Innovation

"Companies will need to meet a number of great challenges over the coming years, but they should stay focused on their core expertise. For pharmaceutical companies, this is access and innovation. Beyond product innovation, companies have to devise new profitable business models to reach patients across the global income pyramid."

Jeffrey Sturchio, president and CEO, Rabin Martin

2017 highlights

• Delivered 16 major approvals as well as six FDA breakthrough therapy designations and 16 major regulatory submissions; nine projects entered our development pipeline
• Launched a patient trial in Africa for KAF156, a novel compound against multidrug-resistant malaria
• Reported the discovery and early validation of a drug candidate for treating cryptosporidiosis, a diarrheal disease that is a major cause of child mortality in lower-income countries
• Reported progress in research of a novel antibiotic candidate, LYS228, for multidrug-resistant infections caused by the Enterobacteriaceae family of Gram-negative pathogens

Key challenges

• Aging populations and growing healthcare spending put increasing pressure on healthcare systems
• Anticipating future health needs, particularly for aging populations
• Developing new antibiotics remains a challenging scientific endeavor
• Rising parasite resistance to current antimalarial therapies threatens progress achieved to date
• Expanding quickly into the private sector with Novartis Access to drive sales volume and subsequently make the program sustainable
Why it is important

Demographic trends are changing healthcare. The world’s population is growing, with an estimated 8.5 billion people expected to inhabit the planet by 2030. At the same time, the population is rapidly aging. According to projections by the United Nations, about 1.4 billion people worldwide are expected to be 60 years or older by 2030, and this is expected to be one of the factors that will fuel a rise in chronic illness. If the growth trends continue, global healthcare spending is expected to grow at an annual rate of 4.3% between 2015 and 2020, reaching a total of USD 8.7 trillion worldwide, projects the Economist Intelligence Unit. By 2020, about half of that spending is expected to go toward treating the three leading causes of death worldwide: cardiovascular disease, cancer and respiratory disease.

We believe innovation that produces breakthrough medicines, devices and solutions will be critical to overcome this challenge as demographic trends increase pressure on healthcare systems to produce the best results at the lowest overall cost.

How we approach it

Innovation is a cornerstone of the Novartis strategy and a foundation of our future. Research and development (R&D) as well as a strong pipeline of potential medicines are critical for our future business and long-term success. We invested USD 9.0 billion on R&D for new drugs and medical devices in 2017, or 18.3% of net sales.

The Novartis Institutes for BioMedical Research (NIBR) is the innovation engine of Novartis. With a global team of approximately 6,000 scientists, physicians and business professionals, NIBR works to discover potential new therapies that could improve health outcomes for patients. In 2017, we launched a new research concept called the Genesis Labs, where employees together with external collaborators can explore transformative ideas that fall outside the scope of existing departments at NIBR. The digital technology sector is increasingly a source of innovation for pharmaceutical research. We are working to harness advances made by software and hardware engineers to make drug discovery more efficient and effective, as well as to improve clinical research. For more details on our approach to drug discovery, see page 43 of our 2017 Annual Report.

NIBR works in concert with our Global Drug Development (GDD) group to bring innovative treatments to patients around the world. Once we determine that a potential new treatment has promise, we decide whether to begin larger clinical trials to test effectiveness and safety in more patients. Since its creation in 2016, GDD has begun moving us toward our goal of more rapid, cost-effective and innovative drug development powered by digital technology and data science. In 2017, we advanced a strong portfolio that aims to address many of the world’s significant unmet medical needs. We doubled the number of drug candidates transitioned from NIBR in the last year, bringing our total development projects in clinical testing to more than 200, with 40 potential filings planned in the US and EU between 2017 and 2020. For more details on our approach to development, see page 46 of our 2017 Annual Report. For full details on our innovation achievements in 2017, see pages 25-27 of our 2017 Annual Report.

We are taking several steps to ensure our potential new treatments can deliver significant health improvements for patients. We assess all our projects on multiple criteria such as feasibility, the potential to change medical practice, and alignment with current capabilities. Our pipeline covers a broad range of disease areas, including chronic, infectious and neglected diseases. As part of our long-term development strategy, we are working to anticipate future health needs, particularly for aging populations. And one of the three pillars of our new Access Principles (see page 18) is to ensure our R&D efforts address high-burden diseases with unmet medical needs and to adapt relevant products to the needs of underserved populations. The growing prevalence of antimicrobial resistance is recognized as one of the major threats to global public health today, and we have ongoing activities to counter the threat of emerging drug resistance.

