Indivior’s R&D mission is dedicated to the development of innovative therapeutics that move the international community one step closer to new treatment options that help patients with substance use disorders (SUDs) worldwide improve their quality of life and well-being.

One of our core guiding principles – focus on patient needs to drive decisions – incentivizes R&D to advance treatment innovations in the face of the growing global addiction crisis.

In 2017, we continued to invest in R&D to pioneer significant new treatment options for those suffering from SUDs, and in partnerships worldwide to realize our vision that all patients will have access to evidence-based treatment for addiction and other co-occurring disorders.

During the year, we delivered two NDA submissions to the US FDA, completed two new state-of-the-art R&D Centers of Excellence, achieved FDA approval for our new product, SUBLOCADE, and formed new strategic research partnerships.

We entered into a multi-partner funding collaboration with Virginia Commonwealth University, Inova Fairfax Hospital and Virginia Tech Carilion Research Institute to study the effects of SUBLOCADE in the emergency room environment to possibly prevent repeat opioid overdoses and potentially change the standard of care for those who are recovering from opioid overdose.

We also showcased Indivior’s scientific expertise and know-how in six peer-reviewed publications and no less than 12 published conference abstracts with a focus on the science in support of SUBLOCADE and RBP-7000.

**SUBLOCADE™: Expanding access to treatment for opioid use disorder**

Our major R&D success of 2017 was the US FDA approval of SUBLOCADE. As the first and only once-monthly injectable buprenorphine formulation to treat moderate to severe opioid use disorder (OUD), SUBLOCADE represents an evidence-based paradigm shift from how we approach treatment of OUD today.

During the development of SUBLOCADE, we worked closely with the FDA through Type C meetings and an End-of-Phase 2 meeting. SUBLOCADE was granted US Fast Track Designation in May 2016. A pre-NDA meeting was successfully conducted in December 2016, which was followed by NDA submission in May 2017, and official NDA filing and PDUFA Priority Review designation in July 2017.
SUBLOCADE™ (buprenorphine extended-release) is the first and only therapy that, at steady state, delivers buprenorphine at a sustained rate of at least 2 ng/mL over a one-month period.

A unique delivery system
SUBLOCADE™ (buprenorphine extended-release) uses the ATRIGEL® delivery system, which consists of a polymeric solution of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in N-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After subcutaneous injection, NMP interacts with body fluids that replace the NMP as it diffuses out of the polymer matrix, triggering polymerization. This traps the buprenorphine inside and forms a solid deposit in place. The depot releases buprenorphine over a one-month period by diffusion as the polymer biodegrades.

SUBLOCADE™ Lifecycle Evidence Generation & Optimization (LEGO)
During 2017, various studies were planned and designed and we will continue to generate and optimize evidence to support SUBLOCADE’s efficacy and strengthen Indivior’s leadership in the treatment of OUD. These included:

- Emergency Room Study – to assess the efficacy and safety of initiating SUBLOCADE in ER settings to potentially prevent repeat overdose events in OUD patients.
- VAS Craving Project – to explore how craving could be used as potential clinical endpoint in clinical trials in OUD patients.
- Buprenorphine Abuse, Misuse, Diversion (AMD) Epidemiology – to investigate the root causes of abuse and misuse in diverted buprenorphine.

The science behind SUBLOCADE™

SUBLOCADE™ sustained-release formulation of buprenorphine. SUBLOCADE™ uses the ATRIGEL® delivery system; a solution consisting of a biodegradable poly-(DL-lactide-co-glycolide) copolymer dissolved in N-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After subcutaneous injection, NMP interacts with body fluids that replace the NMP in the matrix, triggering polymerization. Buprenorphine trapped inside the polymer formed in situ is gradually released over a one-month period as the polymer biodegrades.

How SUBLOCADE™ works

SUBLOCADE™ (300mg) administration leads to buprenorphine plasma concentrations of 2-3 ng/mL, mu-opioid brain receptor occupancy of ≥70% producing significant reductions in drug-liking. The outcome: Abstinence rate

The primary efficacy endpoint (% abstinence from Week 5 through Week 24) was statistically significantly superior (P<0.0001) for both the 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group, with mean percentages as shown in the figure above.
In October 2017, an Advisory Committee of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 18 to 1 in favor of SUBLOCADE™ approval for the treatment of moderate to severe OUD. The FDA decision to approve SUBLOCADE™ marks the end of an eight-year long effort to bring to market this innovative novel formulation of buprenorphine in the ATRIGEL delivery system and expand access to treatment options for OUD. SUBLOCADE™ provides sustained plasma levels of buprenorphine that translate into high and sustained mu-opioid receptor occupancy in the brain over a one-month period, thereby suppressing withdrawal symptoms, reducing the subjective, drug-liking effects of opioid agonists, and ultimately leading to significantly reduced illicit opioid use compared to placebo over a six-month period. Exposure-response analyses established a correlation between buprenorphine plasma concentration, whole-brain mu-opioid receptor occupancy, opioid-free weeks, and withdrawal. The overall safety profile of SUBLOCADE™ in the clinical trials program was consistent with the known safety profile of transmucosal buprenorphine. The most common adverse reactions associated with SUBLOCADE™ (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain.

We believe that SUBLOCADE™ is an important treatment option for patients, families and communities battling the opioid epidemic.
Indivior’s R&D strategy
Our R&D strategy is to develop products that address the major challenges in the treatment of SUDs, which are: efficacy, safety, and delivery including adherence to treatment and reduction in misuse and diversion.

