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# Clinical & Research Excellence Awards 2018 eBook

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Excellence Awards | 2018



**The Clinical And Research Excellence (CARE) Awards** provides an opportunity for the pharma industry to celebrate all its achievements, and pay tribute to the people and teams behind these feats. 2017 was a successful year for the industry as a whole, which was evident by the volume and quality of the entries received for this year's CARE Awards, including the ones showcased within this eBook.

The event itself also allows a wide range of individuals and organizations to come together. Throughout the celebratory evening, old friends were reacquainted and new connections were forged, potentially leading to exciting opportunities for partnerships and collaborations. If you missed out on the festivities, highlights from the evening are available at <http://clinicalresearchexcellence.com>.

To help keep the focus on the innovations happening with clinical research, this eBook offers a selection of thought leadership on R&D issues. Key articles from Scrip, Pink Sheet, and In Vivo, as well as excerpts from a few of Citeline's annual reviews, were hand-picked by the Pharma Intelligence editorial team to provide a view of various trends and insights into the clinical research space.

Thank you to all who entered, and for your commitment to clinical and research excellence. Many thanks to all the sponsors of the evening, and our esteemed panel of awards judges.

We look forward to seeing what 2018 holds for the industry, and to celebrate once again at next year's CARE Awards.

**Mary Jo Laffler**  
Executive Editor, Pharma Insights  
Pharma intelligence

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Content Marketing Director  
Pharma intelligence

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The 2018 CARE Awards Winners

Despite the backdrop of political uncertainty in 2017, the pharma industry continued to persevere and push boundaries. The CARE Awards acknowledged and celebrated a spectrum of key R&D activities that took place throughout last year, ranging from disruptive technology that support both sponsors and patients, to noteworthy clinical trial design and results, as well as showcasing the power of teamwork.

The ceremony was once again hosted by multi-media journalist, Janet Wu, former Anchor and Health Reporter for Boston's NBC station and adjunct professor at Emerson College.

### The 2018 CARE Awards Judging Panel

**Jeffrey M. Bockman, PhD** Vice President, Defined Health

**Laura Brown** Pharmaceutical Training Consultant, Course Director, University of Cardiff

**Joan Chambers** Senior Strategic Advisor, SCORR Marketing

**Denis Curtin, PhD** Chief Scientific Officer, mProve Health

**Laurie A. Halloran, BSN, MS** President, Halloran Consulting

**Marion A. Howard, MD, PhD, MBA** Principal and Founder of Cambridge BioStrategies, LLC

**Cliff Kalb** President, C. Kalb & Associates

**Janice McCourt** Senior VP of BD and Alliance Management, Heat Biologics

**Alison Messom, PhD, MICR** Chairman of the Board of Directors, Institute of Clinical Research

**Michael Murphy** Chief Medical and Scientific Officer, Worldwide Clinical Trials

**Mike Rice** Principal, Defined Health

**Chad Rubin** Managing Director, The Trout Group

## THE 2018 CARE AWARDS WINNERS

### Merck KGaA

*Merkel Cell Carcinoma (MCC) Observational Study for Historic Comparison*

**BEST IN HEALTH ECONOMICS AND OUTCOMES RESEARCH**

### AveXis

*Phase 1 Clinical Trial of AVXS-101 Gene Replacement Therapy for Spinal Muscular Atrophy Type 1*

**MOST SUCCESSFUL EARLY PHASE RESEARCH (PRECLINICAL & PHASE I)**

### Otsuka Pharmaceutical Development & Commercialization

*Autosomal Dominant Polycystic Kidney Disease (ADPKD) Tolvaptan Team*

**MOST INNOVATIVE CLINICAL TRIAL DESIGN (SPONSORED SYNEOS HEALTH)**

### Alnylam Pharmaceuticals

*Hereditary ATTR (hATTR) amyloidosis*

**EXCELLENCE IN RARE DISEASE DRUG DEVELOPMENT**

### ICON

*AMAG Adult Iron Deficiency Trial*

**CLINICAL RESEARCH TEAM OF THE YEAR (SPONSORED BY ORACLE HEALTH SCIENCES)**

### Novartis

*KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion*

**CLINICAL TRIAL RESULT OF THE YEAR (SPONSORED BY CYTEL)**

### Medidata Solutions

*Medidata Strategic Monitoring*

**BEST SPONSOR-FOCUSED TECHNOLOGICAL DEVELOPMENT**

### Bracket

*Bracket Mobile ePRO*

**BEST PATIENT-FOCUSED TECHNOLOGICAL DEVELOPMENT**

### Theravance Biopharma and Mylan

*Revefenacin*

**MEDIDATA CLINICAL PARTNERSHIP OF THE YEAR (SPONSORED BY MEDIDATA)**

### AstraZeneca

**MARQUEE AWARD 'R&D EXCELLENCE'**

### Josef von Rickenbach

*Chairman of the board, co-founder, and CEO of PAREXEL*

**LIFETIME ACHIEVEMENT AWARD**

# US FDA Offers Sponsors More Attention For Sharing Complex Innovative Trial Designs

► By Brenda Sandburg

The US FDA is launching a pilot program to encourage sponsors to develop innovative clinical trial designs and dispel the perception that the agency will not accept novel protocols.

FDA officials gave a preview of the program, which has yet to be announced in the Federal Register, at a March 20 public workshop on promoting the use of complex innovative designs in clinical trials of drugs and biological products. Participants raised questions about the pilot, including how much information sponsors will be required to disclose, indicating the issues the agency will need to flush out to get companies on board.

The workshop fulfills one of FDA's performance goals under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI). The agency is also developing a guidance on complex innovative designs as required by the 21<sup>st</sup> Century Cures Act.

FDA's Dionne Price, acting deputy director of the Office of Biostatistics at the Center for Drug Evaluation and Research, told the workshop that the pilot program is designed for highly innovative trial designs which may require simulations to determine their operating characteristics.

Price said the agency will accept up to two designs submitted by sponsors per quarter and will use them as case studies for education and information sharing. Sponsors in the pilot will have the opportunity to have two meetings with FDA staff within a span of approximately 120 days to discuss the designs.

"The idea of going through the pilot is you get a little bit more regulatory interaction, hopefully pretty fast, and you're contributing to the body of knowledge which advances science," former FDA official Lisa LaVange said.

FDA's former Office of Biostatistics Director Lisa LaVange, now at the University of North Carolina at Chapel Hill, explained that during the PDUFA negotiations there was some

**"On the sponsor side, the feeling was that the more complicated designs took a lot of regulatory interaction because when you get into simulations it takes a bit of back and forth." – Lisa LaVange**

feeling on FDA's side that sponsors were withholding study design ideas because they believed FDA wouldn't accept them. And the agency felt restricted because it couldn't talk about more of the innovative proposals.

"On the sponsor side, the feeling was that the more complicated designs took a lot of regulatory interaction because when you get into simulations it takes a bit of back and forth," LaVange said. "So, we came up with the pilot idea mutually to offer increased interactions on a pilot scale because resources at FDA are limited and reviewers are often fairly strapped for time."

The goal is to provide sponsors with more interactions on complicated trial designs and in exchange FDA can talk about them and there can be more public discussion at professional meetings about certain designs, LaVange explained. She noted that she has been at meetings where sponsors put up different adaptive designs on a screen and said FDA disliked them because its 2010 guidance on adaptive designs stated that they were less well understood.

"I wanted to say, 'no, we didn't mean that,'" LaVange said.

## **Sponsors Want More Information From FDA**

Karen Lynn Price, senior research advisor at **Eli Lilly & Co.**, said it would be important for FDA to clarify the reason a trial design was rejected for the pilot and the pathway for allowing the design to go forward. She also recommended that the agency clarify when and how it will communicate what it learns from the pilot program.

In addition, Price said it would be great to know if there are certain types of designs the agency hoped to see but has not received. “Communicating that would help sponsors to say ‘let’s look at where in our portfolio we might have an opportunity to come forward,’” she said.

Deborah Ashby, Imperial College London, advised FDA to be careful in the range of designs it accepts. She said that if she was on the regulatory side she would start with the easiest and gradually get more complex. She said she’d like to see adaptive designs in the areas where they are most needed, such as in emerging infectious disease.

### Disclosure Will Vary Across Study Designs

Other participants expressed concern about how much information sponsors participating in the pilot would have to disclose.

Z. John Zhong, senior director of biostatistics at **Biogen Inc.**, noted that a working group of the Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization did not feel comfortable with the disclosure of certain information, such as a drug’s indication and sometimes even the sponsor’s name. But he said companies are willing to disclose most aspects of study designs.

LaVange said the idea was that disclosure wouldn’t be the same for every design and there would not be full disclosure of a protocol.

“It may be that nothing about the drug or the sponsor or even the diseases needs to be disclosed. It may be just the elements of adaptation,” she stated. “On the other hand, if there is use of a patient registry you’ll have to disclose something about the disease.”

“Put yourself in FDA’s shoes and think about what would be the most beneficial to the world of drug development for us to disclose,” she added.

LaVange noted that sponsors can propose something innovative without participating in the pilot. “The idea of going through the pilot is you get a little bit more regulatory interaction, hopefully pretty fast, and you’re contributing to the body of knowledge which advances science,” she said.

### Disincentives To Accepting Innovative Designs

In another session of the workshop on other innovative designs, FDA discussed the use of master protocols and the possibilities of using external or historical control data and sharing of control groups across protocols within a specific pathway or marker subgroup.

In discussing what factors impact the perceived acceptability of innovative designs by sponsors and regulatory agencies, a couple of panelists noted potential roadblocks at FDA. Roger Lewis, University of California at Los Angeles, pointed to disincentives for the agency to be flexible.

“It is my impression that the statisticians working on the frontline within the agency are very limited in the time they have to understand complex designs and that leads to a perceived risk in the sense that it is easier to resist a complex design when you don’t have the time to truly understand it,” Lewis said. “We need to find some way to support regulatory professionals so they have the time to do their jobs.”

Lewis also stated that there is a lack of skill and experience of statistical personal in academia and industry and within the agency. He called for an increase in the availability of software that allows one to simulate more complex designs. And he said that industry too has a disincentive to be innovative as the failure of a drug could be blamed on the innovative study design rather than the drug itself.

Steven Goodman, Stanford University School of Medicine, said an innovative design may involve levels of sophistication beyond the comfort level of the review group making decisions. He said the agency needs to have an internal procedure so review of the design is “kicked up to the level” where it is within the comfort zone of the decision-makers.

“I worry that at the top levels there can be a lot of sense, flexibility and wisdom but this may or may not penetrate to the levels where the decisions are being made,” Goodman stated.

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*Published online in Pink Sheet, 3 April 2018*

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 **MOST INNOVATIVE CLINICAL TRIAL DESIGN**

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We would like to thank all who recognized our achievement by voting for us. Together we will move forward and remain committed to advancing human health.



# Orphan Drug Development: Could We Be Seeing The End Of P Values?

► By Michael Cipriano

Could the scientific community be nearing the end of the end of the P value as an efficacy marker in the rare disease drug development space?

It is certainly possible, a panel of experts says. But the key to shifting away from P values toward Bayesian methods would require fitting the approach into the US FDA's regulatory structure.

Speaking at a Duke Margolis Center for Health Policy event March 15 on innovative statistical methods and trial designs for rare disease drug development, a series of FDA officials, industry speakers and researchers spoke of the benefits Bayesian statistics can bring in the orphan arena, where there are often not enough patients for a fully powered randomized clinical trial.

Bayesian statistics involve learning from evidence as it accumulates by combining prior information with current study information on an endpoint of interest, and help to make decisions about the future.

"Pictorially, we can think about this as what we knew, which is out prior; what we see now, that's the likelihood; and then we update that with what we now know," said **Eli Lilly & Co.** Research Advisor Karen Price.

Now, Price contends, what the scientific community needs is a formal mechanism to synthesize known information into the decision-making process, and Bayesian statistics are the platform to do that.

"Every time we see results from a clinical trial, we naturally think about other data that we have seen," Price said.

"Whatever it is, we bring that to our decision-making process," she added. "But we do that in our heads, and we determine on our own how much we weight that piece of information."

Lisa LaVange, a professor at UNC Chapel Hill's Gillings School of Global Public Health's Department of Biostatistics

and formerly director of the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER), offered a similar assessment.

She noted that Bayesian methods would allow FDA to formalize using the information it already knows about a treatment, as orphan drug developers don't have the luxury of starting with a clean slate in Phase III trials. FDA currently uses priors in regulatory decision-making in "a very informal way," LaVange says, such as factoring in clinical data from adults into conducting pediatric trials.

"[Bayesian methods are] a way to sort of put your money where your mouth is," Lavange says. "What do I know about this drug? What do I believe about how it will work in this population before I ever start the study."

"It's almost like a cost/benefit analysis. What is the cost of me not using this prior information? Maybe missing a chance to answer the question that I most need to answer."

University of South Florida Professor Roy Tamura argued that Bayesian methods are the only way forward in the rare disease space if the paradigm allows for the inclusion of known information.

"If we are going to allow prior information, external information into the inference, the only way to go is the Bayes way," said Tamura, also a former statistician for Lilly. "And therefore, there are no more P values. We have to move away from that in this space."

## What Is Stopping The Shift?

However, LaVange noted, Bayesian methods are still a new exercise for FDA, especially for CDER. For instance, drug-makers and the agency would need to reach an agreement on a prior probability distribution before conducting a trial.

"So can we have a paradigm shift and have a decision made based on the probability that the drug works given our prior beliefs, our observed data in this trial and the

computation of the posterior probability, instead of making a decision that, assuming the drug doesn't work, what's the chance of me thinking that it works, incorrectly?" LaVange asked rhetorically.

"But we don't have a tradition of that," LaVange said. "So how high does that probability have to be? 95%? 97.5%? 80%? 60%? Well, maybe it depends on the need and the other drugs that are approved."

John Scott, deputy director of the Division of Biostatistics in the Center for Biologics Evaluation and Research (CBER), also outlined the difficulties about incorporating prior data, specifically with regard to how much information to borrow.