Beyond traditional research and development, we are using innovative approaches to reach more patients with our medicines, while leveraging innovative technologies to help solve a variety of healthcare challenges – from developing breakthrough treatments to making sure that basic medicines are available where they are needed most. Innovation in its many forms supports our efforts to grow in emerging markets and around the world, and can help us respond to patients’ unmet medical needs in both the developed and developing worlds.
R&D for unmet medical needs

We systematically review our product portfolio to identify and prioritize opportunities for adaptive product development or additional product registrations in countries with a high disease burden. In addition, our drug development teams evaluate the special needs of low- and lower-middle-income countries as part of their development plans.

This builds on our past work in adaptive development – the modification of an existing medicine to further improve therapeutic efficacy, safety and access, and to generate a positive health outcome in non-conventional settings. Most often, this is done with a specific focus on poor and vulnerable patient groups, such as children and the elderly.

In 2017, we carried out systematic reviews across our existing early- and late-stage development programs in Innovative Medicines, and we now have more than 20 initial ideas for adapting marketed products that address both communicable and noncommunicable diseases. These ideas are currently undergoing in-depth technical assessments.

One example of our efforts in this area is our drug clofazimine, indicated for many years in combination with dapsone and rifampicin to treat leprosy. It has recently been recommended by the World Health Organization for use in the treatment of multidrug-resistant tuberculosis (MDR-TB). To align with this recommendation and ensure access for populations living in low- and lower-middle income countries, Novartis is working with regulators worldwide to seek registration for the MDR-TB indication. MDR-TB remains a public health crisis, and ending the TB epidemic by 2030 is among the health targets of the Sustainable Development Goals.

R&D for neglected diseases

The Novartis Institute for Tropical Diseases (NITD) is our research group dedicated to finding new medicines to treat neglected diseases. NITD is a small-molecule drug discovery research institute within NIBR that works in collaboration with a number of academic and nonprofit partners, including the Wellcome Trust, the Bill & Melinda Gates Foundation, Medicines for Malaria Venture, and the Swiss Tropical Public Health Institute. Originally founded in 2002 in Singapore, NITD moved its operations to Emeryville, California, in the US in 2017. There, it is co-located with our infectious diseases research team to increase the synergies around research collaboration.

NITD teams are engaged in research efforts that range from target discovery and screening development to compound optimization and preparation for clinical testing. NITD research currently focuses on parasitic diseases such as malaria, cryptosporidiosis and three major kinetoplastid diseases: human African trypanosomiasis (sleeping sickness), Chagas disease and leishmaniasis.

One of the significant achievements of our NITD scientists in 2017 was the discovery and early validation of a drug candidate for treating cryptosporidiosis. Diarrheal diseases, such as cryptosporidiosis, can cause dehydration, malnutrition, stunting and cognitive defects, and they contribute to more than half a million deaths annually. Cryptosporidium is the second most common cause of diarrhea-related mortality in children under 2 years old. The parasite can cause weeks of watery diarrhea and sets up a vicious cycle of malnutrition and increased susceptibility to infection. Currently, there is no vaccine and the only available treatment is poorly efficacious in malnourished children.

In collaboration with the University of Georgia and Washington State University in the US, NITD researchers used transgenic parasites and novel disease models – as well as knowledge from our malaria research programs – in the drug discovery process. Together, these efforts helped identify and validate a potent and specific Cryptosporidium PI(4)K inhibitor, KDU731. KDU731 has been shown to specifically inhibit Cryptosporidium in preclinical models and is currently undergoing safety studies prior to the initiation of clinical trials. The findings were published in the journal Nature.

Investment in neglected tropical diseases was USD 22 million in 2017, down from 2016. This reduction is partially due to the relocation of NITD’s operations from Singapore to Emeryville in the US. A fraction of associates from Singapore moved to Emeryville, and recruitment of full-time equivalent employees at the new location is proceeding rapidly. Key projects met expected milestones during the transition, and the priorities, mission and areas of focus of NITD are unchanged. NITD continues to explore opportunities to maximize its impact, and its scientific strategy is informed by the evolution of science as well as unmet medical needs.

Drug resistance

Antimicrobial resistance (AMR) has recently topped agendas at key global health and economic summits, such as the G7 and G20 summits, the UN General Assembly, the World Health Assembly and the World Economic Forum. Antimicrobials are one of the cornerstones of global healthcare for treating a wide range of infectious diseases and for preventing infection during everyday medical procedures, but their effectiveness is being threatened by multidrug-resistant bacteria. The growing prevalence of AMR is recognized today as one of the major threats to global public health. If uncontrolled, it is estimated that AMR could lead to an additional 10 million deaths per year by 2050 – more than the current total number of deaths from all infectious diseases worldwide.

