# PRODUCT

Amber Somoza, Technical Services, Gilead San Dimas

# Each of the products Gilead researches and develops aligns with therapeutic areas that together **impact millions of people** in both the developed and developing world.

In 2015, our product portfolio comprised 20 marketed treatments in the United States. In 2015 alone, we produced more than 900 million tablets of oral medicines and approximately 9 million vials of liquid medicine. Today, many of our products are category firsts or are among the leading medicines used to treat or cure the diseases they address.

Jose Partida-Trautman, Clinical Operations, Gilead Foster City

At Gilead, sustainability considerations are embedded throughout the development and distribution of our medicines. From the safety and regulatory compliance of our products to the regular efficiency improvements we make to our manufacturing processes, the operations surrounding our portfolio are routinely evaluated for new and innovative ways to further incorporate social and environmental responsibility.

## Supply Chain

Gilead is one of the largest biopharmaceutical companies in the world, with a rapidly expanding product portfolio and a growing pipeline of investigational drugs. We recognize that close oversight and strategic decision-making within our supply chain are necessary to maintaining compliance and continued pursuit of improved environmental performance. Our product-related supply chain activities in 2015 included supplier auditing, ethical sourcing and responsible product distribution practices.

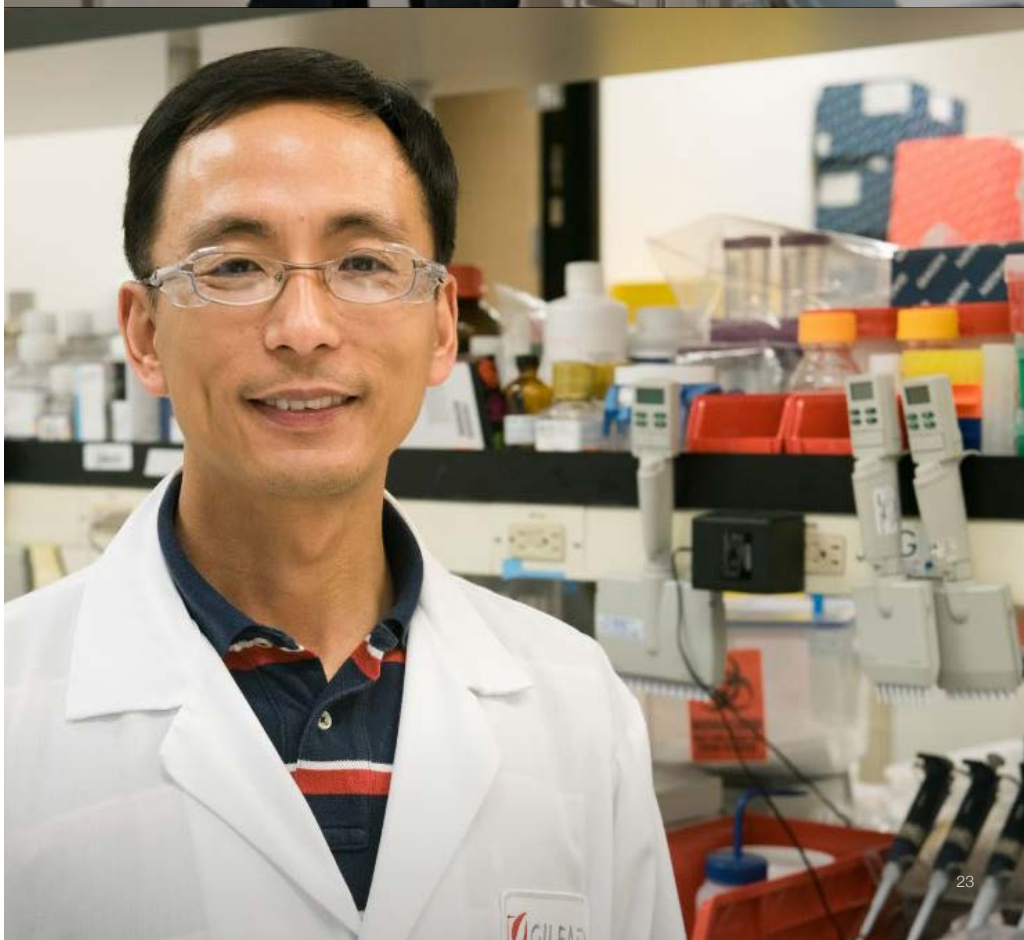
### AUDITING PROCEDURES

In 2015, as in previous years, Gilead performed audits of its manufacturing partners to help ensure compliance with local laws and the company's Code of Ethics. As part of these audits, Gilead management evaluates the partnership for any discrepancies with regulations or the company's own guidelines. If any violations are identified, corrective action is recommended and noted for follow-up evaluations. Certain violations, such as the use of forced labor or the presence of human trafficking, would result in a terminated agreement and the supplying organization would be removed from Gilead's supply chain. During audits performed in the 2015 calendar year, Gilead and independent assessors identified no such violations of our Code of Ethics.

