PERSONALIZED MEDICINE AT FDA

2017 Progress Report

PMC

2017 MILESTONES

1. Record number of personalized medicine approvals
2. Approval of first three gene therapies
3. First approval of tissue agnostic indication for cancer therapy
4. First authorization for marketing of health-related genetic tests directly to consumers
5. First approval of personalized medicine biosimilar
6. First FDA/CMS joint approval and coverage decision for test using next-generation sequencing technology

INTRODUCTION

An Accelerating Trend

The U.S. Food and Drug Administration (FDA) spearheaded several significant developments in personalized medicine in 2017 that demonstrate the agency's commitment to advancing and accelerating the field.

More than one of every four drugs the agency approved over the past four years is a personalized medicine, and FDA approved a record number of 16 new personalized medicines in 2017. Those numbers are a sharp increase from 10 years ago, when personalized medicines accounted for less than 10 percent of new molecular entity (NME) approvals annually.

In addition, the agency approved several significant expanded indications for existing personalized therapies as well as the first three gene therapies ever in the U.S. and the first personalized medicine biosimilar. The agency also authorized the first FDA-approved health-related genetic tests marketed directly to consumers, and worked with the Centers for Medicare and Medicaid Services (CMS) to jointly approve and clear a next-generation sequencing (NGS)-based testing platform.

UNPRECEDENTED PROGRESS

A Record Number of New Personalized Medicine Approvals

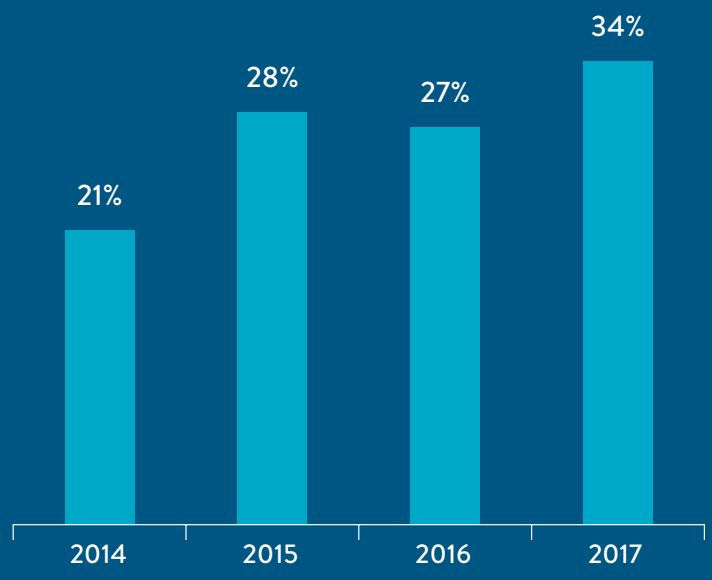
FDA's Center for Drug Evaluation and Research (CDER) approved 46 NMEs — new drugs, agents or therapeutic biologics — in 2017. Of the 46, the Personalized Medicine Coalition (PMC) classified 16 of them — nearly 35 percent — as personalized medicines, the most of any year, topping the 13 (out of 45) approvals in 2015. The number of personalized medicines approved annually has topped 20 percent each year since 2014, when PMC classified 21 percent of NMEs as personalized medicines. In 2015 and 2016, the Coalition classified 28 percent and 27 percent of NMEs as personalized medicines, respectively.

In addition, for the first time ever in the U.S., FDA's Center for Biologics Evaluation and Research (CBER) approved three gene therapies, which are personalized treatments that involve the transplantation of normal genes into cells in place of missing or defective ones to correct specific genetic disorders or modulate specific cellular reactions.

"We're increasingly able to identify patient benefit earlier in the development process because of the ability to better target medicines to the underlying mechanisms of disease."

— **Scott Gottlieb, M.D., Commissioner, FDA**
January 2018

Personalized Medicines Top 30% of FDA Approvals for First Time in 2017



Methodology: PMC defines personalized medicine as an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans. When evaluating NMEs, PMC categorizes personalized medicines 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.

2017 APPROVALS

16 of the 46 new molecular entities FDA approved in 2017 — as well as three gene therapies — are personalized medicines.

1. Kisqali (ribociclib) for the treatment of advanced breast cancer. The decision to use this product is informed by the HR and HER2 biomarker statuses in patients.
2. Bavencio (avelumab) for the treatment of metastatic Merkel cell carcinoma. The decision to use this product can be informed by PD-L1 expression levels in the tumors of patients.
3. Zejula (niraparib) for the maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers. The decision to use this product is informed by the BRCA mutation biomarker status in patients.
4. Austedo (deutetrabenazine) for the treatment of chorea associated with Huntington's disease. The use of this product can be informed by the CYP2D6 biomarker status in patients.
5. Ingrezza (valbenazine) for the treatment of tardive dyskinesia. The use of this product can be informed by the CYP2D6 biomarker status in patients.
6. Brineura (cerliponase alfa) for the treatment of CLN2 type Batten disease. The decision to use this product is informed by the TPP1 biomarker status in patients.
7. Alunbrig (brigatinib) for the treatment of metastatic non-small cell lung cancer (NSCLC). The decision to use this product is informed by the ALK biomarker status in patients.
8. Rydapt (midostaurin) for the treatment of acute myeloid leukemia (AML). The decision to use this product is informed by the FLT3 biomarker status in patients.
9. Imfinzi (durvalumab) for the treatment of advanced urothelial carcinoma. The decision to use this product can be informed by PD-L1 expression levels in the tumors of patients.

