
PERSONALIZED MEDICINE AT FDA

A Progress & Outlook Report



2018 MILESTONES

1. Record number of 25 personalized medicine approvals (42% of all 2018 new drug approvals)
2. Second approval of a cancer drug indication based on biomarker, not tumor type: Vitrakvi (larotrectinib)
3. First approval of a therapy from a new class of personalized drugs called small interfering ribonucleic acid (siRNA) treatments: Onpattro (patisiran)
4. Marketing authorization for first pharmacogenetic and cancer risk-related genetic tests sold directly to consumers
5. Recognition of first public database to support regulatory oversight of variant/disease claims: Clinical Genome Resource (*ClinGen*) database

INTRODUCTION

Unprecedented Progress

The U.S. Food and Drug Administration (FDA) advanced therapeutic approvals and policy initiatives in 2018 that demonstrate the agency's continued commitment to accelerating personalized medicine. FDA approved a record number of new personalized medicines, including the second tissue-agnostic indication for a cancer therapy and the first targeted RNA-based therapy. The agency also approved two personalized biosimilars and expanded the indications associated with many existing personalized therapies.

In its efforts to facilitate access to genomic testing and to integrate real-world data into its regulatory framework, FDA also, for the first time, authorized the marketing of pharmacogenetic and cancer risk-related genetic tests sold directly to consumers and recognized a public genomic database to support claimed relationships between disease and genetic test variants.

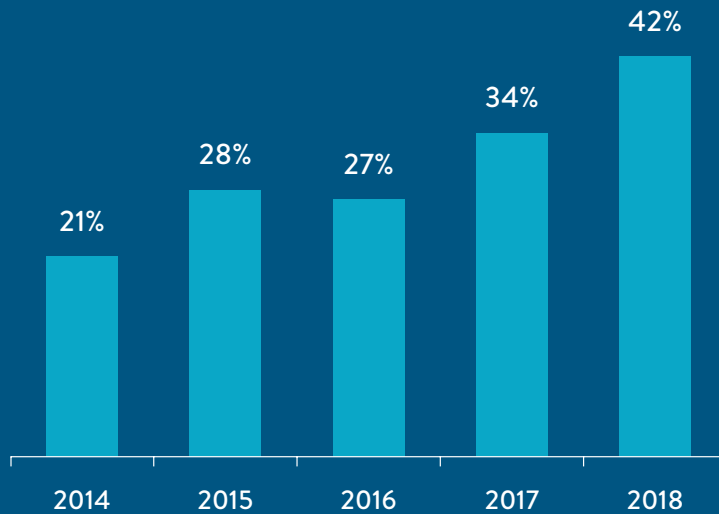
AN ACCELERATED PACE OF APPROVALS

A Record Number of Approvals

FDA's Center for Drug Evaluation and Research (CDER) approved 59 new molecular entities (NMEs) – new drugs, agents or therapeutic biologics – in 2018. Of the 59, the Personalized Medicine Coalition (PMC) classified 25 of them – more than 1/3 (42 percent) – as personalized medicines. The number of personalized medicines approved annually has topped 20 percent since 2014, when PMC classified 21 percent of NMEs as personalized medicines. The Coalition classified 28 percent of NMEs as personalized medicines in 2015; 27 percent in 2016; and 34 percent in 2017.

Thus, more than one of every three drugs the agency approved over the past two years is a personalized medicine. That ratio represents a sharp increase from just 10 years earlier, when personalized medicines accounted for less than 10 percent of NMEs approved annually.

Personalized Medicines Top 30% of FDA Approvals for Second Year in a Row



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.

2018 APPROVALS

25 of the 59 new molecular entities FDA approved in 2018 are personalized medicines. These medicines are listed below, in chronological order by date of approval.

1. **Lutathera** (lutetium Lu 77 dotatate) for the treatment of gastroenteropancreatic neuroendocrine tumors. The decision to use this product is informed by the somatostatin receptor (SR+) biomarker status in the tumors of patients.
2. **Biktarvy** (bictegravir/emtricitabine/tenofovir alafenamide) for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients.
3. **Symdeko** (tezacaftor; ivacaftor) for the treatment of cystic fibrosis. The decision to use this product is informed by the F508del mutation and CFTR mutation biomarker statuses of patients.
4. **Trogarzo** (ibalizumab-uiyk) for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients.
5. **Crysvita** (burosumab-twza) for the treatment of x-linked hypophosphatemia (XLH). The decision to use this product can be informed by the PHEX mutation biomarker status in patients.
6. **Doptelet** (avatrombopag) and **Mulpleta** (lusutrombopag) for the treatment of thrombocytopenia in patients with chronic liver disease. The use of this product can be informed by the Factor V Leiden, Prothrombin 20210A, Antithrombin, or Protein C or S biomarker statuses in patients.
7. **Palynziq** (pegvaliase-pqpz) for the treatment of phenylketonuria (PKU). The decision to use this product can be informed by the PAH mutation biomarker status in patients, and the use of this product is informed by the phenylalanine biomarker concentration in patients.