**"I think it's very hard. I think it's a really complicated thing to even think about." – John Scott**

"How do you go about approaching the question of how many patients worth of data should you borrow into the new study?" Scott asked rhetorically.

"I think it's very hard. I think it's a really complicated thing to even think about," he added.

FDA officials have touted the use of the Bayesian approach and adaptive trial designs at previous meetings, including for data extrapolation for pediatric product development (Also see "FDA Encourages Pediatric Master Protocols With Bayesian Approach" - *Pink Sheet*, 27 Sep, 2016.) In a *New England Journal of Medicine* article last year, CDER Director Janet Woodcock and LaVange, who was still at FDA at the time, publicized their support for novel clinical trial designs using master protocols. (Also see "Master Protocols Are Both Welcome And Inevitable – US FDA's Woodcock" - *Pink Sheet*, 6 Jul, 2017.)

But so far, such innovations in clinical trial design have produced more enthusiasm than regulatory results. Woodcock previously admitted that it will likely be a long time before modernization of the clinical trials system can take place. (Also see "Clinical Trial System 'Broken,' But Modernization Long Way Away – Woodcock" - *Pink Sheet*, 20 Sep, 2017.)

Although the FDA has not formally adopted a Bayesian approach into regulatory decision making, current and former agency officials stressed throughout the meeting that the agency is "open for business" in exploring new avenues for innovative trial designs.

### **An Obsession With P Values**

Several of the experts also agreed that the scientific community has an obsession with the P value as a measure of efficacy, and that it has become deeply ingrained into the mindset of orphan drug development.

"A change has been long needed in how we approach and analyze these things," said Pharmaceutical Research and Manufacturers of America's (PhRMA's) Chief Medical Officer Rich Moscicki in a later panel. "And the necessity with such small sample sizes available to us, the necessity of having to move beyond our obsession with the p value I think is incredibly important to be stated."

Moscicki, who only recently joined PhRMA after serving as deputy director of science operations in CDER, noted that Bayesian methods are centuries old, but only now is the medical community having serious discussions about incorporating them into a regulatory framework. (Also see "Moscicki's Move From FDA To PhRMA About 'Best' Use Of Leadership Skills" - *Pink Sheet*, 18 Oct, 2017.)

Scott said FDA is a guilty party in facilitating the obsession. "I want to extend an apology on for the collective guilt for my profession that we've traumatized you into thinking not only that p values are the way to measure effectiveness, but even that they may be a way to measure effectiveness," he said.

### **How To Move Forward**

Panelists also offered an array of solutions to help facilitate the shift of the regulatory paradigm.

Moscicki described the "wedding" of Bayesian approaches with registries and natural history studies as "absolutely key to getting as much information as we can when the sample sizes are indeed so small."

Scott spoke of the need for individual case studies, such as "specific individual examples of decisions being made in a principled way, of data being borrowed in a way that makes

sense.” Individual case studies can then help to provide guidance on best practices, Scott said.

Many speakers throughout the day spoke of the importance of the patient voice, as rare disease patients are in a position to provide valuable data to industry about their experience. For instance, Gianna McMillan, graduate program coordinator at Loyola Marymount University’s Bioethics Institute, stressed the importance of leveraging qualitative data from patients to help inform future researchers.

In an interview with the Pink Sheet, Mark McClellan, director of Duke Margolis and a former FDA commissioner, said

he feels the paradigm shift is already underway, noting that FDA tries to consider the totality of the evidence in drug review.

“So I think this is a journey that FDA is being already on,” McClellan said. “It’s being accelerated by these emerging efforts, often patient-sponsored, to bring together lots of natural history data and the capacity for platform studies, and just learning more, and getting more experience about some leading cases for using Bayesian type methods.”

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## New Novartis CDO Bodson Outlines Digital Health Ambitions

► By Mike Ward



Bertrand Bodson

With a wealth of data management experience from his time at Sainsbury’s Argos, EMI Music, Bragster.com and Amazon, Bertrand Bodson is relishing the opportunity of marrying digital technologies and data science to enhance the development and delivery of treatments to patients. He believes it will not only shake up the conventional pharma commercial model it will also catalyze a cultural shift within the industry.

“I think big gains will be made by fundamentally changing the way we work across the entire product lifecycle. From research and development to manufacturing to – how we engage and educate doctors and patients about our products and services. A successful digital transformation also requires a culture change – we need to unleash the power of our people as well as adopt more agile ways of working. Having joined **Novartis AG** from the retail sector, I can also see the benefits of us shifting from a mainly product-oriented company to one more focused on enhancing the customer experience – digital, data and technology will be the key to making that happen,” he told *Scrip*.

Describing the digital health opportunity as a blank canvas, he is excited at the opportunities to reimagine medicine and the use of technology to solve some core healthcare

challenges, including access to medicines. “Digital technologies and data science have the potential to help us unlock the next chapter in medical innovation, from transforming our commercial models to enhancing the customer experience and accelerating the pace at which we find and get drugs to market,” he added.

In his new role, Bodson says success will involve bringing new, more targeted, more effective drugs to the market quicker and more efficiently. “It’s combining data and patient insights to design improved clinical trials that reflect the diversity and needs of patients, ultimately generating better outcomes for patients,” he added.

**“It’s combining data and patient insights to design improved clinical trials that reflect the diversity and needs of patients, ultimately generating better outcomes for patients.” – Bertrand Bodson**

Bodson expects data science and digital technologies to have an impact across the whole value chain. Indeed, he envisages a future in which patients, supported by providers and their own personal medical data, will be empowered to play a more active role in managing their own disease prevention and treatments. Furthermore, he anticipates increasingly integrated payer-provider systems exerting greater oversight of doctor decision-making to control costs and improving outcomes.

“Physicians and other healthcare providers will play an important – but different – role in guiding patients through the healthcare system, focused on informing them about their conditions, and helping them make key decisions about their care,” he forecasts.

To achieve its digital health ambitions, Novartis will need to look outside its traditional competitor space and work with external partners and experts in data, digital and design who bring with them a start-up mentality. “The best partners will be those who can help us make the most of our data and of-

fer us deep expertise in addressing specific challenges using the latest digital technologies e.g. solving data privacy issues across the healthcare industry,” he noted.

Moreover, he is keen for Novartis to embed across its whole business some of the agile working practices of start-ups into its own culture to encourage small cross-functional teams of seven to eight people who are empowered to make fast decisions focused on customer/business needs. It means supporting a culture that encourages curiosity and learns from failure. Bertrand believes such teams can have more impact than much larger teams. He wants the company to be considered the destination of choice for future talent, “not just for those focused on the science, but that tech and data experts too are excited by what we can all achieve together”.

As part of its strategy to keep disruptive digital health developments on its radar, the company’s German arm has launched a Digital Health Award to identify promising start-up ideas. This year’s competition attracted more than 80 entries.

Specifically, one area Novartis is focusing on is how it can apply next generation data science to clinical processes. With its Nerve system, a computing mechanism it began co-developing with Quantum Black in 2016, Novartis is using predictive analytics to design, monitor and generate insights across its global operations. The program combines data on clinical trial operations from multiple internal systems, applying machine learning and advanced analytics, to predict and monitor trial enrolment, trial cost and trial quality. This is enabling Novartis to increase automation, maximize efficiency and make data-driven decisions and has already delivered a 10-15% reduction in patient enrolment times in pilot trials.

“We will also have the capability for deeper analysis and more complex data-driven decision making, such as a dosage planning system that will help us better calculate the exact amount of drug we need to produce for our clinical trials to remain operational at the highest levels – ensuring we avoid both shortages and surpluses, which of course cost time and money,” he explained.

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*Published online in Scrip, 6 April 2018*

To those who say “impossible,  
impractical, unrealistic,” we say:

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We’re developing an innovative new class of medicines called RNAi therapeutics, which we believe have the potential to transform the lives of people living with rare genetic, cardio-metabolic and hepatic infectious diseases.

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CHALLENGE ACCEPTED

 **EXCELLENCE IN RARE DISEASE  
DRUG DEVELOPMENT**

# Alnylam Pharmaceuticals



Jeffrey Cehelsky of Alnylam (right) receives the award from ICON's Executive Vice President, Program Management, Kim Boericke

Alnylam is deeply honored to have received the Clinical and Research Excellence (CARE) Award in the category of “Excellence in Rare Disease Drug Development”. We are sincerely grateful for this recognition.

As a Company committed to patients with limited or no treatment options, this award truly resonates with our core values, one of which is Passion for Excellence, because patients deserve no less.

APOLLO represents the hard work and perseverance of countless individuals and is a study that has paved the way for a whole new class of medicines with the potential to transform the lives of patients afflicted with rare and other diseases. We are deeply indebted to the patients, caregivers, physicians, and nurses across the world who participated in APOLLO and were instrumental to the success of this landmark study. And, a thousand thanks to the many Alnylam employees for their enduring contributions and ingenuity.



# Pharma Struggling To Assimilate Flood Of Clinical Trial Data

► By John Davis



The time it takes to develop a new pharmaceutical is getting longer because of the sheer volume of data that is collected in clinical trials, despite the use of new data management technologies, claims a new US analysis.

The increase in drug development times is being blamed on the rising scope and complexity of clinical trial protocols, which has led to a growing volume of clinical data being collected from numerous and disparate data sources, says the lead author of the analysis, Ken Getz of the Tufts Center for the Study of Drug Development, in Boston, Massachusetts.

There are also concerns that clinical trial protocol changes, compatibility issues between different electronic applications, and the still relatively common use of paper case report forms, are also holding back progress, say the US researchers.

Finding ways to reduce the R&D data mountain have already been suggested by commentators, including advocating the use of machine reading and machine learning technologies, and other aspects of artificial intelligence.

The president of the European Federation of Pharmaceutical Industries and Associations (EFPIA), **Merck KGAA's** Stefan Oschmann, has targeted the better use of health data as one of the aims of his tenure at the association. (Also see *"Pharma Could Do Better With Data, Say IBM, McLaren"* - *Scrip*, 16 Jun, 2017.)

Industry regulators are also evaluating the use of big data, with a joint EMA/EU Heads of Medicines Agencies taskforce working on a strategy on the use of big data to support the development and assessment of medicines. (Also see *"A Whistle-Stop Tour of 2017 - From An EU Regulatory Point Of View"* - *Pink Sheet*, 29 Dec, 2017.)

## Tufts Analysis

The time from the end of a study to completing data collection, referred to as the time from last patient, last visit to database lock, has increased from an average of 33.4 days in 2007 to 36.1 days in 2017, the Tufts analysis estimates.

Nearly a third of the 257 drug developers surveyed by the Tufts research team still use paper case-report forms, and 77% of sponsors and contract research organizations reported they had difficulty in loading data onto their primary electronic data capture (EDC) systems because of incompatibility, technical demands and integration challenges. Sponsors and contract research organizations use on average six applications to support clinical trial activities, the researchers note.

But changes to the design or execution of clinical trials were also rife: protocol changes accounted for 45.1% of database-build delays reported by sponsors and CROs, Getz *et al* said.

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*Published online in Pink Sheet, 7 March 2018*

2018

# Medtech Insight Awards

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**September 23rd 2018**  
**Awards ceremony**  
**takes place:**  
**Kimpton Monaco**  
**Hotel, Philadelphia,**  
**USA**

## Case Studies: How Patient Input Is Changing R&D

► By Sue Sutter

The philosophy underpinning the patient-focused drug development (PFDD) movement – that it's important to find out what symptoms are most bothersome to patients, and what they would like to see in new treatments – is increasingly being embraced by drug developers as they plan their clinical programs for new compounds.

Below are two examples of how the growing attention to the importance of the patient voice, coupled with the US FDA's own PFDD initiatives, have impacted recent drug development programs. [For a thorough assessment of FDA's patient-focused drug development initiative, see Pink Sheet's *From Listening To Advising: The Maturation Of US FDA's Patient-Focused Drug Development Program.*]

**New Patient-Reported Outcome For Sickle Cell Disease For Global Blood Therapeutics Inc.**, which is developing voxelotor (GBT440) for sickle cell disease, FDA's February 2014 PFDD meeting on the disease directly impacted the company's work on a new patient-reported outcomes (PRO) instrument.

At the meeting, patients said their ideal treatment would be something that targets the underlying disease and organ damage, rather than just providing symptom relief. Although patients can figure out ways to manage the pain associated with sickle cell disease, they can do little to address the long-term complications of the disease, they said. (Also see *"Sickle Cell Patients Weigh Clinical Trial Participation At FDA Meeting" - Pink Sheet, 17 Feb, 2014.*)

"Really directly because of that meeting ... we realized that there was a tremendous opportunity to take what we were hearing and what FDA was also hearing and embark on a more structured and formal effort to get more of that feedback from patients" to develop an instrument that would directly measure what they said was important, said Josh Lehrer, senior VP-clinical development at Global Blood Therapeutics (GBT).

The traditional clinical endpoint in sickle cell drug development has been based on vaso-occlusive crises (VOC), which

are episodes of severe, intense pain that can land patients in the hospital. However, this endpoint is problematic for a number of reasons, including that it measures only crisis events requiring healthcare intervention and not the more frequent episodes of pain that sickle cell patients experience.

Voxelotor modulates hemoglobin's affinity for oxygen, which GBT believes inhibits hemoglobin polymerization in sickle cell disease. Because the molecule has the potential to modify the disease and downstream symptoms, using VOC as a primary endpoint could leave a lot of benefit unmeasured and result in much longer trials, Lehrer said.

Although GBT expected to have to do extensive education with FDA about problems with the VOC endpoint, the agency's PFDD meeting "really did that," Lehrer said. "The meeting served to educate us but also FDA and the division to understand" the issues with the traditional endpoint and encourage an open mind to think about new approaches, he said.

The company developed the Sickle Cell Disease Severity Measure (SCDSM), a PRO instrument comprising nine questions about pain intensity and duration, energy, fatigue, weakness, breathing, and mental concentration. The instrument is administered electronically each day.

Each of the nine questions has four response options grading either symptom severity or the amount of time during the day that the symptom was experienced. The Daily SCD Symptom Severity Score is based on the response to the nine questions.