10. Nerlynx (neratinib maleate) to reduce the risk of breast cancer recurrence. The decision to use this product is informed by the HER2 biomarker status in patients.
11. Vosevi (sofosbuvir, velpatasvir and voxilaprevir) for the treatment of hepatitis C. The decision to use this product is informed by HCV genotype status in patients.
12. Idhifa (enasidenib) for the treatment of relapsed or refractory acute myeloid leukemia (AML). The decision to use this product is informed by the IDH2 biomarker status in patients.
13. Mavyret (glecaprevir and pibrentasvir) for the treatment of hepatitis C. The decision to use this product is informed by the HCV genotype status in patients.
14. Verzenio (abemaciclib) for the treatment of advanced breast cancer. The decision to use this product is informed by the HR and HER2 biomarker statuses in patients.
15. Mepsevii (vestronidase alfa-vjbk) for the treatment of Mucopolysaccharidosis type VII (Sly syndrome). The decision to use this product is informed by the MPS VII biomarker status in patients.
16. Hemlibra (emicizumab-kxwh) for the treatment of hemophilia A. The decision to use this product is informed by the factor VIII antibody status in patients.

Newly Approved Gene Therapies

1. Kymriah (tisagenlecleucel) for the treatment of acute lymphoblastic leukemia (ALL). The treatment is a genetically modified autologous T-cell immunotherapy.
2. Yescarta (axicabtagene ciloleucel) for the treatment of large B-cell lymphoma. The treatment is a genetically modified autologous T-cell immunotherapy.
3. Luxturna (voretigene neparvovec-rzyl) for the treatment of retinal dystrophy. The treatment is a fully integrated gene therapy to correct a specific RPE65 mutation in retinal cells.

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Significant New Indications

Even the large number of newly approved therapies classified as personalized medicines in 2017 does not provide the whole picture. The growing list of personalized medicines available to doctors and their patients also includes many significant new personalized medicine indications for previously approved drugs in 2017. These approvals redefine the drugs' intended populations and provide patients with more effective personalized treatment options. The list of new personalized medicines in 2017 should therefore be complemented with reference to newly approved indications for Revlimid (lenalidomide), Keytruda (pembrolizumab), Ibrance (palbociclib), Tecentriq (atezolizumab), Kalydeco (ivacaftor), Zykadia (ceritinib), Opdivo (nivolumab), Zelboraf (vemurafenib), Alecensa (alectinib), Adcetris (brentuximab vedotin), Sprycel (dasatinib), Sovaldi (sofosbuvir), Bosulif (bosutinib), Perjeta (pertuzumab) and Tasigna (nilotinib) for new molecularly defined subsets of patients.

The expanded approval of Keytruda (pembrolizumab) for all solid tumor types in advanced cancers with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) is particularly significant as it marks the first time an oncology drug has been approved based on a biomarker, regardless of where the tumor is located in the body.

"[These expanded] approvals point to an encouraging future for 'precision medicine' — an approach for disease treatment that tailors medical therapies, including medications, to the needs of individual patients."

— **Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA** on the approval of new personalized medicine indications for Kalydeco and Keytruda (July 2017)

NEW FRONTIERS

Notable Precedents

Direct-to-Consumer Authorization

This year also marked the first time FDA has authorized the commercialization of health-related genetic tests sold directly to consumers. By allowing the marketing of 23andMe's Personal Genome Service Genetic Health Risk tests for 10 diseases and conditions, FDA has brought clarity to companies seeking to market genetic tests that provide information on an individual's genetic predisposition to certain medical diseases or conditions.

A Personalized Medicine Biosimilar

The first personalized biosimilar was also approved in 2017. Ogivri (trastuzumab -dkst) for HER2-positive breast cancer is a biosimilar for Herceptin (trastuzumab), which was first approved in the U.S. in 1998.

Joint Approval & Coverage Decision for an NGS-Based Test

For the second time in their history, FDA and CMS also announced in 2017 a joint approval and coverage decision under the Parallel Review program. The review was completed this time for an NGS-based testing platform when FDA and CMS jointly approved and cleared Foundation Medicine's FoundationOne CDx. While this has led to questions regarding the setting in which CMS intends to pay for NGS-based tests, it demonstrates the viability of the Parallel Review pathway.

CONCLUSION

A Promising Paradigm

These significant developments reflect the extraordinary pace of scientific innovation in personalized medicine, progress that is largely due to the pharmaceutical and diagnostic industries' commitment to personalized medicine as well as the leadership at FDA.

While ongoing challenges in the areas of scientific discovery, diagnostic regulatory policy, coverage and reimbursement, and implementation of new technologies into clinical practice are still outstanding, the science leading health care away from one-size-fits-all, trial-and-error medicine and toward the utilization of molecular information to improve outcomes and make the U.S. health system more efficient is clear.

"FDA has an important role to play in advancing this targeted approach to treating disease by building a modern framework that ensures we're providing the guidance and resources needed to efficiently develop these novel products using new technology."

— **Scott Gottlieb, M.D., Commissioner, FDA**
December 2017

ABOUT US

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system.

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MEDICINE COALITION

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