8. **Mektovi** (binimetinib) for the treatment of metastatic melanoma. The decision to use this product is informed by the BRAF biomarker status in the tumors of patients.
9. **Braftovi** (encorafenib) for the treatment of metastatic melanoma. The decision to use this product is informed by the BRAF biomarker status in the tumors of patients.
10. **Tibsovo** (ivosidenib) for the treatment of relapsed or refractory acute myeloid leukemia (AML). The decision to use this product is informed by the IDH1 mutation biomarker status in the tumors of patients.
11. **Krintafel** (tafenoquine) for the treatment of Plasmodium vivax malaria. The decision to use this product is informed by the G6PD biomarker status in patients.
12. **Mulpleta** (lusutrombopag) for the treatment of thrombocytopenia in patients with chronic liver disease. The use of this product can be informed by the Factor V Leiden, Prothrombin 20210A, Antithrombin, or Protein C or S biomarker statuses in patients.
13. **Onpattro** (patisiran) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis. The decision to use this product is informed by the TTR biomarker status in patients.
14. **Galafold** (migalastat) for the treatment of Fabry disease. The decision to use this product is informed by the GLA variant status in patients.
15. **Takhzyro** (lanadelumab-flyo) for the treatment of types I and II hereditary angioedema. The decision to use this product is informed by the C1-inhibitor biomarker levels and function in patients.
16. **Pifeltro** (doravirine) for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients.
17. **Vizimpro** (dacomitinib) for the treatment of advanced non-small cell lung cancer (NSCLC). The decision to use this product is informed by the EGFR biomarker status in the tumors of patients.
18. **Libtayo** (cemiplimab-rwlc) for the treatment of cutaneous squamous cell carcinoma (CSCC). The decision to use this product can be informed by the PD-L1 expression levels in the tumors of patients.

19. **Revcovi** (elapegademase-lvlr) for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID). The decision to use this product is informed by the ADA mutation biomarker status in patients.
20. **Tegsedi** (inotersen) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis. The decision to use this product is informed by the TTR biomarker status in patients.
21. **Talzenna** (talazoparib) for the treatment of advanced breast cancer. The decision to use this product is informed by the BRCA mutation biomarker status in patients.
22. **Lorbrena** (lorlatinib) for the treatment of advanced non-small cell lung cancer (NSCLC). The decision to use this product is informed by the anaplastic lymphoma kinase (ALK) biomarker status in the tumors of patients.
23. **Vitrakvi** (larotrectinib) for the treatment of solid tumor cancers with a specific gene fusion. The decision to use this product is informed by the neurotrophic receptor tyrosine kinase (NTRK) gene fusion biomarker status in the tumors of patients.
24. **Firdapse** (amifampridine) for the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS). The use of this product can be informed by the N-acetyltransferase 2 (NAT2) biomarker status in patients.
25. **Xospata** (gilteritinib) for the treatment of relapsed or refractory acute myeloid leukemia (AML). The decision to use this product is informed by the FLT3 mutation biomarker status in the tumors of patients.

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Emerging Trends Related to Approvals of Personalized Therapies

Expedited Review

Over the past five years, an increasing number of NMEs have gone through expedited review programs, which were put in place only recently, before being approved. Of the 25 new personalized medicines approved in 2018, 24 were subject to some form of expedited FDA review. Each of these expedited approvals was made possible by the agency's orphan drug designation, priority review, fast-track, or breakthrough therapy programs.

Cancer Indications Based on Biomarker, Not Tumor Type

The approval of Vitrakvi for the treatment of all solid tumor types in cancers with the neurotrophic receptor tyrosine kinase (NTRK) gene fusion is particularly significant, as it marks the first time an NME has been approved for use based on a biomarker, regardless of where in the body the tumor originated. The approval is only the second histology-agnostic, biomarker-defined oncology drug indication (with the first being for Keytruda, which won an expanded indication for all solid tumor types in advanced cancers with "microsatellite instability-high" or "mismatch repair deficiency" in 2017).

The Emergence of siRNA Treatments

The approval of Onpattro, an infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR), is also particularly significant, as it marks the first FDA approval of a new class of personalized medicine drugs called small interfering ribonucleic acid (siRNA) treatments, which work by selectively targeting and silencing a portion of RNA involved in causing disease.