### ETHICAL SOURCING

In 2015, Gilead continued to focus on the ethical sourcing of materials and upholding the quality standards of our products. All of our suppliers must observe Good Manufacturing Practice (GMP) regulations as designed by the Food and Drug Administration and other relevant controlling agencies. GMPs require strict adherence with regards to facility cleanliness, record keeping, process control and other measures that ensure product quality and safety for the end consumer.

**TOP:** Tanya Duo and Travis Schwantje, Process Development, Gilead Alberta
**BOTTOM:** Guofeng Cheng, Biology, Gilead Foster City



Gilead utilizes current government data from our supplier countries of origin to monitor ethical concerns. If any supplying region is found to be particularly at risk for manufacturing issues, members of Gilead management personally visit sites and evaluate for compliance. An important regulation for our suppliers is the United States Trafficking Victims Protection Act's (TVPA) standard, a set of regulations that safeguards against the use of forced labor or human trafficking. We source from countries listed as compliant with TVPA, and any supplier from a region still making efforts to ensure full TVPA compliance is subject to additional oversight from Gilead.

In addition, Gilead includes provisions in our supplier agreements obligating the supplier to comply with Foreign Corrupt Practices Act, applicable anti-corruption laws, applicable environmental laws and agree not to engage in forced or child labor.

## DISTRIBUTION

In order to transport Gilead medicines in a safe and controlled manner, we utilize shipping and logistics environments that adhere to the appropriate temperature and security standards for each drug product. In 2015, Gilead completed a review of our air freight packaging, replacing single-use, temperature-controlled containers with recyclable and reusable methods in specific markets. Reusable small parcel containers were implemented on routes between Canada, Ireland and within the United States. Thermal blanket wraps are used to minimize temperature excursions for pallet shipments for active pharmaceutical ingredients (API). For global ground distribution, our logistics partners' fleets maintain climate-controlled trailers, eliminating the need for additional temperature-controlled packaging.

## GREEN CHEMISTRY

As a drug advances through clinical studies and is approved for launch, our scientists further develop the process used to make approved drug substances. Gilead's Commercial API Process Optimization (CAPO) group based in Alberta, Canada, investigates the most efficient and sustainable methods for bringing approved medicines to commercial scale.

## ACTIVE PHARMACEUTICAL INGREDIENT PROCESS

Improving the sustainability and efficiency of the API process for our HCV medicines has a significant impact on Gilead's environmental performance because the drug substances involved are found in several of our highest-impact drugs by manufacturing volume.

CAPO has been working to improve the API process for one of our HCV therapies since 2013. In 2015, Gilead piloted the third iteration in process improvements at its manufacturing facilities and contract manufacturing organizations. The multiyear optimizations centered on yield improvements, energy efficiency and solvent/waste reduction. After verifying that these optimizations were feasible at full scale, Gilead began testing the latest API process in commercial reactors in 2015. Following rigorous tests, the optimizations successfully demonstrated viability, and we are now in the process of generating the data required for regulatory approval in the countries where Gilead manufactures and distributes HCV medicines. Overall, the new API process achieved:

- An overall 27 percent reduction in solvent usage,
- A 10 percent improved yield,
- A reduction in the number of aqueous washes, resulting in a 50 percent wastewater reduction.

## SOLVENT RECYCLING

When drug substances are approved, there are often opportunities to refine and improve the process to achieve chemically identical results while substituting out undesirable inputs such as organic solvents. Limiting organic solvents helps to lower Gilead's environmental impact because these solvents typically come from unrenewable sources and may have hazardous or toxic properties. We have undertaken efforts to reduce the use of organic solvents. In 2015, Gilead implemented solvent recovery and recycling in the active pharmaceutical ingredient manufacturing system for drug substances found in one of the company's antiretroviral therapies, greatly reducing the amounts of several organic solvents required for manufacture.

**The new API process achieved an overall 27 percent reduction in solvent usage.**

## ERNEST LEE AND THE FLOW CHEMISTRY APPROACH

Ernest Lee | Senior Research Scientist, CAPO Team

A research scientist at Gilead since 2010, Ernest oversees innovative approaches to pharmaceutical manufacturing including continuous processing, or flow chemistry.