Although the primary endpoint of GBT's Phase III HOPE study is change in hemoglobin, key secondary endpoints are proportion of days with SCD symptom exacerbation as calculated from the SCDSM, and change in SCDSM total symptom score.

The 400-patient trial enrolled its first patient in January 2017 and is expected to complete in the first half of 2019.

"That PFDD meeting was a big impetus, and it also made our job of working with FDA and bringing them around to

see the value of this much easier,” Lehrer said.

### Endpoints Reflect What’s Important To Amyloidosis Patients

For **Alnylam Pharmaceuticals Inc.**, an externally led PFDD meeting provided confirmation that it was pursuing clinically meaningful secondary endpoints in the Phase III trial of patisiran, an RNAi therapeutic in development for hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

Neuropathy is a prominent feature of hATTR amyloidosis, and Alnylam, in consultation with clinical experts and regulators, designed the Phase III APOLLO trial with a primary endpoint based on the modified Neuropathy Impairment Score+7 (mNIS+7), a composite measure of neurological impairment that provides a quantifiable way to assess disease burden, Executive VP-R&D Akshay Vaishnav said.

However, Alnylam recognized that a change in the mNIS score over the course of a trial may not mean much clinically to an individual patient, Vaishnav said. Consequently, the company incorporated six secondary endpoints aimed at fleshing out the clinical meaningfulness of patisiran’s benefit.

The secondary endpoints included: a quality-of-life instrument that is sensitive to small fiber, large fiber and autonomic nerve function; a motor function/strength assessment; a measure of body mass index and nutritional status; an instrument that assesses activities of daily living; an assessment of ambulation that measures gait speed; and a questionnaire used to evaluate patient-reported autonomic neuropathy symptoms.

These secondary endpoints reflect the concerns expressed during the company’s own consultations with patients in the run-up to designing APOLLO, Vaishnav said. Amyloidosis patients were worried about the ability to walk, maintain muscle strength and body weight, engage in activities of daily living, and occurrence and severity of diarrhea, he said.

The APOLLO trial started at the end of 2013. In November 2015, the Amyloidosis Research Consortium (ARC), at FDA’s suggestion, hosted an externally led PFDD meeting at which patients talked about the disease impact on their daily lives and what they would like to see in a new treatment.

The meeting was modeled on FDA’s PFDD initiative, although it took place before formal agency guidelines for such externally led meetings. There have been a total of 10 externally led meetings conducted to date pursuant to FDA’s guidelines.

“What we heard from ARC and others at that meeting was completely in line with what we had incorporated” in the APOLLO study, Vaishnav said. “It was great the message was consistent.”

After the PFDD meeting, the company revisited the secondary endpoints in APOLLO but concluded they addressed the symptoms and concerns that were of interest to patients and there was no need to change the endpoints, he said.

The APOLLO study was completed in 2017. Patisiran demonstrated a statistically significant benefit on the neuropathy primary endpoint and all of the secondary endpoints at 18 months, with a significant reduction in disease symptoms and disability, and improvement in quality of life, nutritional status, strength and ambulation compared to placebo, the company said.

“It’s a happy story because there are a number of these important endpoints – robust primary and very consistent secondary endpoints that flesh out the clinical meaningfulness,” Vaishnav said. The secondary endpoints should provide reassurance for patients that the drug has the potential to help them with a diverse range of symptoms and activities, he said.

Alnylam completed a rolling NDA submission in December, and the company is optimistic that the secondary endpoint data will make it into the product labeling.

FDA has begun implementing a statutory provision requiring it to make public a statement about patient experience data reviewed as part of an application.

Vaishnav said the experience underscores the need for drug developers to speak to patients “particularly for these rare diseases where the clinical manifestation and the clinical suffering of patients isn’t always fully outlined in the literature. In these rare diseases, it’s critically important to have patient consultation.”

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*Achievement of Stable Normal Factor IX Blood Levels  
in a Preclinical Subcutaneous Dosing Model*



From left to right: Fletcher Payne, Dr. Howard Levy, and Dr. Nassim Usman

**We are delighted to be chosen** as a finalist for the Pharma Intelligence CARE Awards **Most Successful Early Phase Research** category for our preclinical study of subcutaneously-administered Factor IX in a dog model of hemophilia, performed in collaboration with the University of North Carolina. The results showed that subcutaneous delivery of our next-generation Factor IX CB 2679d achieved mild to normal activity in the circulation and allowed us to pivot to prophylactic subcutaneous Factor IX dosing in individuals with hemophilia B, unlike all other approved Factor IX agents. We hope to deliver a better treatment option to those suffering from this life-threatening disease.

We are proud to be recognized for our innovative approach towards helping those with hemophilia. We would like to thank those who have participated in our trials, as well as the entire hemophilia community for their support as we progress this Factor IX candidate through the clinic. We thank Pharma Intelligence for our consideration for this award and congratulate the other finalists for their accomplishments.



## State Of Pharma R&D: Ex-Takeda's Yamada Takes The Long View

► By William Looney



Tadataka "Tachi" Yamada

Biopharma R&D today remains a high-interest promissory note on the future of medicine. Redeeming that note periodically with therapies that advance the standard of care allows the drugmaker to survive, to grow – and to renew itself. Yet efforts to “de-risk” the drug pipeline process and render it scientifically and financially predictable have become harder still as the bar to innovation gets higher and more selective.

Deloitte's 2017 survey on returns from biopharma research confirms the long-term decline in the R&D productivity ratio (between capital outlays and cash inflow from sales) among the 12 largest biopharma companies, from an average posted return of 10% in 2010 to less than 4% in each of the last two years.

At the same time, however, there is strong anecdotal evidence of variations among companies in R&D performance – some drugmakers just seem to do better at extracting wins from their pipelines than others. Could it be that where you stand on the overall curve of approved new chemical entities (NCEs) is what counts? And is success the result of random acts of serendipity or is there a replicable formula that raises the odds of success?

To provide some personal context to the state of today's R&D enterprise, In Vivo spoke recently with Tadataka “Tachi” Yamada, a physician polymath who has worked many sides of

the industry's research ecosystem, leading multibillion-dollar R&D programs at **GlaxoSmithKline PLC** and **Takeda Pharmaceutical Co. Ltd.**; heading global health programs for the world's largest private health philanthropy, the Bill & Melinda Gates Foundation; and serving as a member of the National Academy of Medicine venture partner at Seattle-based Frazier Healthcare Partners. This latter position puts him on the boards of several start-up biotech companies with novel drug discovery platforms linked to recent advances in identifying the biological origins of disease.

Even in his current role as a venture capitalist, Yamada retains his commitment to global health, noting that increased access for neglected populations in resource-poor environments is a great stimulus to product and process innovation, applicable to rich markets as well as poor. In the following Q&A, Yamada looks at what's new – and what isn't new – in a field where every researcher has at some point experienced the same teachable moment: when you strive to make a medicine, so many things can go wrong.

**IN VIVO: While R&D performance among big pharma has been mixed in recent years, it is not due to a lack of experimentation – your own record in leading process innovations at GSK and Takeda proves that. What do you see as the most significant changes in the way drugmakers manage the research enterprise to bring promising new compounds to market?**

**YAMADA:** There has been a profound shift toward external sources of innovation as the driver in delivering results from the big pharma pipeline. What was a trickle of ideas from outside only a decade ago has become a flood, and the trend now extends to cooperation with rival drugmakers as well as small biotech, academic institutions, the VC community and even patient groups. Companies are tapping their balance sheets for those transformative M&A transactions, but they are also funding smaller projects with external partners to supplement – or even compete with – internally sourced activities. We are beginning to see an amazing level of cross-fertilization with organizations outside the traditional

drug space, as new computational and bioengineered platforms emerge for “virtual” in silico testing that can handle lead generation much faster than the traditional lab-based experimentation involving living subjects.

An interesting approach to externalization is the increasingly popular “build to buy” strategy in which pharma companies will pay a smaller biotech to do the product development work externally and thus avoid the bureaucracy and encumbrances of a large organization model. Then the pharma company will acquire its biotech partner after certain milestones have been met. Recently, I helped broker a deal between a start-up company, PVP Biologics Inc., led by a team of scientists associated with the University of Washington’s Institute for Protein Design, and my former colleagues at Takeda Pharmaceuticals, to help fund a promising compound, KumaMax, for treatment of the symptoms and intestinal damage associated with celiac disease. Takeda will provide funding to take this therapeutic candidate through a Phase I proof-of-principle study, a commitment of resources which otherwise PVP Biologics could only have secured under less favorable terms through venture capital. It’s an increasingly common example of how innovation today is a collective rather than a unitary endeavor, one highly dependent on inter-disciplinary insights and applications. The trend to redirect resources around a more diverse set of opportunities is certainly stimulating from a purely scientific standpoint. But it can raise tensions in the research organization due to the hard choices involved in addressing areas where externally and internally sourced projects conflict or overlap. On a purely intellectual level, it offers a way out of projects of marginal value whose internal owners are hard to dislodge in the absence of an appealing alternative. More important, competition from outside is forcing big pharma organizations with a long-standing commitment to risk-averse behaviors to begin acting like an entrepreneurial start-up.

That’s why I see external R&D innovation as a disruptive game-changer, even if culturally the change in mind-set can be hard to pull off. Nevertheless, companies have little choice but to act as advances in technology challenge the discovery status quo and create more options to speed the move from bench to bedside. Major investments are required to seize these opportunities; some will play out, others will not, and, as often happens in R&D, the downstream payoff may be long in coming. I expect all these

forces will combine to hasten R&D’s transition from the old “bricks and mortar” infrastructure, along with the heavy investments in human capital required to maintain it, to a smaller, flexible, more open and broadly dispersed model of performance – the new global ecosystem of research.

**Are there any unanticipated challenges associated with this new emphasis on working productively with numerous outside partners to de-risk up-front development exposures and maximize a compound’s potential against existing standard of care?**

One of the hardest tasks for biopharma companies today is to license-out a promising compound that may not have the best chances to succeed in their own hands. As development costs soar, even the largest drug companies lack the budgetary resources to move all the assets in their pipelines forward to commercialization. Valuing the asset to ensure it is licensed out at an appropriate price by the licensor is harder today because of the unpredictable impact of therapeutic and market volatility within that asset’s prospective life cycle. There are dynamic time and duration constraints that complicate the determination of how much – and how long – an asset will deliver the revenues expected from both parties. Also problematic is that business development teams get little credit for this kind of transaction as opposed to in-licensing an asset; to make matters worse, they might even be blamed for underestimating the value of the asset as accrued by the licensee over time.

**By most measures, R&D, at least among the big pharma players, is failing to deliver the returns expected by investors and society at large. Is this a long-term crisis or simply a transitional situation?**

I believe the criticism of R&D productivity performance is misleading – and a bit unfair. We should start by asking a simple question: what is the ultimate task of an R&D organization within a pharma company? It is to build and maintain a pipeline of compounds sufficient to allow the company to renew itself. On that measure, everyone appears to be doing that, through a combination of internal investments, M&A and deal-making that includes licensing, joint ventures, asset swaps and risk-sharing contracts. Few if any pharma companies have gone bankrupt just because they had a poor track record on R&D. You can even say that the means exist to make every pipeline sufficiently productive to allow a company to survive.

In fact, it's hard to find an acceptable measure by which to evaluate industry success in fighting disease. One benchmark is the number of novel drugs approved by the FDA each year. Until five or six years ago, the numbers were trending inexorably downward, prompting many to bemoan the inevitable death of the pharma industry. However, in the recent past more new drugs have been approved than ever before. Clearly there are many factors that determine the number of new drugs approved in any given year and it's still premature to predict the demise of our industry.

The challenge of making a new medicine might be exemplified best in examining the fate of two drug development programs that I had the opportunity to participate in. Takeda Pharmaceuticals experienced a long period in which not a single NCE was approved by the FDA. When I first joined Takeda in 2011 I found only one promising asset in the late stages of development, a GPR40 agonist which had the potential to be a first-line oral treatment for type 2 diabetes disease. Analysts forecasted the product to deliver up to \$3 billion in annual sales once approved by the FDA. However, near the very end of our clinical trials we encountered three patients with a toxicity signal indicating that severe liver failure might be possible with the drug. This was a safety signal that we had not predicted from our preclinical toxicology studies and we had not observed previously in thousands of patients who had been exposed to the drug. In any case, the risk to patients was sufficiently great that we had no choice but to terminate the drug and forfeit the \$400 million we had spent on its development.

Shortly thereafter, we had to confront another potential reversal on a monoclonal antibody treatment for inflammatory bowel disease. The regulators were concerned about the risk for progressive multifocal leukoencephalopathy (PML), an aggressive CNS viral disease, and a side effect seen in an antibody against a similar but not identical target. They required us to confront the question directly through an expensive high-risk trial, that would expand the safety database to 2,000 patient years. This required re-allocation of over \$100 million from an R&D budget that had already been set for the year and committed to other drug development programs, most of which were considered to be more promising than the antibody in question, which had always been a stepchild in Takeda's portfolio. Nevertheless, we did exactly that,

much to the consternation of many in our R&D organization whose programs were terminated or delayed as a result. Even one case of PML would likely have killed the drug's commercial potential. Yet it turned out that the decision was a correct one – no cases of PML were detected, the drug was approved and launched under the brand name Entyvio [vedolizumab] and it is now a blockbuster, the most successful product in Takeda's portfolio.

These were two cases with diametrically opposite outcomes. One led to abandonment of a potentially great product at a late stage because of a toxicity signal that only emerged at the very end of Phase III – data from the two earlier phases revealed no such signal. The other was a gamble we took to commit to answering a question of potential toxicity that, had it been borne out, would have certainly inhibited the prescribing of the drug by physicians. The gamble paid off and finally handed Takeda a well-deserved win.

What these two case studies demonstrate is that human biology is never completely predictable. Inherent scientific uncertainty involving complex interactions between biology, chemistry and the laws of physics cannot be willed away with an economics mind-set driven by zero tolerance for risk. The idea that the productivity of biopharma R&D is on a linear path of decline and that this trend can be reversed through one-off process efficiencies is misguided. The more we are able to shed light on some of the mysteries of the human body the more likely we will be able to proceed with greater success in drug discovery and development. Nevertheless, there is an element of serendipity to making new medicines that will never go away.

