for the marketing of a new drug or a new indication for a marketed drug requires a positive benefit risk profile and substantial evidence of effectiveness. The indication is based on the eligibility criteria and outcomes of the clinical trial(s) underpinning the regulatory approval. For precision medicine, drugs are often developed with companion diagnostics that are necessary for selection of the subgroup of patients, in contrast to personalized medicine which may be directed at a single patient. Most drugs are approved with a fixed dosage regimen for the approved population, but some drugs and biologics are approved with instructions to tailor therapy for individual patients, whether it be dosing, combination with other therapies, or selection among a class of medications. Hence, more often than not, personalized medicine directed at individual patients is achieved through the practice of medicine rather than regulatory action. (Fertil Steril® 2018;109:964–7. ©2018 by American Society for Reproductive Medicine.)

Key Words: Biomarker, FDA, personalized medicine

DEFINITIONS

The terms personalized medicine and precision medicine are often used interchangeably, but their meaning can vary. *Precision medicine* is defined as the refinement of the taxonomy of diseases, or conditions, by characterization of subgroups of patients expected to respond differently to an intervention. For instance, lung cancer, which was historically defined based on histology and clinical stage, can now be defined using genetic testing that identifies subgroups of patients who have a greater likelihood of responding to therapies that target a driver mutation (1). Thus, precision medicine does not mean the development of a drug for a single patient but rather a subset of patients with a disease that has been redefined by a more precise taxonomy.

The tests, whether they are biomarkers or genomics, used to characterize the disease or condition are often new and thus need to be developed with the drug as a companion diagnostic to ensure that there are adequate instructions for the safe and effective use of the drug (2). For the purposes of this article, *drug* applies to both small molecules and biologics. The ultimate goal of precision medicine is the identification of a subset of patients with a common pathophysiology who are most likely to benefit from the medical intervention. The National Research Council prefers precision medicine as the more precise term when discussing targeted therapies (3).

The term *personalized medicine* is less precisely defined. Many consider it a synonym for precision medicine, but personalized medicine can also be used to connote treatment of individual patients, rather than groups. Personalized medicine of individual patients depends on many contextual factors independent of the underlying disease as defined by precision medicine. These factors may include customized dosing, concomitant therapies, response to therapy, drug metabolism and patient preferences.

Personalized medicine, using the definition of individualized therapy, presents significant challenges to both drug developers and regulators. First, the multidimensional aspect of personalized medicine increases the complexity of drug development exponentially. Imagine performing a controlled study with the multiple arms needed to assess these variables. Second, a drug that is intended for just one patient raises both practical and economic considerations. Precision medicine divides traditional diagnoses into multiple subpopulations where the main challenge may be a low prevalence of the targeted population. Development of a drug intended for just a single patient requires an N = 1 study design, which is not viable from

Received January 24, 2018; revised and accepted March 19, 2018.
J.P.J. has nothing to disclose.
Reprint requests: Jonathan P. Jarow, M.D., Office of the Center Director, Center for Drug Evaluation and Research, WO51 RM6364, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993-0002 (E-mail: jonathan.jarow@fda.hhs.gov).

Fertility and Sterility® Vol. 109, No. 6, June 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.03.027

a practical perspective. For a drug developed for just one patient, there is no market for the drug after that single patient has been tested. By contrast, individualized dosing of a drug approved for a large population has been frequently employed in the management of cancer, pain, and diabetes.

The regulatory approach to these drugs has been to provide general guidance and leave the rest to the practice of medicine. For instance, the product labeling for insulin contains the statement, "The desired blood glucose levels as well as the doses and timing of antidiabetic medications must be determined individually." The same is true for drugs approved for ovarian stimulation during in vitro fertilization cycles, where product labeling states that "the dose of gonadotropins should be adjusted according to individual response." Thus, the U.S. Food and Drug Administration (FDA) has managed personalized medicine primarily through drug product labeling that recognizes the importance and allows for physician judgment in the management of individual patients, rather than requiring approval for each individual patient.