A pre-requisite for addressing these challenges is understanding SUDs as the result of long-term molecular and cellular adaptations in key neural networks.

R&D partnerships
In 2017 we continued to develop partnerships and collaborations that allow us to understand patients’ unmet needs and accelerate the development of new medications.

We developed plans to collaborate with Virginia Commonwealth University (VCU), Inova Fairfax Hospital and Virginia Tech Carilion Research Institute to study the effects of SUBLOCADE™ in the emergency room environment to possibly prevent repeat opioid overdoses and potentially change standards of care.

We also entered a new strategic collaboration with Addex Therapeutics to explore GABA-B positive allosteric modulators (PAMs) as an attractive target to potentially treat various SUDs. Our joint research efforts could help to open new medication pathways for alcohol and cocaine use disorders.

We are also committed to further consolidating our prospective patient outcomes research, which is key to demonstrating the value of medical therapies to patients, physicians, and payers, and can drive new meaningful treatment options for patients suffering from SUDs.

**Strategic driver: Infrastructure**

**State of the art research and development centers**

During the year, we completed our new R&D Center of Excellence in Hull (UK) (54,000 sq ft) and the extension of our R&D facilities in Fort Collins (CO, USA) (18,500 sq ft).

The new Hull facility is a $30 million R&D center dedicated to pioneering novel treatments for patients struggling with SUDs. The new center, which will house over 50 employees, is equipped with cutting-edge technologies, including a 400MHz Nuclear Magnetic Resonance spectrometer, and is constructed to environmental and energy-saving standards, including the installation of a 25kW solar panel farm to increase use of renewable energy.

As Indivior’s largest capital investment in R&D, it is hoped the new center will enable us to leverage science and research to help understand the neurobiological underpinnings of SUDs and advance the SUD treatment paradigm.

In the US, our $11 million investment in Fort Collins has increased the site’s footprint from 23,000 sq ft to 42,000 sq ft. It establishes Fort Collins as a leader in parenteral product development from a chemistry, manufacturing and controls (CMC) perspective.

Altogether, the new UK and US facilities will allow us to significantly expand our capabilities through pilot plant storage, formulation laboratories, analytical laboratories, chemistry laboratories, stability chambers, office spaces, and support spaces. Not only will these facilities help us remain at the cutting edge of innovation and discovery, they will help keep our employees safe, and support our independence as an organization.

**Hull: At a glance**

$30m  
Cost of Hull facility

50  
Employees

400MHz  
Nuclear Magnetic Resonance spectrometer
Research & development continued

R&D strategic drivers
In 2017, we made progress against our four R&D strategic drivers: Infrastructure see page 31, People, Processes and Portfolio.

People
Throughout 2017, we focused on bringing new talent into our organization and establishing strong leadership teams. We know that any business is only ever as good as the quality of the people and talent it can recruit. Our facilities enhancements in 2017 deepened the appeal of our organization as a place of scientific excellence where people can thrive and make a difference. Our hiring campaign also focused on lessening organizational layers, building cross-functional networks, rewarding successes, and promoting a 'right decisions' mindset based on sound scientific grounds.

Processes
Another area of focus was improving the quality of our processes and interactions within R&D Functions and with ex-R&D Functions. Our key initiatives, designed to enhance how we work together and make the right decisions on behalf of patients, included:

- Implementation of a Continuous Improvement Team.
- Partnership between Medicine Development Leaders (MDLs) and Global Therapy Leaders (GTLs) and implementation of a Manufacturing Process Continuity Team (MPCT).
- Collaboration with Information Technology Department to move R&D towards industry standard, compliant and scalable platforms to support growth and submission activities and address any immediate compliance and support risks.

Portfolio
During 2017, we made significant progress across of our portfolio development. True to our vision and mission, we focused on developing innovative treatment solutions for OUD and its co-occurring disorders, such as schizophrenia. We also continued to address the challenge of alcohol use disorder (AUD).

Significant pipeline milestones for the year include:

Opioid use disorder

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<th>Product</th>
<th>Milestone</th>
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| SUBOXONE® Sublingual Tablet   | - Data from two pivotal pharmacokinetics (PK) studies used to support application for two additional dosage strengths (SUBOXONE 12mg/3mg and 16mg/4mg Sublingual Tablets) in Canada. Final approval received from Health Canada (HC) with Notice of Compliance (NOC) in September 2017.  
- Three clinical trials finalized and used to submit an NDA to the Chinese FDA in December 2016. NDA submission under review by CFDA. |
| SUBOXONE® Sublingual Film     | - SUBOXONE Film added to List of Drugs for an Urgent Public Health Need in British Columbia, Canada, in June 2017 and for use in the Correctional Service Facilities in December 2017. |
| SUBLOCADE™ injection for subcutaneous use (CIII) | - SUBLOCADE™ received US FDA approval in November 2017 as the first and only once-monthly injectable buprenorphine formulation to treat moderate to severe opioid use disorder. |
“The US filing of RBP-7000 represents a significant milestone for Indivior in addressing unmet patient needs in schizophrenia. It is a demonstration of our ongoing commitment to developing innovative treatment options and in helping to battle the challenges associated with this serious disease.”

Christian Heidbreder
Chief Scientific Officer