### **Looking forward, what do you see as the most exciting areas of new science with the most potential impact on patient care?**

We are already at the stage where small molecules and antibodies are ceding ground to the potential therapeutic applications from cells and genes, nucleic acids, peptides and small proteins. A fast-emerging retinue of RNA therapeutics will boost the potential of these platforms into new treatments and cures. We will see advances in the design of proteins or peptides, to deliver drugs individually tailored to the disease profile of a patient. I am currently an advisor to the University of Washington's Institute of Protein Design, which has led much of the

fundamental academic work in this field. I am helping to translate the institute's fundamental research into early-stage commercial projects underway at two spin-off companies. One encouraging initiative the institute is pursuing is developing self-assembling nanoparticle-based virus-like particles presenting antigens in a multimeric array to induce immunity against infections. Ultimately, this technology could be applied to address non-communicable diseases such as cancer.

Another area I am excited about is the microbiome. Humans harbor more than 10 times as many organisms in their microbiomes than the number of cells in their bodies. The composition of any one individual's microbiome is unique; that uniqueness will influence what the host person will experience in terms of disease. For example, recent studies showed that the microbiome may play a role in the hypertension induced by excess salt in the diet through specific bacteria that regulate immune cells in the host. Other studies have linked dietary trehalose to the growth of pathogenic *Clostridium difficile* in the gut. What I especially like about this field is the possibility that drugs directed at regulating the bacteria in the gut might be able to address human pathology without exposing the human hosts to the risks of the drugs. The dangers to the patient are inherently less.

**In addition to managing large R&D operations in the private sector, you have been actively engaged in efforts to raise the industry footprint on global health issues. Why is global health and access to the poor a business issue, beyond mere charity?**

There was little investment by the pharma industry in addressing global health challenges prior to the end of the 1990s, with the exception of Merck & Co. Inc.'s river blindness [onchocerciasis] and SmithKline Beecham's elephantiasis treatment programs. Establishment of the UN Millennium Development Goals along with the efforts of new and larger global health initiatives such as the Bill & Melinda Gates Foundation; the Global Alliance for Vaccines Immunization (GAVI); the Global Fund to Fight AIDS, TB and Malaria; and President George W. Bush's PEPFAR program proved that with proper investment progress can be made against some of the world's largest health problems, even in the poorest countries. The work of these organizations quickly showed that investment in global health delivers a positive economic and social return. Additional challenges such as

the SARS pandemic and the Ebola crisis showed that some problems of the developing world could not be contained in the countries where they started but had the capacity to spread to even the richest countries overnight – no one is immune. Lessons learned from global health initiatives have served to underscore the importance of strong health care systems that promote access to basic care. This is as true for Europe and the US as it is for sub-Saharan Africa. What industry does in resource-deprived settings can carry benefits to rich health care systems by restoring the emphasis on public health and finding better ways to provide products and services at lower cost.

In this context, there are a couple of initiatives that may have important implications for the global pharmaceutical industry. The first is a growing commitment by governments to the idea of “universal health coverage.” This loosely defined concept may mean many different things but at its core is the principle that all people should have access to basic medical services – including drugs – that provide therapy for important non-communicable diseases like diabetes, hypertension and even more advanced conditions like cancer. The Clinton Health Access Initiative, on whose board I serve, is now coordinating access to cancer chemotherapy drugs in a number of African countries with support from major drug multinationals like Pfizer. This in turn has expanded interest in new logistics and delivery platforms at a cost far lower than the norm, a development that is worth applying elsewhere as the exemplar of “frugal” process innovation.

The second is how multilateral agency efforts to assess the economic stability of a nation, which have a direct effect on its credit rating, might be extended to rate the commitment and quality of its health systems infrastructure. This arises from the observation that during the Ebola crisis the affected nations lost over 10% of their GDP overnight, while adjacent countries like Nigeria, with better developed health systems, were able to contain the spread of the deadly virus. Such a policy, if enacted by key organizations like the International Monetary Fund (IMF) could lead to rapid growth of upgraded health infrastructures, including a more functional medicines market covering essential drugs as well as more innovative products. Ultimately, even the poorest nations of the world could become important markets for the pharmaceutical industry if it pays attention to its role in helping to build the health infrastructures in those countries.

### Is there a potentially disruptive issue that you believe will have the most adverse impact on biopharma's overall license to operate?

The biggest threat stems from the widening perception that the US innovative industry is becoming irrelevant, a marginal player in health, with products that are largely ineffective and cost too much. Many influential constituencies believe biopharma does little to benefit the average patient, and that the government must therefore step in and replicate the work of the industry on drug discovery and development. The notion that public initiatives can replace the resources, expertise and general know-how of the private sector in bringing a new drug to market is far-fetched. The fact that this is even being contemplated suggests that not much is being done to educate the public on just how hard it is to make a new medicine.

### Is the pharma industry accountable for its reputation problem?

The challenge is there because of the way our industry has behaved in practice. The evidence is clear: a substantial portion of the industry's growth in recent years can be attributed to jumbo pricing of new medicines and uncontrolled price increases for existing medicines whose innovative attributes have been around for some time. Going forward, pharmaceutical companies must be able to demonstrate the true medical, social and economic value of its medicines in order to justify the price tags attached to them. The industry must be seen as contributors and partners in the effort to enhance the welfare of nations, not predators that only suck out the resources allocated to improving health. It can do this by redoubling its commitment to what it does best, creating innovative solutions for complex medical problems with unmet need. If the industry does that well I have no doubt that it will be appropriately and richly compensated.

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## Pfizer's Reference Point On Trial Innovation: Ask The Patient

► By William Looney



Head of Clinical Innovation Craig Lipset

- Pfizer's three top challenges in trial management are patient recruitment, trial site selection, and data access and interoperability. The latter issue is important in realizing a major opportunity to leverage technology advances to achieve two goals: richer, more insightful data streams and stronger engagement with patients and providers.
- So what? Biopharma still does not test the upper limits of what is needed to improve trial management. The reason why has less to do with regulation or technology than with risk-averse company cultures – there is little recognition that a status quo mind-set is itself a source of risk.

The landscape for clinical trials is flush with invasive growth, seeded by disruptive new technologies and the necessity to cope with a range of human impacts, from

lags in patient enrollment to rising investor expectations for chart-busting gains against existing standard of care. Biopharma's emerging response to this sprouting tangle of challenges is, surprisingly, to embrace a culture of trial innovation – and to make collaboration with patients and other external stakeholders a strategic endpoint of its own. To explore the current state-of-play in driving innovations in the trial space, *In Vivo* spoke last month with **Pfizer Inc.**'s head of clinical innovation, Craig Lipset, who outlines what the world's largest drugmaker is doing to bring new ideas to a network of 300 trials underway involving more than 55,000 patients.

**IN VIVO: Biopharma's revenues and reputation depend on the progress of the clinical trial – a time-honored but still imperfect vehicle for the aspirations of millions of patients with unmet medical needs. Improving trial performance is a topic of endless debate, but can we agree that the fundamental mission of the biopharma enterprise remains the development of new drugs?**

**CRAIG LIPSET, PFIZER:** On that point we have consensus! When you examine the time and up-front costs involved in moving a compound from discovery to approval and commercialization, there is nothing more important to this industry. I joined Pfizer 12 years ago. I had been working at a small, 30-person biotech company in the Boston area, where I was responsible for clinical and regulatory operations, when I was approached by what was then Pfizer's Global Research Division (PGRD) to help identify technologies derived from other verticals in the health care sector to drive improvements in Pfizer's own clinical research. The work happened to coincide with my own passion for innovation in the design and execution of drug trials – the most critical aspect of our industry's lengthy product development cycle, and one that offers endless opportunities to get closer to the patient. At the time, I thought I might stay at Pfizer for a couple of years, at most, but today I am still here. The reason is the impact of drug development innovation on patient outcomes is even more critical today than a decade ago. All the new ground-breaking science emerging from the lab makes the consequences of failure for the patient more profound. Pfizer itself has an internal culture driven by a consuming interest in innovation in drug development. And I continue to draw strength from it.

### **How is Pfizer organized in drug development and where do you sit in the company's sprawling R&D network?**

When I joined Pfizer in 2006, drug development and clinical trials were located in a single, very large R&D organization. Soon after, the company took the opposite approach and – in what I call the clinical trial diaspora – trials were conducted at different locations throughout the company. Drug development itself was dispersed, so if one part of the enterprise turned down a novel trial approach, another unit might take it on, allowing for multiple shots on goal and giving internal innovation the chance to flourish. The problem, which ultimately proved unsolvable, was the disincentive this decentralization imposed on our being able to scale up these innovations with the full-on commitment they required. Instead, we had a disaggregated effort that failed to mobilize our full strengths as an enterprise. Since 2016, Pfizer has pursued a different approach, with a single, integrated global drug development organization led by a C-suite level chief development officer (CDO), Rod MacKenzie. This newly centralized function brought together all the elements that fuel a clinical trial, including most of the science, R&D operations, clinicians and statisticians, among others. Rod is the ultimate owner of drug development – the single point of contact – and this has allowed my team to go a lot farther in introducing more innovations in how we design, conduct and process our trials. In that respect, the changes have led to a renaissance for my own group, which now bears the title Clinical Innovation. In the new consolidated development operation, we focus on four priorities: first, and perhaps most important, raising the profile and experience of patients in our trials; second, leveraging innovations in digital (mobile, wearables), health information technologies and social media, to improve trial efficiency, access and transparency; third, building more collaboration and partnering between Pfizer and outside stakeholders in trade and professional associations, academia and government; and fourth, serving as a laboratory to help generate ideas on topics like the integration of research conduct within the health care system and making research participation less disruptive. In a larger sense, what we do is make sure that opportunities and ideas that come from outside Pfizer are identified, evaluated and, if appropriate, brought forward for decisions on scaling these up here first. We strive to be relatable

internally as well, understanding current challenges in the development business and helping to address them with thoughtful pairings of solutions we might obtain from outside. It's important we gird this work with focus and persistence, to ensure any new options are tested to generate the evidence necessary to secure buy-in from management. We just don't bring people in, exchange handshakes and leave it to others to move that option forward. You cannot just expect things to happen in a big organization like Pfizer, with its many teams of scientists.

**What's different about your job today than when you started? How has the strategic and operational climate for clinical trials changed over the last decade?**

The biggest transformation is in the expectations of our stakeholders and what we in industry think is feasible from all the effort expended in our trials. When I joined the industry, the belief was the upper limit of change rested on process improvements and realizing the commitment to operational excellence. Obviously, these two areas continue as the cornerstone of much of what we do today. However, there is a real desire now to move beyond today's processes and embrace more forward-looking innovation. There is an interest in embracing disruption, particularly if it ends up replacing a process with something new, one that might bring us to a destination we cannot even imagine today. This is the implicit charge that my team and I have from Pfizer leadership, which is to stretch and try new things to make our trials more relevant to the science and beneficial to patients. Another big change is the embrace of collaboration with others in the industry. When I joined Pfizer, the idea of working with competitors on clinical research process and trial conduct was anathema. What gradually became evident is that many actions individual research sponsors took up on their own to transform drug development were piecemeal and thus failed to add much value – in fact, in some cases, it might have slowed us down. Groups like TransCelerate Biopharma, a non-profit group of 19 major global drug companies, show that this industry's major players are willing to aim for a higher collective standard of excellence. Today, I think we all appreciate how working solo created small differences that added up to more distraction, noise and chaos – where was the added value in remaining secretive? Not much. Finally, I'd say the skills required to prevail in this space have shifted toward

the art of persuasion – the ability to sell your ideas. This is critical to the work I do here at Pfizer. It has always been easy in a science-driven organization, populated by highly credentialed academics and clinicians, to look down on the need to “sell” anything. But look closer and you will see that every grant application written by an academic is actually a sales proposal. Internal sponsors of a new molecule must sell their clinical proposition repeatedly, in a long process where the incentive for the next-stage gatekeeper is to relegate their work to the “fail fast” category. It's actually a positive to be a good salesman – to listen well, understand what the pain point of the customer is, and thus ensure that the product being pitched is geared to solving a real problem. Too often, those proposing an innovative solution lose sight of what it means for the stakeholders who are expected to adopt the asset – and pay for it. The message can't just be “we have a great new hammer”; instead it's what is the impact of this tool on the specific problem and for what result?

**Can you identify the three most important issues driving the conduct of biopharma clinical trials right now?**

Patient recruitment continues to be the most critical challenge we face in running our trials. There is a serious gap in patient awareness about participating in this vital aspect of medicines research, which is reinforced by the difficulty the industry has had in engaging physicians to be more active in sharing trial options with their patients. Most patients we are looking to recruit for our studies already have the relevant diagnosis and are on existing therapy under the supervision of a practicing physician. Frankly, it's a problem when we try to go directly to patients through ads or other forms of patient outreach instead of working with the treating physician. The best way is to encourage both parties to have an informed conversation about participating in a trial, and that requires doing a better job to give the physician the tools and the information he or she needs to support that conversation. It's all about shared decision-making. This kind of encounter can be time-consuming, but in the end you tend to get a better engaged trial participant, with less turnover. The second salient issue is trial site selection and management. It's harder today than in the past to identify the right sites, staffed by motivated professionals, with access to the right patients for

the trial. Data alone has not helped improve the odds as much as we hoped, even though more and more of it is being applied to evaluate the feasibility of different locations and optimize the chances for a successful set down. Adoption of advanced analytics and machine learning to pull all this together coherently could help bridge the gap, which in many cases depends on ad hoc human interpretation. The third issue I'd cite is data interoperability – the ability to realize the productivity and improved health outcomes from being able to connect and share the individual patient's electronic health record (EHR). I don't want to make short shrift of this issue, but you can tell my enthusiasm for the role that patients can play as their own best data aggregators in support of clinical research. I have another extended thought here as well. There are many new technologies for evaluating health data – artificial intelligence (AI) and real-world evidence (RWE) come directly to mind. It's vital that, as these technologies advance, we share our experiments and lessons on what works and what doesn't. It would be a tragedy if we apply what are limited resources solely to our own company interests rather than making all this potentially rich data work in the best interest of patients everywhere.