We have invested in the discovery of new antibiotics, and infectious disease researchers in Emeryville lead these efforts at Novartis. In 2017, we reported progress in researching a novel antibiotic candidate, LYS228, for multidrug-resistant infections caused by the Enterobacteriaceae. This family of pathogens is listed as a “critical” threat to public health by the World Health Organization and as an “urgent” threat by the US Centers for Disease Control and Prevention.
Next-generation antimalarials are also urgently needed to tackle rising parasite resistance to current therapies. One important and promising compound in clinical development is KAF156, the first in a new class of antimalarial compounds called imidazolopiperazines. Results of a proof-of-concept study published in 2016 showed this has the potential to clear malaria infection and block transmission of the disease. Additionally, we are investigating another compound with a novel mechanism of action against malaria called KAE609 (cipargamin). For more information about our malaria research and development programs, see page 56 of our 2017 Annual Report.

In January 2016, Novartis signed the Davos Declaration on Combating AMR, together with more than 100 other international companies and key industry bodies from 21 countries. In September 2016, Novartis was one of 13 leading pharmaceutical companies that committed to the Industry Roadmap for Progress on Combating AMR, which outlines more concrete measures to implement the Davos Declaration. Through this roadmap, the signatories have pledged to reduce the environmental impact from the manufacturing of antibiotics.

Addressing AMR historically has been embedded in our overall approach to Pharmaceuticals in the Environment (PIE). The AMR Roadmap includes commitments to establish and implement a common framework for managing antibiotic discharges by 2018, to develop a practical mechanism to demonstrate that our supply chain meets the standards in the framework, and to establish science-driven, risk-based targets for antibiotic discharges by 2020. In 2015, Novartis set a 2020 target to limit the release of drug substance effluents from its manufacturing sites to 10 times less than the predicted no effect concentration (PNEC) in receiving surface waters. This is intended to ensure that the contribution from manufacturing effluents into the environment is negligible. Progress on this target is monitored closely.

Additionally, in 2017 Novartis joined the AMR Industry Alliance, which formally brings together pharmaceutical, generics, diagnostics and biotech companies in an effort to ensure that we collectively deliver on the specific commitments made in the Industry Declaration on AMR and the AMR Roadmap.

An Antibiotic Manufacturing Framework has been drafted by the AMR Alliance Manufacturing Working Group (consisting of the 13 AMR Roadmap signatories). It provides a methodology for responsible antibiotic manufacturing, including managing antibiotic discharge, while the evolving science to derive a consistent methodology for establishing AMR-relevant emissions limits continues.

Beginning in 2018, Novartis will apply the following criteria of the Antibiotic Manufacturing Framework at our own antibiotic manufacturing operations to ensure these operations meet common minimum expectations, such as:

- Complying with local laws, environmental permits, company standards, and codes of conduct
- Exercising appropriate duty of care for all discharges and waste streams containing antibiotics
- Ensuring water and solid waste management programs are in place to prevent untreated discharge of manufacturing waste containing antibiotics
- Completing appropriate training in line with industry best practices
- Ensuring these environmental programs are evaluated periodically for efficacy
- Conducting facility reviews and following up with an action plan to address any findings

Through our Third-Party Risk Management program, we are also considering supplier performance on AMR as part of our supplier selection process. As a member of the Pharmaceutical Supply Chain Initiative, we use a platform for collaboratively assessing the environmental management performance of our suppliers.

**Business model innovation**

Beyond research and development, we are using innovative approaches to reach more patients with our medicines. Novartis Social Business was created a year ago to capitalize on the individual strengths of several of our industry-leading access-to-healthcare programs, each of which aims to increase the health and well-being of patients in lower-income countries. These include our Healthy Family programs, which have broken even in India, Vietnam and – most recently – Kenya. For more details on our Healthy Family programs, see pages 22 and 33 of this report.

Another flagship program within Novartis Social Business is Novartis Access, launched in 2015. Novartis Access builds on our Healthy Family programs as an evolution in our social business approach. The program offers a portfolio of 15 medicines against chronic diseases together with capacity-building activities to strengthen the ability of healthcare systems to prevent, diagnose and treat these diseases. The volume potential in the countries we are targeting made it possible to offer the portfolio at USD 1 per treatment, per month to governments, NGOs and other public sector healthcare providers in these lower-income countries.