Expanding Indications

Even the large number of new therapies classified as personalized medicines in 2018 does not provide the whole picture, however, on the growing list of personalized medicines available to doctors and their patients. In addition to the 25 personalized NMEs, FDA approved many significant new personalized medicine indications and/or drug combinations for previously existing drugs in 2018. These approvals redefine the drugs' intended populations and provide patients with more effective personalized treatment options. The list of new personalized medicines in 2018 should therefore be complemented with reference to newly approved indications for Lynparza (olaparib), Gilotrif (afatinib), Verzenio (abemaciclib), Imfinzi (durvalumab), Blincyto (blinatumomab), Rubraca (rucaparib), Opdivo (nivolumab), Yervoy (ipilimumab), Tagrisso (osimertinib), Tafinlar (dabrafenib), Mekinist (trametinib), Kymriah (tisagenlecleucel), Xalkori (crizotinib), Venclexta (venetoclax), Keytruda (pembrolizumab), Kisqali (ribociclib), Tecentriq (atezolizumab), Imbruvica (ibrutinib), Rituxan (rituximab), Hemlibra (emicizumab-kxwh), and Adcetris (brentuximab vedotin) for new molecularly defined subsets of patients.

The Emergence of Personalized Medicine Biosimilars

Two new biosimilars for existing personalized medicines were also approved in 2018, including Truxima (rituximab-abbs), the first biosimilar to Rituxan for the treatment of adult patients with CD20-positive, B-cell non-Hodgkin lymphoma (NHL), and Herzuma (trastuzumab-pkrb), as a biosimilar to Herceptin for the treatment of human epidermal growth factor receptor 2 (HER2) overexpressing breast cancer and metastatic gastric cancer.

POLICY PRECEDENTS

Modernizing Regulatory Oversight of Diagnostics and Treatments

It was a busy year for FDA in terms of public policy actions that have the potential to support and advance personalized medicine. The agency finalized several guidance documents to ease regulatory burdens for targeted therapeutics and diagnostics developers. For example, FDA finalized guidance on *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*; *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics*; and *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases*. The agency released draft guidance documents related to *Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products and Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment*, which may help industry navigate development of tissue-agnostic indications.

FDA also took steps to advance digital health technologies; modernize the frameworks applicable to the oversight of emerging types of diagnostic tests; and facilitate the use of direct-to-consumer (DTC) genetic testing.

Notable Policy Developments

Digital Health

FDA moved forward with its plan to update its approach to digital health by advancing its pre-certification program and launching the *FDA Premarket Digital Safety Program* and *Digital Health Incubator*. These digital health initiatives may encourage the use of personalized medicine by helping match new personalized medicine products with the patients who are most likely to benefit or by helping to identify potentially serious therapeutic side effects sooner.

Legislative Framework for Oversight of Diagnostics

FDA Commissioner Scott Gottlieb, M.D., also underlined this year that regarding the issue of diagnostics regulation – including oversight of laboratory-developed tests – the agency will work with Congress on a solution. FDA provided technical assistance on the *Diagnostics Accuracy and Innovation Act (DAIA)*, which was designed to address and reform diagnostics regulatory oversight. Legislators incorporated some of the agency's suggestions into a new draft bill released this year called the *Verifying Accurate Leading-edge IVCT Development (VALID) Act*, which is meant to be a thoughtful multi-stakeholder legislative approach to the many outstanding issues related to diagnostics regulation. Getting agreement from multiple stakeholders to advance a bill that modernizes regulatory oversight for diagnostics could bolster personalized medicine by encouraging investments in personalized medicine tests.

Recognition of Public Genetic Variant Database to Support Regulatory Oversight

After finalizing guidance for stakeholders and FDA staff on the *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics*, FDA, for the first time, recognized a public human genetic variant database to support claimed relationships between tested genetic variants and disease. FDA recognized *ClinGen*, a National Institutes of Health-supported database, for this purpose. The use of public databases to aid in regulatory decision making is meant to increase the use of real-world data for oversight purposes and relieve some of the clinical development burden that can be associated with lengthy studies and high costs. As such, it will likely help encourage the development of personalized medicine diagnostics.

Direct-to-Consumer Genetic Testing Authorizations

FDA also authorized for the first time the commercialization directly to consumers of two important subsets of health-related genetic tests: cancer risk testing and pharmacogenetic testing.

By allowing the marketing of 23andMe's limited BRCA variant test for breast and ovarian cancer risk, FDA has authorized for the first time a test for cancer risk that is available without a prescription.