**The bar for proving a new drug candidate is safe and efficacious has also been raised – it's now necessary to show a clear clinical differentiation against current standard of care. In Pfizer's view, does this add to the cost and complexity of drug development or does it bring a refreshing clarity and focus to your work?**

We see both trends at work. The pressure is on because that bar on performance keeps getting higher. Drug development is more competitive than ever; most therapeutic segments are crowded with potential game-changing entrants vying for attention from investors, payers, providers and patients. Such competition has given a lift to the diagnostics space. Newer complex biologics must rely on biomarkers to ensure their benefits are targeted to the right sub-sets of patients. Advanced, digitally enabled endpoints are emerging to help demonstrate the value of new medicines. Payers clearly want that. Complexity is also paving the way for innovations in study design, recruitment and management because trial sponsors need better and smarter ways to generate evidence.

**You have a special affinity for the patient's interest, noting in several public forums recently that patients are the most disruptive force in today's clinical trial space.**

Every biopharma company is devoting significant resources to understanding what patients want from clinical trials. The phrase you hear today inside Pfizer is “patients first.” Every biopharma company claims to be moving toward “patient centricity,” though there is a startling lack of agreement on what that means. Our group has addressed the confusion by focusing on three priorities to drive Pfizer's relationship to the patient. The first is to meet the information needs of the patient before, during and after he or she participates in a clinical trial. What are their expectations after a trial ends? With that knowledge, we pursue deliverables – including patient-friendly summaries of trial results – to share with our trial participants. Pfizer has committed to this in all countries where local law and regulation allow us to do so. Another area we have led is on experiments to give patients access to the electronic data we collect on them as research participants. Both commitments stand out as firsts for the industry; other companies are now following our lead. The second priority is on the patient's trial experience, with an emphasis on reducing the hassle factor: is a visit to a test site necessary or can we obtain the information remotely? The third priority is to apply insights from patients to jump-start the re-design of our trial protocols. In fact, every draft protocol submitted to Pfizer's trial protocol review committee is challenged with a simple question: what insights did you gather from the participants and how did it affect the design of the study? If the answer is “I don't know,” or “I didn't ask,” then chances are you are not going to get a favorable response. My group's responsibility is to create the tools that allow Pfizer teams to tap these insights from patients in each of the therapeutic areas that comprise our core business. The outreach matters. Things change for the better when the trial sponsor is engaging with patients early in the process, and throughout the development life cycle.

**What about the concerns of many patient advocates that the biopharma industry is inconsistent in its claims to being patient-centric – the messaging lacks credibility.**

These concerns are valid and fair. Often in the past, biopharma firms would go to patient groups only when there was a crisis. If a company was slow in recruit-

ing patients, it would ask the advocates for help; but after the advocates intervened, dialogue would stop. In truth, the failure to engage on a truly mutual basis rests on something more ambiguous. The complexity of regulatory requirements for drug approval means that a drug company, despite its best intentions, may not be able to meet an advocate's desires for change. The problem is when patient groups perceive their voice is not being heard, or that changes are not taking place post-engagement. It's incumbent for the company to be proactive in sharing back this information – to make it a priority to share what has changed, what did not change, and why. Given today's punishing trial cycle, continuity in ties between the patient community and the company is the building block of trust. I see the importance attached to trust through my external work, as a scientific advisory board member of the Foundation for Sarcoidosis Research. Many advocacy groups are small and lack resources, so they benefit when big pharma does reach out. What they don't want is an exchange of emails only to hear nothing back – about the outcome or the impact.

### **How has the digital revolution re-shaped the contours of the typical clinical trial? Is technology ahead of practice?**

Digital health applications vary in their maturity and relevance to our industry. It is not a linear progression. Mobile and wearables carry the greatest impact right now because of their potential to enhance the patient experience and enable novel data capture, while artificial intelligence, machine learning and the blockchain are still evolving in terms of having a demonstrable impact. Electronic informed consent tools are helping patients to be better informed while improving the quality of clinical studies. We have to keep scaling up progress on health information technology (HIT) because it is right behind mobile in being a viable contribution to the design and conduct of trials. It will lead to improvements in trial design and execution. Specifically, data from electronic health records (EHR) will soon be entrenched at the core of how data is sourced for our trial programs – it's coming in the near term. HIT will also enable drug companies to better find and match trial participants to specific studies. Looking at these trends overall, I believe that technology and drug development logistics are fairly well aligned.

### **Aren't the challenges of accessibility, utility and interoperability eroding the promise of EHR? Isn't it still true that most patients find it too hard to access their data, resulting in a high level of opt-outs for these instruments? The premise today is that patients just don't "do" EHR.**

I am a futurist at heart. I strongly disagree with this conclusion. I recently did a TED Talk laying out my view about the convergence between data and the patient. The truth is that patients today have an unprecedented level of access to their own electronic health records. Two months ago, Apple introduced its new iOS version 11.3. Embedded was a fresh enhancement of the Apple Health app, which consumers can find as a default application on the ubiquitous iPhone. With this new app, a patient can obtain health data from dozens of health systems throughout the country, streamlined through their patient portals and without any barrier to accessing it. What Apple did is adopt the so-called FHIR (Fast Healthcare Interoperability Resources) standard for data interoperability, following in line with other enabling initiatives from the federal government such as Sync for Science (<https://syncfor.science.com>) and Blue Button 2.0 (<https://bluebutton.cms.gov>). In March, the Trump administration added to the momentum on interoperability by announcing the MyHealthEData Initiative on patients' rights to control use of their own health record. The policy makes it clear that providers and health plans must share data with patients, in a uniform and usable electronic format. It is also remarkably consistent with policies initiated by the Obama administration, demonstrating that patient data ownership is truly a bipartisan concern. Now it may take a little time, but the die is cast. Instead of a patient visiting the clinic to be interviewed by the principal investigator in person, the patient, having first given permission, will simply swipe, and, in an instant, provide the investigator with an electronic record on trusted clinical data to populate the study's database. The savings in time and effort will be measurable and significant.

### **Is Pfizer ready for this act of data consolidation – are you prepared to capture that data, process it and transform the raw material into insights capable of driving better decisions?**

We are making progress. Real-world evidence (RWE) for regulatory decision-making was a theoretical construct only a few years ago, but the industry is getting smarter

every day in making RWE the primary tool for establishing the value of its medicines, postmarketing. It's a real source of insight; virtually all therapeutic areas, at every stage of the product life cycle, are tapping in to it. Is AI the next wave that will completely transform the way we develop medicines? The jury is out; we will have to see. I see enthusiasm about the possibilities from AI, but I also continue to confront a lot of skepticism. In my view, however, this is a debate from the sidelines. It is now irrefutable that the field of medicine will have more data along with the capacity to interpret it for the benefit of more – many more – patients.

**What is the current state of collaboration within the industry on trials and drug development in general? The Hever Group of biopharma R&D leads has expressed concern about too much duplication of effort. Is this a concern for you?**

This was true in the past, but the situation has changed. Most of us in the industry realized some time ago that, to be effective, our collaborations had to be carefully structured and vetted to define their scope of work and to provide clarity on the expected results. There is no room for redundancy – the Innovative Medicines Initiative (IMI) the industry is funding in Europe should not tackle the same issues, with the same scope and solutions, that TransCelerate is pursuing. Pfizer works on both programs so we have an incentive to push back to ensure collaboration across consortia channels, or what our chief medical officer, Dr. Freda Lewis-Hall, refers to as “meta-collaborations.” One early action we helped initiate was to create a single repository of knowledge on what was actually going on in the industry collaborative space. Faster Cures, a division of the Milken Institute, stepped up to help and now manages a dedicated website (<http://www.consortiapedia.fastercures.org>) to monitor the work product of more than 500 research-based collaborations to ensure that such work avoids those obvious cases of “mission creep.”

**The infrastructure for the conduct of clinical trials is under stress. Is Pfizer using its size and resources to ensure you get the best from the teaching hospitals and academic institutions you depend on to deliver the results the FDA expects?**

Yes. We are active in efforts to embed our research capabilities in health systems and institutions here in the US and abroad. I serve on the board of the MedStar

Health Research Institute in Washington, DC. MedStar-Health operates a network of 12 hospitals in the District and Maryland, with over 4 million clinic visits and hospital admissions annually. We are working to leverage their system's scale and reach to stimulate more trial patient referrals, take advantage of their thousands of treating physicians for investigator and other research roles, and tap MedStar's investments in EHR technology to optimize trial conduct. It is part of an initiative to build a more strategic relationship with these large health systems.

**Can you provide more detail on the objective here?**

Finding the right investigation site is a growing challenge for trial management. In many trials, we must establish as many as 100 – or more – such sites, distributed among many disconnected institutional networks. Building more strategic alignments with a few big health system partners might allow us to reach the same number of patients with greater efficiency, along with a lot more opportunity in enabling data from a big system's integrated technology network, including EHR.

**Is there a Pfizer “best practice” you can cite that has helped advance the company's contributions to innovation in clinical trials?**

We leaned out far on the REMOTE trial (Research on Electronic Monitoring of Overactive Bladder Treatment Experience), which was the first trial conducted virtually under an FDA Investigational New Drug Application (IND), using digital and web-based technology that eliminated the need for participants to be treated at a physical clinic location. The objective was to replicate the results of an earlier in-person study on the Pfizer drug Detrol LA (tolterodine tartrate ER) and thus open the door for a more patient-friendly “virtual” approach to clinical research. The trial itself was not a total success, but it did demonstrate the viability of virtual as a new pathway that could work for patients. Since conclusion of the REMOTE study in 2013, at least three biopharma companies have invested in a virtual trial model, in each case with tangible financial support from the VC community working across multiple start-ups with a commitment to the approach. What I see as the real marker of success is the transparent approach we took in communicating our experience to others in

the industry and to the outside world, including collaboration with regulators like the FDA. We did this deliberately. I would rank as my own biggest accomplishment the more recent decision of Pfizer to report trial results to all participants and lead the industry in returning individual health data collected in our trials over to the patient. We have reinforced this through our advocacy work, in groups that range from the Multi-Regional Clinical Trials Expert Group (MCRT) to TransCelerate. I believe we have made the notion of providing deliverables to the patient acceptable and accessible to the rest of the biopharma industry.

**Looking at the regulatory field, is the FDA a roadblock to progress in “humanizing” the gold standard of the RCT?**

As an industry, we do not test the upper limits of what is required in drafting and conducting our trial programs. The constraining factor is not technology – nor is it regulation. When we launched the REMOTE study, FDA’s Center for Drug Evaluation and Research (CDER) director, Janet Woodcock, inserted a supportive quote, attributable to her, in our press release. My colleagues at Pfizer and the industry were amazed; they didn’t expect that level of support. It made it impossible to suggest the FDA was too conservative and did not want to see our experiment go forward. In addition, the Clinical Trials Transformation Initiative (CTTI) (<https://ctti-clinicaltrials.org>), which serves as a champion of appropriate use of new digital technologies in medicines development, could not have gotten off the ground without the decision of the FDA to push it forward. Personally, I believe the FDA wants us to do more so they have real plans to react to. They want it to stimulate their own thinking. Of course, it can be frustrating when you look at FDA guidance document calendars on a single strategic issue like RWE and realize it will take the next five years to fully implement them all. But it’s a mistake to brand the FDA as a luddite. The real barrier, in my view, is company culture and the willingness of colleagues to embrace change and an appropriate level of risk. Drug developers have a choice: opt for status quo thinking or be a catalyst for real innovation in drug development. That

decision requires individuals and leaders to appreciate that status quo itself brings risk.

**If this interview were to take place five years from now, in 2023, what would we be talking about?**

We’ll be discussing the rise of platform trials, based on the ability for multiple molecules to be tested and evaluated under a single master protocol, with a shared trial infrastructure powered by advanced electronic technologies. This will make it easier for patients to enter the right study tailored to their personalized disease profile. The process will be less burdensome for industry as there will be less need to create a specific infrastructure from one study to the next. The volume of data we capture will increase significantly, due partly to the onset of validated digital biomarkers, and it will be more accessible and convenient to obtain, at lower cost. In addition, I expect we will be looking at the complementary expansion of observational studies, building on the momentum from the National Institutes of Health’s (NIH’s) long-term All of Us Research Program (<https://allofus.nih.gov>) on precision medicine involving 1 million patient volunteers. And there is the Google Verily Life Sciences LLC Project Baseline (<https://projectbaseline.com>), a four-year observational study covering 10,000 people from diverse backgrounds to investigate risk factors to prevalent conditions like CVD and cancer. Both initiatives are collecting large amounts of data available to all comers and could seed the growth of the seamless patient profile, incorporating data from trials supplemented by ongoing information obtained observationally. Hence our work as drug researchers will be bolstered by a continuous flow of insights, drawn from a diverse, progressively richer database focused on individual health status, all registered consistently over time. In other words, in 2023 we will be talking about one big highway of data leading us forward – and away from those incremental trial-specific research detours that often turn out to be dead ends.

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# Microbiome Clinical Studies Loom Large In 2018

► By John Davis

2018 looks set to be the year when the microbiome comes of age, clinically at least. Data are expected from early clinical studies using an array of approaches, which, if successful, will drive increased business activity in this area and increased interest from big pharma.

The microbiome's proponents rate its prospects high. "The microbiome is one of two important fields for the future of medicine," claims the CEO of **Vedanta Biosciences Inc.** Bernat Olle, saying it is on par with gene editing for its future importance in advancing the understanding of human biology.

The microbiome field is both expanding and going deep in specific applications, he told *Scrip*, and manipulating microbiomes may have a role to play in diverse conditions including cardiovascular, CNS, cancer and some rare diseases. "The field may well need to prioritize where it wants to place its resources first," Olle said.

Big pharma may not, so far, be directly involved in microbiome R&D, but it is not ignoring the field, noted Isabelle de Crémoux, CEO and managing partner of Paris-based VC, Seventure Partners, who is expecting a "big transaction, either an acquisition or a collaboration" with big numbers, in 2018, or shortly thereafter.