When Novartis Access launched, the decision was made to first focus on the public sector before expanding into the private sector. However, challenges and learnings from two years on the ground have led to the decision to speed up the implementation of Novartis Access in the private sector to enable faster product uptake. Results from a program analysis conducted by Boston University corroborate this. The results showed...
that while more than 50% of chronic diseases are diagnosed in the public sector, more than 40% of patients buy their medicines in the private, for-profit sector. This further substantiates the theory that Novartis Access needs to expand beyond distribution of its medicines through public and faith-based facilities.

Starting in January 2018, Novartis Social Business will be present in the public and private market in seven countries (Cambodia, Laos, Malawi, Nepal, Rwanda, Tanzania and Uganda) offering Novartis Access medicines as well as the entire Novartis product range registered locally, either as a portfolio or as individual products. We hope this enhanced flexibility will enable us to better respond to country requirements across all income levels. Depending on the outcomes and based on our experience on the ground, we will consider expanding this approach to more countries in the future.

**Innovative technologies**

We use innovative technologies to help solve a variety of challenges - from developing breakthrough treatments to making sure that basic medicines are available where they are needed most. For example, we are exploring using machine learning to replace certain lab experiments with computer simulations, and generating DNA-encoded libraries to rapidly expand our collection of small molecules that serves as a starting point for potential new medicines. We are also investing in a variety of emerging technologies that could help make the drug development process smarter, faster and cheaper, including advanced analytical tools aimed at improving the efficiency and effectiveness of our trials. To learn more about how we are harnessing advances in technology within R&D, see pages 44 and 46 in the 2017 Annual Report.

Technology can be an enabler in overcoming barriers to access, especially for patients in remote areas. The Novartis Foundation telemedicine program in Ghana uses mobile technology to centralize expertise and coach health workers in rural communities to strengthen healthcare capacity, avoiding unnecessary referrals and reducing costs for patients. Ghana Health Service and the Ministry of Health are now rolling out the initiative, and the entire country is expected to soon be covered by telemedicine services.

Managing stock-outs can be another major access challenge in many developing countries, especially for health centers in rural areas. To improve the management of drug inventories in these areas, SMS for Life was launched in 2009. SMS for Life helps eliminate stock-outs of essential medicines through simple, affordable and widely available technologies, including mobile phones, smartphones and tablet computers, the internet and electronic mapping. It enables health facilities that dispense essential medicines to report their stock levels to the district medical officers who are responsible for treatment availability. Building on the success of SMS for Life, a new and enhanced version – SMS for Life 2.0 – was launched in December 2016 in Kaduna State, Nigeria’s third most populous region, in partnership with the Kaduna State Ministry of Health and Vodacom.

Using smartphones and tablet computers, local healthcare workers can track stock levels of essential antimalarials; vaccines; and HIV, tuberculosis and leprosy treatments, and send notifications to district medical officers when stock levels are low. Tablet computers also allow for disease monitoring by supporting data collection of basic disease parameters in line with a country’s needs. The program enables healthcare workers to monitor surveillance parameters of malaria; maternal and infant deaths; and seven other diseases, including measles, yellow fever and cholera. Additionally, SMS for Life 2.0 enables training of healthcare workers in local facilities using on-demand eLearning modules. These resources can also be used to increase public awareness on key health topics.

In addition to the launch in Nigeria, Novartis and our nonprofit partner Right to Care signed a memorandum of understanding in 2016 with the Zambian Ministry of Health, with the goal of deploying SMS for Life 2.0 in more than 500 health facilities in the northern provinces of the country. The program, which will include stock reporting, disease surveillance and eLearning, was developed in cooperation with Vodacom and was launched at the end of 2017.

SMS for Life 2.0 is also under discussion in other sub-Saharan African countries. Further, the system could be extended to treatments against noncommunicable diseases such as diabetes and high blood pressure. The first rollout of an adapted version of the SMS for Life digital platform will launch in Pakistan in 2018 to help track patient access and adherence to treatment.

**How we perform**

Innovation remains at the very heart of everything we do at Novartis, and we invested a total of USD 9.0 billion in R&D in 2017. We made progress in priority disease areas with high unmet medical needs, and we achieved several key milestones in our pipeline. A total of nine projects entered our development pipeline, and we delivered 16 major approvals as well as six FDA breakthrough therapy designations and 16 major regulatory submissions. We also made steps in advancing our pipeline for infectious and neglected tropical diseases, where we invested USD 22 million.

Innovative business models continue to play a key role in our efforts to bring our medicines to more patients – and they also continue to evolve as we learn from our experiences on the ground and adapt to changing circumstances in markets where we operate. We are using these experiences to guide our activities, as we believe they will teach us important lessons about how to best operate in parts of the world that are currently underserved, while helping us grow our business in lower-income countries.