FDA also authorized 23andMe's Personal Genome Service Pharmacogenetic Reports test for providing information about 33 genetic variants that may be associated with a patient's ability to metabolize some medications. Although the decision to allow the marketing of these tests directly to consumers has raised the profile of personalized medicine, it has also generated confusion among the genetic testing community because FDA simultaneously cautioned consumers that the tests should not be used to make treatment decisions without confirmatory clinical laboratory test results and consultation with a health care provider.

OUTLOOK FOR LASTING INNOVATION

Scientific Opportunities

Over the last few years, personalized treatments have been developed that can cure hepatitis C and leukemia and restore vision loss from congenital blindness. The overall survival and progression-free survival rates for breast, lung, and colorectal cancer patients have improved significantly. Many cystic fibrosis patients can now expect to live long lives and breathe freely. Considering the rapid growth in shared public data and its use in drug development — fueled by modernized FDA policies — a continuation of seminal breakthroughs for rare diseases is expected.

These significant developments reflect the extraordinary pace of scientific innovation in personalized medicine. This progress is largely due to the commitment to personalized medicine by the biopharmaceutical and diagnostic industries as well as FDA. The agency's efforts to advance patient-centered drug development, recognize new adaptive or innovative platform trial designs, and facilitate the use of real-world evidence have begun to accelerate the development of innovative personalized medicine products that can improve patient care.

Policy Challenges

But future progress cannot be taken for granted. To ensure that industry leaders continue to develop groundbreaking personalized medicine tests and treatments and that patients have access to these products, policymakers, as they have in the past, must favor policies that encourage the advancement of the field. It is especially important that policymakers establish a predictable funding environment for FDA's activities — with levels that are sufficient to support its work — and that decision-makers in the public and private sectors collaborate to overcome the reimbursement challenges associated with personalized tests and treatments that turn increased up-front costs into downstream benefits for patients and health systems.

Appropriations for FDA

Investors will only continue to prioritize the development of innovative personalized medicine products and services that hold enormous potential for patients and society for as long as they are reasonably certain that FDA, which serves as a gatekeeper for the products that reach patients, will have the resources necessary to complete its work in a timely manner. Any uncertainty in relation to the future of agency funding has the potential to disrupt highly sensitive investment markets. The U.S. government's failure to appropriate full funding for the agency's activities in the first quarter of 2019, for example, has already begun to affect investors' interest in biomedical innovation.

Adequate appropriations for FDA are therefore critical not only for ensuring that the agency can continue to approve personalized medicine products that benefit patients, but also for sustaining investors' interest in developing those products in the first place.

Reimbursement Challenges

While emerging personalized medicine technologies and platforms have the potential to make drug development more economical and make health systems more efficient by targeting treatments to only those who will benefit, they are also challenging reimbursement systems accustomed to one-size-fits-all medicine. Indeed, personalized medicine has led payers to think differently about coverage and reimbursement of high-value diagnostics. The approval of tissue-agnostic drugs such as Vitrakvi, for example, will force payers to figure out policies for pan-cancer indications and associated genetic testing.

But despite the increased pressure to provide access to diagnostic testing that guides personalized treatment options, several policies have been proposed that threaten patient access to the treatments themselves. The Centers for Medicare and Medicaid Services (CMS), for example, has announced plans to apply step therapy to physician-administered Part B drugs, which would require some patients to try less expensive standard treatment options before getting access to a more expensive treatment option, even if it will be more effective. Driving treatment decisions by cost considerations rather than determining what treatment would work best for an individual patient fundamentally conflicts with personalized medicine, and in many cases will increase downstream costs brought on by continued progression of disease and more adverse side effects associated with the wrong treatment. The administration has also proposed that the U.S. tie Medicare Part B drug payment rates to an international pricing index, which would likely discourage investment in further research to develop personalized medicines.

The key to advancing more sophisticated payment policies that recognize the value of personalized medicine tests and treatments is to accumulate evidence of the clinical and economic value of personalized medicine. FDA is doing its part by establishing policies that promote personalized medicine and efficiently approving high-value personalized medicine products.

CONCLUSION

Sustaining a Promising Paradigm

The era of personalized medicine has arrived. Innovation is at an all-time high, as reflected in the high number of personalized medicines documented in this report. Scientific discovery is accelerating to reach into health conditions and disease variants that had not been accessible before, while technological advancements are providing new tools to capture vast amounts of data on individual patients, which, in turn, will fuel a further acceleration and expansion of personalized medicine.

These developments continue to pose challenges related to scientific discovery, diagnostic regulatory policy, investment incentives, coverage and reimbursement, and the implementation of new technologies into clinical practice. But the science, more than ever, is leading the health system away from one-size-fits-all, trial-and-error medicine and toward the utilization of molecular information to improve outcomes and make the health system more efficient.

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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