"Many microbiome companies are now entering the clinical stage; there's more investment going into the field, and more companies being set up," said De Crémoux in an interview. When clinical results are obtained, microbiome companies are likely to attract collaborators including big pharma, and such companies might even enter the field by acquiring technology platforms. Seventure's Health for Life Capital fund is one that is focused on the microbiome and nutrition.

One stand-out during 2017 for the CEO of dermatology-focused microbiome company, **SkinBio Therapeutics PLC**, Cath O'Neill, was the research being conducted in academia and elsewhere on the gut-brain axis, and how the biology of the gastrointestinal tract can affect mood and even conditions like anxiety and depression. "That's a staggering thought isn't it," she told *Scrip*.

There's even a suggestion that the microbiome may play a role in autism spectrum disorders. San Francisco-based **Second Genome Inc.** said in Oct. 2017 that it was launching a study to evaluate the role the human microbiome might have on the pathology of autism spectrum disorders. (Also see "Second Genome CEO Predicts Paradigm Shift With Microbiome Discovery" - *Scrip*, 16 Feb, 2017.)

## Growing Interest

Interest in the microbiome is undoubtedly growing. Since 2014, more than 60 companies have been set up annually to explore some aspect of the microbiome, and the number of patents applications, and granted applications, is growing rapidly, reported de Crémoux. At the beginning of 2017, there were more than 600 granted patents involving the microbiome, just over a third from US sources, and more than 1,600 clinical trials underway in more than 13 different disease indications, she said.

De Crémoux highlighted the diverse approaches and different types of therapeutic being explored in the microbiome space, including NCEs, peptides, probiotics, bacteria and phages, and their application against numerous targets. In the immunoncology field, companies are evaluating microbiome-related peptides that could act as neo-antigens, and are also looking at combining their investigational products with IO drugs.

A biotech with a microbiome platform can also apply it across industry sectors. For example, the UK's SkinBio Therapeutics is developing a cosmetic, a medical device and a prescription medicine, based on its dermatology-based microbiome platform. The technology involves obtaining a lysate of a probiotic gut bacterium that can then be used topically in several settings. It could protect skin against UV damage as a cosmetic application, while for the medical device, certain bacterial lysates are being developed to prevent infection of surgical sites. Finally, for a pharmaceutical, a lysate is in early development for the treatment of eczema.

SkinBio listed on the UK AIM stock market in April 2017, raising £4.5m, but it's not the only company applying microbiome-related technology to dermatological conditions; the US company **MatriSys Bioscience Inc.** is evaluat-

ing the use of live biologic therapeutics (LBTs) platform in early Phase I/II studies in atopic dermatitis/eczema. (Also see “Venture Funding Deals: Takeda Ups Its Bet On Immuno-Oncology Play Maverick” - *Scrip*, 7 Feb, 2017.)

But one microbiome company that is likely to be closely watched during 2018 is Cambridge, Mass.-based **Seres Therapeutics Inc.** which started the Phase III ECOSPOR III study with SER-109, a biologically-sourced consortium of bacterial spores purified from healthy screened human donors, in the middle of 2017.

It plans to enroll 320 patients with multiply recurrent *Clostridium difficile* infections from sites in the US and Canada and if successful SER-109 could be the first FDA-approved microbiome product, according to the company. (Also see “Pipeline Watch: Phase III Starts For Seres’ SER-109, Leo’s Tralokinumab And Alkermes’ ALKS-5461” - *Scrip*, 16 Jun, 2017.)

A second US company, **Synthetic Biologics Inc.**, has two microbiome-related products that are poised to enter Phase III trials in 2018, SYN-004 (ribaxamase) for protecting the gut microbiome against the adverse effects of beta-lactam antibiotics, and SYN-010, to reduce the impact of methane-producing pathogens in order to treat the underlying cause of irritable bowel disease syndrome with constipation. (Also see “Synthetic Biologics CEO On Pipeline Advances And The Microbiome” - *Scrip*, 15 Dec, 2017.)

### Rational Consortia

The use of fecal “donations” to replace pathogenic bacteria in the gut with healthy bacteria has shown promise in the treatment of recurrent and refractory gastrointestinal infections like those caused by *C. difficile*, and some companies have taken the idea further by using pure clones of bacteria, an approach taken by Cambridge, Mass.-based Vedanta Biosciences, an affiliate of UK-quoted **PureTech Health PLC.**

Vedanta has built up a library of more than 40,000 bacterial isolates from around the world, many of which have been characterized, fully sequenced, and stored in a pure form. “It’s like a pharmaceutical company having a library of small molecules that can be screened for activity against a target,” Olle remarked.

Vedanta has also designed tools that can track, for example, several different strains of micro-organism that have

been administered to the gut at the same time, so that the durability of colonization can be measured with precision, in a manner analogous to measuring the pharmacokinetics of a chemical compound.

At the beginning of Dec. 2017, Vedanta started a Phase I study of its lead product, VE303, believed to be the first consortium of bacteria in powder form to enter the clinic, and aims to develop it for the treatment of recurrent *C. difficile* infections of the gastrointestinal tract. The oral capsules contain live bacteria sourced from the company’s clonal cell banks and manufactured in cGMP-compliant facilities. The Phase I study should be completed in the first-half of 2018, and a Phase II study should start later in 2018. The work is supported by Carb-X, a financing mechanism that provides non-diluting funding from the Wellcome Trust and from the US BARDA program.

Vedanta expects to start two other clinical trial programs in 2018; VE202, developed in its collaboration with **Janssen Biotech Inc.** and with potential in the treatment of inflammatory bowel disease, and VE416, a potential product for the treatment of peanut allergies in adults.

Further back in development is a bacterial consortia, VE800, which when combined with checkpoint inhibitors has been found to induce anticancer CD8+ T cells in animal models of melanoma and colon cancer, improving survival and showing infiltration into tumors. This follows work showing that patients who are non-responders to checkpoint inhibitors are depleted in bacteria that are strong inducers of CD8+ T cells. Vedanta is now working on the manufacture of the bacteria consortia with an IND planned for late 2018. The company raised \$50m back in 2016 to advance its potential products into the clinic. (Also see “Microbiome Drug Developer Raises \$50m For First-In-Human Studies” - *Scrip*, 6 Jun, 2016.)

Another company interested in the treatment of cancer is Japan’s **Anaeropharma Science**, whose lead product, an anaerobic bacterium, *Bifidobacterium longum*, has entered a Phase Ib/IIa clinical study in the US. The hypothesis is that it will proliferate in the anaerobic core of tumors, where one of its enzymes, a cytosine deaminase, will convert an administered cytotoxic agent into an active form, killing the tumor cells.

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# Gene Editing: A Powerful, Growing Modality In Regenerative Medicine

► By Amanda Micklus

These regenerative methods have far-reaching potential and mark an important next wave of research targeting genetically defined diseases, as well as chronic or life-threatening disorders that are underserved or not yet addressed.

Broadly defined, the regenerative medicine market encompasses a wide range of treatment modalities that help to repair, replace or regenerate lost functionality in tissue that has been damaged because of disease, injury or aging. How regenerative medicine is specifically characterized can vary, but it generally includes therapeutic- or pharmaceutical-based treatments, devices or types of engineered materials.

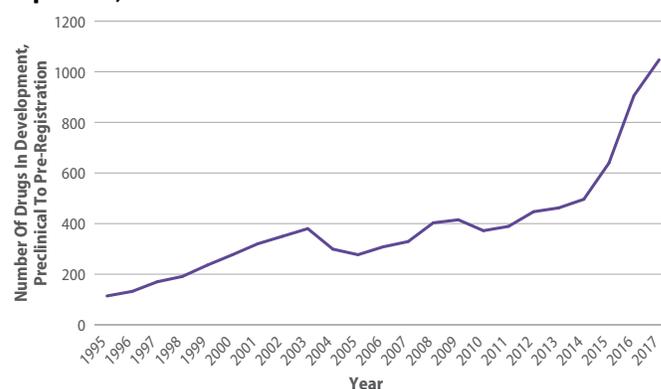
Government initiatives have been helping to move the regenerative medicine field forward, including the 2007 regulation introduced in the EU to govern advanced therapy medicinal products (ATMPs), and most recently, the creation of the regenerative medicine advanced therapy (RMAT) designation in the US under the 21st Century Cures Act.

In parallel, there has been exponential growth in the regenerative medicine therapy pipeline. In 1995, there were 114 drugs from preclinical through to pre-registration phases in development; by 2017, that figure had increased to over 1,000. The volume has been steadily growing year on year since 2010. A sharp uptick starting in 2015 was the result of an investment resurgence in this area, particularly in gene therapy, which had dropped off following patient deaths in clinical trials at the end of the 1990s. This revival was also prompted by the promise of the field following several product launches outside of the US.

The regenerative medicine pipeline is led by *in vivo* gene therapies, which account for 30% of the volume. The next generation of these products has improved in safety over initial treatments. Gene therapy developers have become more targeted when it comes to the patient populations being treated and more niche indications, and by focusing in on parts of the body that are somewhat separated from the immune system and antibodies that might attack. There have also been improvements in the delivery vectors



**Exhibit 1. Growth In Regenerative Medicine Pipeline, 1995–2017**

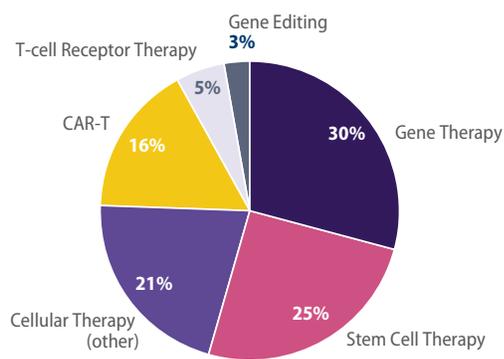


Source: Pharmaprojects

used. Altogether, the potential for gene therapies to offer single-treatment cures of genetically defined diseases will ultimately continue to move this class forward.

In the current pipeline, only approximately 3% of the volume of candidates are gene editing therapies. While the proportion is small, gene editing presents a unique and potentially paradigm-changing opportunity in the regenerative medicine market. The underlying principle of gene editing is to make precise changes to DNA in a cell. As opposed to gene therapy – which essentially provides

## Exhibit 2. Pipeline Therapies By Product Type



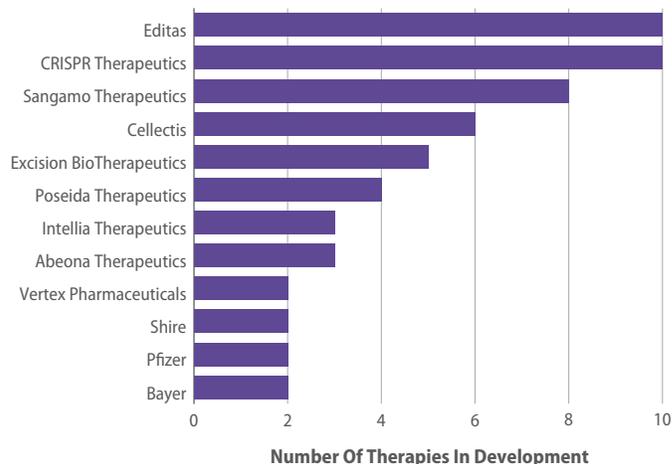
Source: Pharmaprojects

a gene or genetic instructions for the cell to use – gene editing permanently and more precisely changes a cell’s genome. There are high hopes this modality will provide a way to radically impact how diseases are targeted. The technologies in place to perform gene editing take varying approaches but ultimately the goal is to improve treatment, and possibly generate cures for thousands of inherited disorders caused by genetic defects.

Across the gene editing therapy pipeline, the most active companies range from discovery-stage biotechs to large pharmaceutical companies. The key clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) companies are well represented, including **Editas Medicine Inc.** and **CRISPR Therapeutics AG**, which each have 10 candidates in development (either as an originator or licensee). Among the big pharma (companies with annual revenues in excess of \$15bn) and mid pharma peer sets, **Shire PLC**, **Pfizer Inc.** and **Bayer AG** have stakes in gene editing.

The pipeline of gene editing drug candidates is dominated by clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) technology. There are nearly 60 gene editing therapies currently in development from preclinical through Phase II (the most advanced stage for any gene-edited candidate in the pipeline presently), and 74% of them use the CRISPR/Cas9 method. It is a clear indicator of the interest and investment in this latest generation of gene editing technologies for the long

## Exhibit 3. Most Active Gene-Editing Companies



Source: Pharmaprojects

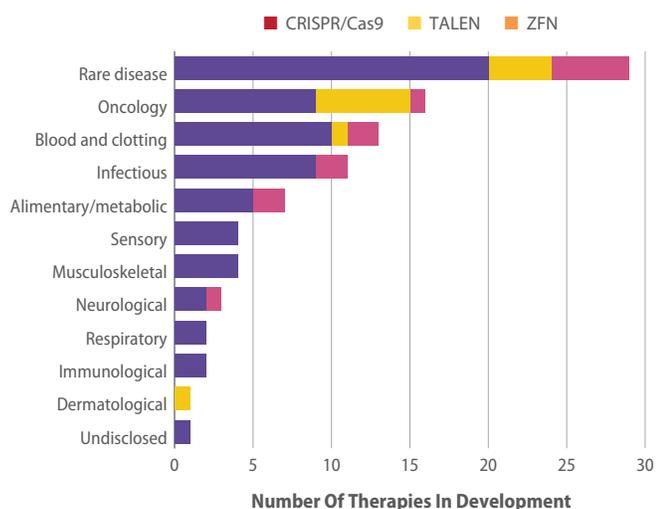
term, and companies’ vision that it has the most potential for producing new therapies as a result. At much smaller proportions, zinc-finger nuclease (ZFN) therapies account for 14% of the pipeline (all of these exclusively owned by **Sangamo Therapeutics Inc.**), and transcription activator-like effector nuclease (TALEN) candidates take a 10% share (sourced solely from **Collectis SA**, which has been the most advanced with TALENs programs in the pipeline).