Flow chemistry is an alternative to reactor-based processing that has traditionally been adopted by scientists working in the petrochemical, polymer and other bulk industries. But Ernest says that manufacturers in the pharmaceutical industry have long viewed flow chemistry as a desirable priority for reaction and process management because it enables temperature to be managed more efficiently. Flow chemistry also provides scientists with an ability to easily scale up and down, achieve significant energy and waste reductions and improve safety.

"We've managed to use this method in the processes for our commercial products by introducing continuous stir tanks. We're also using flow chemistry in the processing of our development candidates," says Ernest.

As continuous, multistep reactions in flow chemistry can limit exposure to toxic intermediate compounds, the process offers increased efficiency and environmental performance. Gilead continues to investigate possible areas where the process could be implemented.


Zhongxin Zhou, Process Development, Gilead Alberta

### ENZYMATIC REACTIONS

In addition to solvent recycling, Gilead is currently researching enzymatic reactions as opportunities for sustainability improvement in the product development process. In some cases, enzymatic reactions can replace chemical reactions. Enzymatic reactions are generally preferred to chemical reactions because of their better efficiency, lower solvent requirements, ability to replace toxic reagents and overall yield improvement. In 2015, Gilead achieved the use of lipase-based enzymatic reactions in one of its HIV pipeline protease inhibitors. We also investigated viable enzymatic reaction substitutions in the preparation of certain drug substances found in one of our HCV medicines.

## Manufacturing Process

Gilead's manufacturing sites feature state-of-the-art technology that enables innovative research and the development of lifesaving medicines. In 2015, Gilead processed approximately 600 metric tons of active pharmaceutical ingredients. We consistently seek improvements to our equipment and the facilities that compose Gilead's laboratories.

## INTEGRATED ELECTRONIC LABORATORY PROGRAM

The systems used to process data across Gilead's research, commercial and quality testing laboratory sites are sensitive and complex. Management applications are responsible for measuring and logging important information for a variety of material purposes. In 2015, Gilead completed a series of integrated electronic laboratory upgrades to support pharmaceutical development, product testing and manufacturing processes. The electronic laboratory consists of linked computerized systems that have been validated for use in Good Manufacturing Practice operations. These new systems help improve lab safety, reduce waste and ensure compliance.

Components of the electronic laboratory program include automated data capture for lab measurements, electronic notebooks and streamlined resource management tools. Having completed the rollout in 2015 to sites in Foster City, Edmonton and Oceanside and an external analytics partner, this electronic laboratory program drives sustainability benefits such as paper reduction. Electronic notebooks replace paper notebooks, logbooks, data entry forms and other print forms across multiple lab locations. In addition, quality and safety considerations can be better assured through improved consistency, data integrity and automatic issue flagging.

## AUTOMATION

Analytical chemistry is an integral part of establishing the quality of Gilead drug substances and drug products, and sample preparation in pharmaceutical labs is a time- and resource-intensive operation. Past technological innovations in instrument design at Gilead have decreased analysis time by up to 75 percent. Efficiency improvements like these have the added benefit of reducing chemical waste generated during analysis.

In 2015, Gilead installed automated instrument facilities that are now available for use in quality testing processes for our drug products. Using traditional methods, analysis scientists extracted tablets into a volume of chemicals of about 1 to 2 liters per sample, the amount required to ensure an accurate manual quality test. Using automation, Gilead can now accurately perform the analysis using only 250ml of chemicals per sample—a reduction of 80 percent versus manual methods.

## SAFETY

Our operations and activities are subject to extensive regulation by numerous government authorities in the United States and other countries. Federal and state statutes and regulations govern the testing, manufacture, safety, efficacy, labeling, storage, record keeping, approval, advertising and promotion of our products. Our Environmental Health & Safety (EHS) group manages quality and safety standards at all sites where our products are manufactured. In 2015, the EHS team managed all the retrofits and upgrades at manufacturing facilities described in this chapter in order to maintain full compliance with local law and corporate guidelines.

## TAKEBACK PROGRAM

As part of our facilities management operations, Gilead does not release any active pharmaceutical ingredients into the environment from any of our sites as waste. Gilead is a member of the Pharmaceutical Product Stewardship Work Group (PPSWG), an organization that works with drug companies to navigate proper and compliant disposal of unused or unwanted medicines. Participation in groups such as PPSWG helps us better manage the lifecycle of our products, specifically end-of-life procedures.

In 2015, Gilead contributed to drug takeback and safe disposal programs in two counties in California: Alameda and King. Run by the local municipal governments, these programs offer tips on responsible drug disposal and staff drop-off locations that consumers can use to safely return unwanted medicines.