DEFINING A DISEASE

The indication statement in product labeling of a drug defines the disease or condition being treated—known as the *indicated population*—and is typically derived from the eligibility criteria used in the clinical trials underpinning the approval of the drug. There may, however, be modifications to the indicated population based on the outcomes of these clinical trials. Moreover, the indicated population may be broadened or narrowed based on the outcomes of postmarketing studies.

Diseases were historically defined by phenotypic findings: symptoms, physical examination, and laboratory, radiological, and pathological findings. A population identified with a specific disease or condition was often composed of a heterogenous population with multiple underlying pathophysiologies who thus exhibited a highly variable response to a single treatment. The modern era of genomics, as well as other omics, has ushered in a more precise characterization of the subgroups within a phenotypically defined disease as well as has the development targeted therapies to address specific abnormalities observed in these subgroups. For example, cancer was historically classified by tissue of origin, histology, and stage of progression, but it is now further defined based on genetic testing in various ways.

Once a drug has been approved for marketing, physicians can select a therapy for an individual patient or subgroup of patients based on current standards of care as part of the practice of medicine, regardless of whether that population is in the indicated population. By contrast, a drug developer must demonstrate that the drug is safe and effective for its intended use to gain regulatory approval for a new labeled indication.

APPROVAL STANDARDS

The FDA's approach to the evaluation of marketing applications for new medicines is guided by a legal framework of statutes and regulations. The ultimate decision to approve the marketing of a new drug, or new indication for a marketed drug, is based on the benefit-risk analysis for the drug's intended use. Statute requires that there be *substantial evidence* of effectiveness, which is defined in statute as being evidence based on adequate and well-controlled clinical trials by qualified investigators (U.S. Food Drug and Cosmetic Act) (4).

It is widely recognized that there are circumstances in which it may not be practical or ethical to randomize patients to a placebo or to perform a second trial after the first successful trial. In the latter circumstance, a single trial with supportive evidence can be sufficient to meet this standard. For conditions in which it is not ethical to randomize patients to placebo due to the serious nature of the disease or availability of effective therapies, it is acceptable to use either external controls or perform a noninferiority trial against an active control, respectively (5). External controls can be used for diseases with a well-defined natural history. For example, a randomized controlled study is not needed for vasectomy reversal because the spontaneous pregnancy rate for vasectomized couples is virtually zero. In addition, a reduced number of trials and trial participants may be acceptable for drugs intended for rare diseases so long as sufficient evidence is provided to be confident in the benefit-risk analysis. It is important to keep in mind that studies of 100 patients with a rare disease may represent a much more substantial percentage of the U.S. population with the disease than studies of tens of thousands of patients with a common disease such as hypertension.

ESTIMATION OF A DRUG'S EFFECT

The efficacy outcome of a clinical trial is typically expressed as the average (or median) effect of the drug in the population studied, known as the *estimand*. The 95% confidence interval surrounding that estimand are less commonly emphasized. Drug developers go to great lengths to reduce the variability, known as noise, in the design and conduct of clinical trials to achieve greater precision in the measurement of a drug's effects. This is vital to the demonstration of superiority to a comparator for drugs with a relatively small effect size. Nevertheless, variability persists, and most individual patients in the trial and in subsequent clinical practice do not experience the estimand result.

Variability in response is due to known factors—only some of which are quantifiable—and unknown factors. Variations in drug exposure due to pharmacology or adherence can play a significant role and are measurable. Therapeutic dose monitoring can be used to correct for this variation, but it is only typically employed for drugs with a narrow therapeutic window. Variation of the underlying pathophysiology of the disease is another major factor accounting for the variability of response. There are many examples where better characterization of the underlying pathophysiology of a disease through precision medicine has reduced the variability in response, but we have yet to abolish variability. This should not be surprising because we are still scratching the surface of our understanding of the genetics of complex diseases, and there may be multiple pathways in play. Moreover, even for patients with single-gene inborn errors of metabolism there can be other intervening environmental factors