While CRISPR/Cas9 candidates are the most abundant in the gene editing pipeline by volume, they are further back in development, reflecting the relative newness of this method in gene editing drug development. All of the CRISPR/Cas9 therapies are in preclinical studies, although there is ongoing academic research to test the application of CRISPR/Cas9 in humans. In contrast, ZFN, which has been in practice a lot longer by Sangamo, is incorporated into more advanced programs. The majority of ZFN candidates (those from Sangamo) are in Phase II.

Similar to CRISPR/Cas9, there is a higher volume of TALEN therapies in the preclinical setting, although Collectis has two candidates in Phase I, including programs partnered with Pfizer and Servier.

Rare diseases, many of which are genetically defined, are the primary targets for gene editing candidates in the pipeline. The same holds true when filtering down to most gene editing methods. For both CRISPR/Cas9 and ZFN technologies, the volume of therapies in development is higher for rare dis-

## Exhibit 4. More Gene-Editing Therapies For Rare Diseases



Source: Pharmaprojects

ases than for any other therapy area. Other primary therapy areas where overall gene editing is active include oncology, blood and clotting diseases, and infectious diseases. (It is worth noting that these therapy area categories also include rare diseases that are counted in the separate “rare disease” category.) CRISPR/Cas9 therapies have a broader reach, with development in several other areas. In contrast, TALEN editing candidates to date have been focused on cancers, many of which are rare diseases themselves.

Within the broad category of rare diseases are several unique indications that are active in development. Leading that group of rare disorders is thalassemia, for which four preclinical therapies are in the pipeline. Both **Poseida Therapeutics Inc.** and Editas are working on candidates themselves, while CRISPR Therapeutics and Sangamo Therapeutics have secured bigger partners: **Vertex Pharmaceuticals Inc.** and **Bioverativ Inc.**, respectively.

In addition to thalassemia, sickle cell anemia and Duchenne muscular dystrophy are being pursued within rare diseases via a high volume of gene editing therapies. Various cancer indications are also the subject of multiple gene editing candidates in the pipeline. Among the specified cancers, lymphomas are the most active (including Hodgkin’s lymphoma and myeloma, which are considered rare diseases), with this development exclusively being done

by Collectis. For many of the other oncology candidates, the tumor types at this point have not yet been identified because of the early-stage nature of the work being done.

Within the commercial biotech community, both **Intellia Therapeutics Inc.** and Editas could be the next to initiate Phase I trials in CRISPR/Cas9 therapies, and would be the first development-stage companies to do so. Intellia and Editas may file their IND applications within the next couple of years.

Intellia is potentially the closest to reaching the clinic with a CRISPR/Cas9 therapy for transthyretin amyloidosis, an abnormal build-up of amyloid deposits in organs and tissues. The company presented preclinical data at the American Society of Gene & Cell Therapy Annual Meeting in May 2017 showing a high reduction of serum transthyretin protein levels in two animal models. Intellia may submit its IND in early 2018. Since 2016, Regeneron Pharmaceuticals has been co-developing the transthyretin amyloidosis candidate and holds co-promotion rights.

Editas may have been ahead of Intellia in starting its human trials, but a manufacturing issue disclosed in May 2017 has delayed Editas’s IND filing to mid-2018. Editas’s lead CRISPR/Cas9 candidate aims to treat leber congenital amaurosis 10, a retinal disorder that causes severe visual impairment. Editas optioned this program, among others for ocular diseases, to Allergan in March 2017. Editas is still gathering preclinical data and now must contend with the manufacturing delay, which the company says is related to quality control around the input materials needed to produce the adeno-associated viral vectors. Editas’ CEO Katrine Bosley said the company had lost its time slot with its contract manufacturing organization.

Not to be outdone by the other two, CRISPR Therapeutics could be beginning its own human studies soon in Europe. In May 2017, the company said that it was planning to file a clinical trial authorization by the end of 2017 for its beta-thalassemia therapy CTX001, to which Vertex holds a licensing option under a 2015 deal. The manufacturing process has already been vetted by Germany’s Paul-Ehrlich Institute and the UK’s Medicines and Healthcare Products Regulatory Agency.

Published online in *Scrip*, 27 November 2017



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## CLINICAL RESEARCH TEAM OF THE YEAR

Paratek Pharmaceuticals,  
Omadacycline Clinical Development Team

## CLINICAL TRIAL RESULT OF THE YEAR

Paratek Pharmaceuticals, Phase 3  
Clinical Trial Results For A Novel Antibiotic



**We are honored to be recognized** alongside the other impressive nominees, all of whom are pushing innovation and advancing research for the benefit patients.

Thanks to the tremendous contributions of the Clinical Research Team at Paratek, we have successfully executed a global Phase 3 development program for omadacycline, a novel antibiotic that is currently under review by the FDA for the treatment of community-acquired bacterial pneumonia and acute skin and skin structure infections.

Across the industry, our work is vitally important; we do it because we know that patients are counting on us. At Paratek, we appreciate the opportunity to celebrate that spirit and commitment. We have an exciting year ahead and look forward to witnessing the success of the many other companies honored at the CARE Awards and the advances they will make for patients.



# Alzheimer's Biomarkers Gain Prominence In Drug Development Guidance

► By Brenda Sandburg



Striving to advance Alzheimer's disease drug development, the US FDA has revised its draft guidance to give sponsors more leeway in trial designs.

The new draft guidance, released on Feb. 15, specifies categories of patients based on different stages of disease progression, and notes the clinical endpoints acceptable for these stages. The agency decided to revise its initial guidance in response to discussions with the patient community. The document is one of five guidances for development of drugs to treat neurological conditions that the agency issued as part of the modernization of its new drug review program.

"This draft guidance has a potential for multiple advances," Maria Carrillo, chief science officer at the Alzheimer's As-

sociation, told the Pink Sheet. "It opens the door for more research targeting cognition as a single endpoint" and not waiting until someone has functional disability as well, and second, it "opens the door to biomarker alone studies."

FDA issued the initial draft guidance for developing drugs for the treatment of early stage Alzheimer's disease in 2013. It advised sponsors to demonstrate evidence that a drug would have a beneficial effect on both cognition and function.

In the revised guidance, FDA says the independent assessment of daily function and cognitive effects is an acceptable approach. And it states that "for drugs with the potential to lead to measurable functional benefit without

a corresponding cognitive benefit, assessment of an independent cognitive endpoint is important.”

For patients in the earliest clinical stages of AD (Stage 2 patients), the agency said it “will consider strongly justified arguments that a persuasive effect on sensitive measures of neuropsychological performance may provide adequate support for a marketing approval.”

The agency explained that such arguments should be predicated on the certainty of diagnosis of enrolled patients, the certainty of their future clinical course, and the certainty of the relationship of the observed effects on sensitive measures of neuropsychological performance and characteristic pathophysiological changes to the evolution of more severe cognitive deficits and functional impairment.

### Does Biomarker Represent Change In Clinical Outcome?

With regard to biomarkers, the guidance says: “Assessment of various biomarkers may provide supportive evidence for a drug that has an established clinically meaningful benefit, but the effects on biomarkers in AD are not sufficiently well understood to provide evidence of a persistent effect on disease course.”

“Currently, there is no consensus as to particular biomarkers that would be appropriate to support clinical findings in trials in early AD. For this reason, sponsors at present have insufficient information on which to base a hierarchical structuring of a series of biomarkers as secondary outcome measures in their trial designs,” the guidance says. “Sponsors are therefore encouraged to analyze the results of these biomarkers independently, though in a prespecified fashion, with the understanding that these findings will be interpreted in the context of the state of the scientific evidence at the time of a future marketing application.”

Carrillo explained that researchers could look at biomarkers and plan a long enough clinical trial so that there was sufficient evidence that the biomarker represents a change in clinical outcome. If no such evidence emerges, a follow-up study would be required to confirm the predicted clinical benefit.

Carrillo noted that there are quite a few trials being conducted through public-private partnerships that are using this approach. They include the A4 (Anti-Amyloid in Asymptomatic Alzheimer’s) study, which is funded by the National Institute on Aging, **Eli Lilly & Co.**, and several philanthropic organizations and is coordinated by the University of Southern California’s Alzheimer’s Therapeutic Research Institute. Another trial is the DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit), a prevention trial for at-risk families with dominantly inherited Alzheimer’s disease, based at Washington University School of Medicine.

Carrillo commended FDA for working in partnership with the scientific community on an evidence-based approach to modernizing the guidance.

Carrillo and FDA’s Billy Dunn, director of the Division of Neurology Products, and the other members of the National Institute on Aging-Alzheimer’s Association workgroup, are co-authors of a paper proposing a biomarker-based definition of Alzheimer’s disease for use in research settings, which is scheduled to be published in April in *Alzheimer’s & Dementia: the Journal of the Alzheimer’s Association*.

### A Sector Full Of Setbacks

The guidance comes as companies have faced setbacks with Alzheimer’s disease investigational programs. **Merck & Co. Inc.** announced on Feb. 13 that it was discontinuing development of its late-stage Phase III candidate verubecestat, a beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitor for treatment of prodromal Alzheimer’s disease. (Also see “M&A Pressure Mounts For Merck & Co After Alzheimer’s Drug Dismissed” - *Scrip*, 14 Feb, 2018.)

And the following day, **Biogen Inc.** announced it was increasing the patient size of its two ongoing Phase III studies of its potential Alzheimer’s therapy aducanumab. The company did so to maintain the statistical power of the studies after more variability was seen in the primary endpoint than expected. (Also see “Biogen Spooks With Phase III Aducanumab Changes” - *Scrip*, 15 Feb, 2018.)

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Published online in *Pink Sheet*, 15 February 2018

# Thank You for Awarding Theravance Biopharma and Mylan the 2018 Clinical Partnership of the Year



Our core purpose is creating medicines that help improve the lives of patients suffering from serious illness. Our research efforts are focused on inflammation and immunology, with the goal of designing localized medicines that target diseased tissues, without systemic exposure, in order to maximize patient benefit and minimize risk. We possess unique experience in developing localized medicine for the lungs to treat respiratory disease. Those insights are part of the foundation of knowledge we rely on in pursuit of transformational medicines to address significant needs of patients.

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 **CLINICAL PARTNERSHIP OF THE YEAR**

# Theravance Biopharma And Mylan



Ed Moran of Theravance Biopharma (left) and Pat Weaver of Mylan Respiratory (center) receive the award from Medidata Solutions' Vice President of Product, Stacey Yount

**We are proud to receive** the **Clinical Partnership of the Year Award** with our great partner, Mylan. Together, we have worked relentlessly to advance revefenacin, a novel therapeutic which we believe has the potential to deliver significant benefits to chronic obstructive pulmonary disease (COPD) patients.

With the core purpose of creating medicines that help improve the lives of patients suffering from serious illness, the entire Theravance Biopharma team strives to apply insight and innovation at each stage of our business, from research to commercialization.

Our research efforts are focused in the areas of inflammation and immunology with the goal of designing localized medicines that target diseased tissues, without systemic exposure, to maximize patient benefit and minimize risk.

We thank those that voted for us to receive this honor, as well our team members who contributed to the revefenacin development program. Most importantly, we express our gratitude to the patients and investigators who participated in clinical trials of revefenacin.



# Pharma R&D: Annual Review 2018

► By Ian Lloyd

## Introduction

Welcome to Pharmaprojects' 2018 review of trends in pharmaceutical R&D. For over a quarter of a century now, I've been taking an annual look at the evolution of pharma R&D, and in this report, I'll look at how things are sounding for the industry at the start of 2018. We'll assess the industry trends by examining the pipeline using data from Informa Pharma Intelligence's Pharmaprojects, part of the Citeline suite of products, which has been tracking global drug development since 1980. This report will be followed up by our annual supplement reviewing the New Active Substance launches for the year just gone. But here, we will be focusing on research and development as it is now, how it is changing, fluctuating and being fine-tuned, and where it has been headed during 2017.

As a lifelong music lover and sometime DJ, I've chosen a musical theme for this year's review. Drug development itself can be likened to a symphony, album, mixtape or DJ mix: it's not enough to just have all the individual parts in place; for a really harmonious journey, each element needs to flow into the next in a way which is coordinated, balanced and mellifluous. The instruments need to be in tune and the constituent parts must be moving at sympathetic rhythms. This report will look at the hits and misses currently flooding the pharma airwaves. Is the industry's top tune *The Edge of Glory*, or is it more a case of *I Will Survive*, or even worse, *The End*?

Music, like pharma R&D, always evolves over time. I often wonder what the 14-year-old me, surrounded by disco, punk, new wave and Abba in 1978, would have made of the music I listen to now in 2018. Would it have sounded strange and futuristic, or would I have been surprised by how little the fundamentals had changed? And what I wouldn't give to hop into a time machine and sample the sounds of a further 40 years hence! Just like the pop world, the pharma industry is in a constant state of flux, evolution, and progress, but I suspect in many ways, similarly, the fundamentals haven't really changed as much as we might imagine. The song remains the same.

However, there's no doubting that science and technology continue to march to the beat of progress, and over 40 years, techniques for compound identification, patient

screening, and drug delivery have changed beyond recognition. In the music world too, techniques for delivery have rapidly changed; in my lifetime alone, vinyl gave way first to cassette tape, then to CDs, which have themselves been replaced first by digital downloading that is now giving way to streaming. But still in pharma, some classical techniques, like vinyl records, stubbornly refuse to die.

One of the most common criticisms of the current pop charts is how homogenous they have become. There is an argument that streaming, with the ease it provides of skipping to the next track after just a few seconds' listening, is leading popular artists to avoid anything which sounds jarring or stands out too much from the crowd. This is leading to a narrowing of the musical palette. Some parts of pharma stand accused of succumbing to a similar artistic conservatism, as companies abandon high-risk areas and focus on where they feel more comfortable – witness Pfizer's recent decision to exit the notoriously failure-prone neuroscience arena. The big stars are increasingly moving MOR (middle- of-the-road), leaving the experimentalism more to outsiders and emerging talents.

All this is taking place to a background of political discord more atonal than an orchestra playing a Schönberg piece in a wind tunnel. The freestyle jazz- like tweets squeaking out from President Trump's Twitter account have led many to want to stick their fingers in their ears, while his emissions on pharma have sent mixed messages to say the least – the populist impulse to bash the industry often tonally clashing with his business-focused actions, like reducing the corporate income tax rate. Meanwhile, in the UK, everything appears to have been drowned out by the cacophony that is Brexit. Elsewhere in Europe, there are further Wagnerian rumblings as far-right parties continue to make advances in national elections, a trend likely to continue in Italy and Hungary this year. In Europe, where once it seemed all were in harmony, there have been “musical differences” which now threaten to split the band. Against this inharmonious soundtrack, can pharma continue to expand its soundscape and score some genuine global number one megahits?

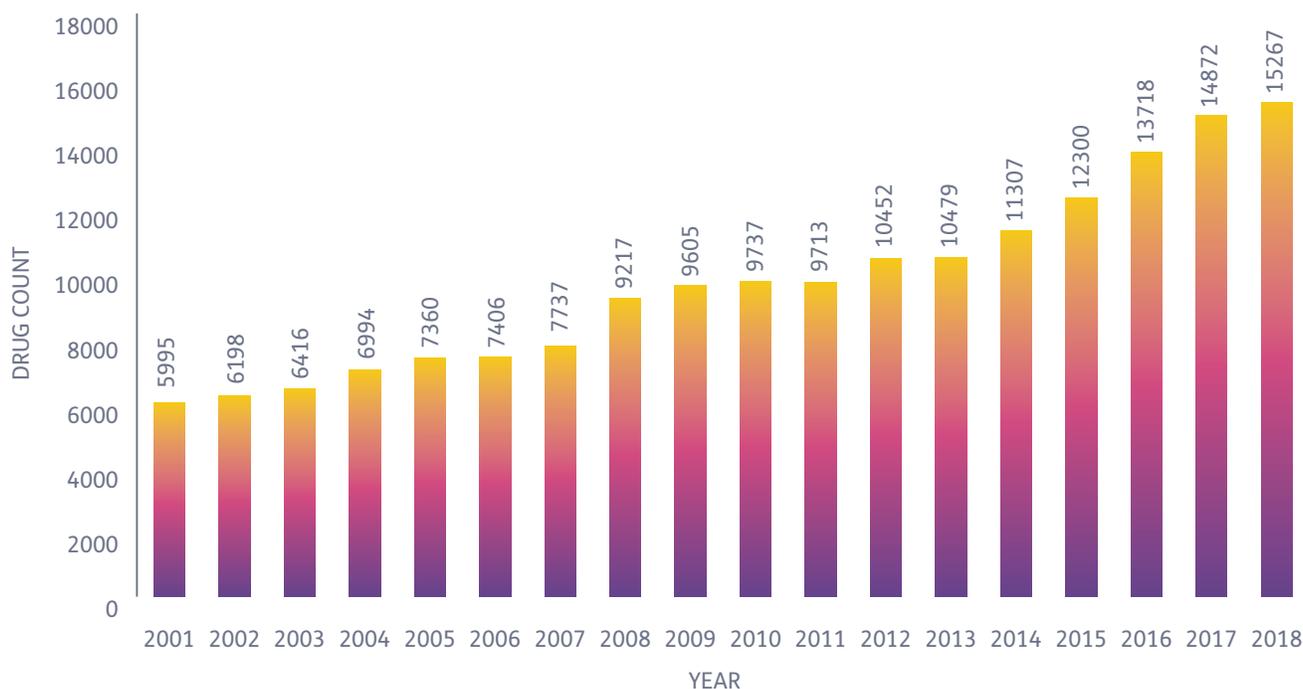
## Total Pipeline Size

### Still hitting the high notes, but the tempo slows

We start our symphonic survey by introducing the headline act: this year's figure for the total number of drugs in R&D. Figure 1 shows the total number of candidates in the R&D pipeline as of January 2018, and how this has changed since the start of the century. By pipeline here, we mean that we are counting all drugs in development by pharma-

ceutical companies, from those at the preclinical stage, through the various stages of clinical testing and regulatory approval, up to and including launch. Launched drugs are still counted, but only if they are in still in development for additional indications or markets.

Figure 1: Total R&D pipeline size by year, 2001–18



Source: Pharmaprojects®, January 2018

This year, there has been another increase in the total pipeline size, which now stands at 15,267 – another *All Time High*. But while this is undeniably impressive and represents the seventh consecutive year of expansion, there has been a slowdown in the rate of increase this year, with the 2018 pipeline growing by just 2.7%, well down the scale from last year's rate of 8.4%. Is pharma hitting a bum note? Well, not necessarily. Continuing efforts by our editorial team to improve the currency and accuracy of our pipeline data may have somewhat flattened the figures this year more than in previous ones. More regular reviews of drug records

have, in some cases, led to greater 'weeding out' of drug projects which are lying dormant or have become inactive. It's tough to estimate the extent of this effect, but it's fair to say that in the absence of any organic pipeline growth, this would have led to a net shrinkage in the number of R&D projects. Ergo, the pipeline is still growing, it's just a little harder to ascertain at what rate.

Pharma, like music, often undergoes a long and complex process before its products are released to consumers. The US rock band Guns N' Roses famously took 15 years to record

their album *Chinese Democracy*, allegedly spending around \$13m in the process (other groups have reportedly taken even longer, but may not have been officially together throughout the period). Drug development can take just as long, can cost up to 1,000 times as much, and can similarly undergo changes of focus, content and production along the way. Finally, after countless remixes, both industries must release their products to their markets and see how many units they can shift. Poor album sales can see an act rapidly dropped from their label's roster; similarly, disappointing productivity or prescription levels place a pharma company in peril. Lack of success for both industries will lead to trimming of pipelines. Ultimately, for both pharma and for pop, it's about the dollars, euros and yen.

So, the continuing growth of the pharma pipeline would seem to be intrinsically linked to its output. Early reports on the 2017 pharma new releases indicate that it was a good year. In 2016, the number of new active substance (NAS) launches was lower than the preceding year (41 in 2016 versus 46 in 2015), but early indications are that the 2017 number will exceed that – certainly US new drug approvals, at least, have hit a 21-year high. We are in the process of carefully curating our data to produce the definitive global figure, and will report this and highlight other NAS trends and innovative drugs in our “NAS Supplement” to this report, which will be published in the spring. But so far, the fact that the overall pipeline numbers continue to grow is a positive sign, even if the industry hasn't exactly turned the volume up to eleven.

## The 2018 Pipeline by Phase

### Plenty of debut singles, but the middle-eight is sounding a bit flat

Breaking the pharma pipeline down its phases – the separate movements of pharma's symphony – gives a bit more insight into the shape of the pharma industry in 2018. Figure 2 does just this, looking at the global status of each drug in the pipeline so that each is counted only once. There are some interesting variations in pitch across the pharma album this year. The number of drugs at the preclinical stage of development, the figure that one would expect to be most prone to the effects of internal editorial actions, actually shot up by 7.3%, far outpacing the pipeline's average growth rate to move beyond 8,000 for the first time. This was fuelled by a massive 3,807 new drugs debuting in development, although this figure itself fell slightly short of 2016's record 4,005. Many of these preclinical projects are coming out of tiny start-ups, the pharmaceutical equivalent of a teenager uploading their bedroom crooning to YouTube for the first time

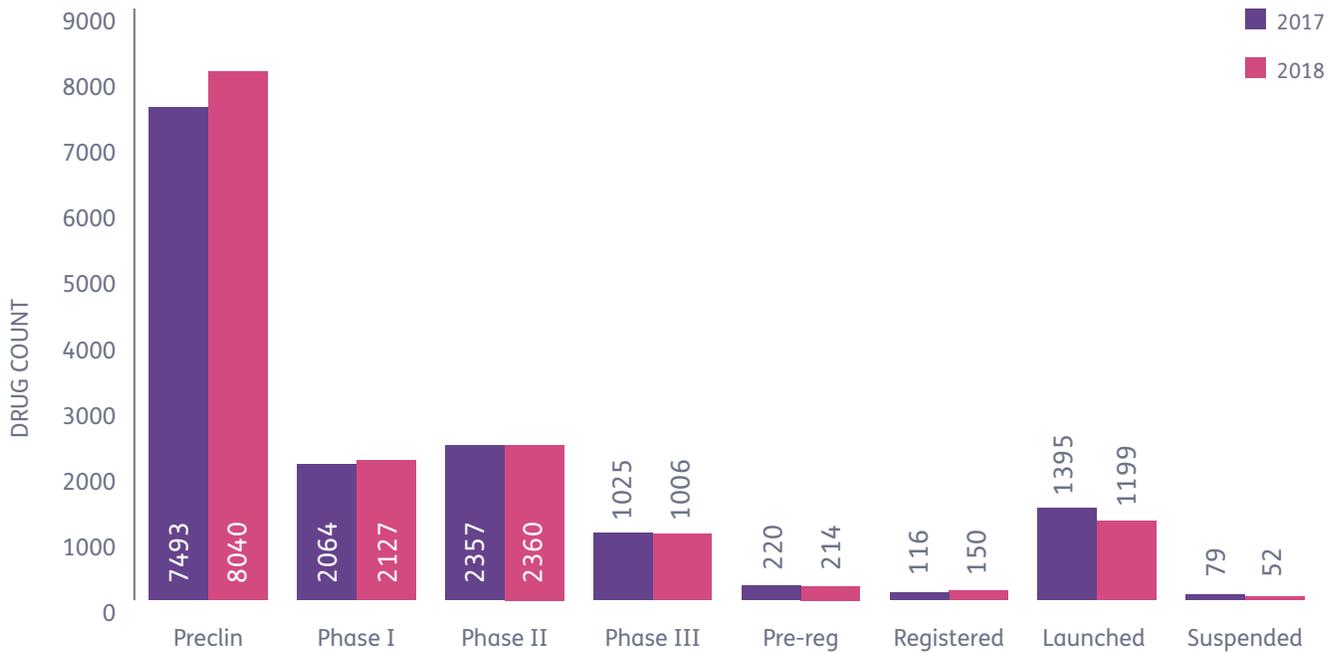
At the other end of the scale, we unearth a big contributor as to why the overall pipeline expansion rate appeared to slow this year. Included in our figures are drugs which are launched, but still under active development for additional markets or additional indications. But once a drug is no longer being rolled out further and its development is essentially complete, we move these drugs over to the Fully-Launched status and they no longer count in our pipeline figures. As Figure 2 shows, despite around 100 drugs being

launched in 2017, the number of active launched drugs fell by around 200 – indicating that around 300 launched drugs must have exited the active space in this manner.

However, it is at the clinical development stages, where the data are usually considered the most robust due to integration with our sister product Trialrove, that the tune begins to hit a minor key. The number of drugs currently at the Phase I stage has increased slightly above the overall rate (up 3.0%), but the figure for Phase II appears to be flat, while there is actually a decline of 1.9% at Phase III (Figure 2). To put this into more context, Figure 3 looks further back down the years to get a better handle on emerging trends over time.

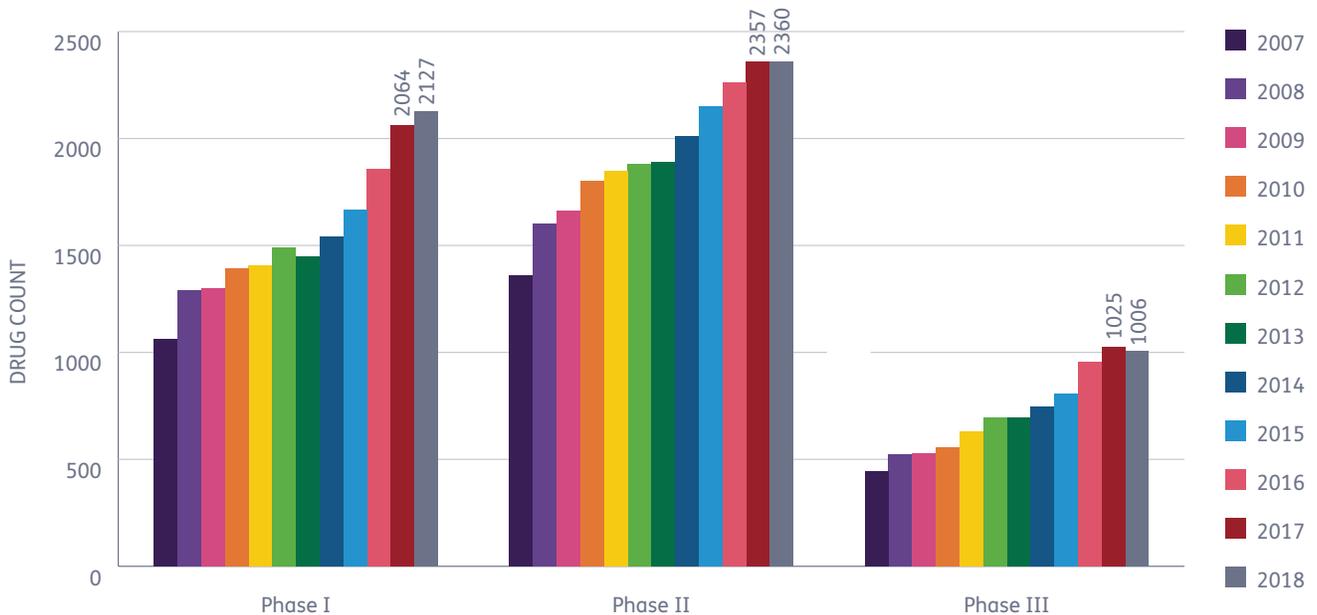
Undoubtedly, the previously described tightening of our internal drug review process will have contributed to depressing the 2018 numbers here. But as Figure 3 shows, rates of increase were already slowing last year at the Phase II and Phase III stages, so this may just be a continuation of that trend. This may not be entirely a bad thing. Clinical trials are a huge expense, so the industry simply having more and more drugs in the clinical stages of development, unless it is similarly matched by increases in drug launches, will become untenable. As can be seen, the numbers of drugs at each clinical stage are about double those seen a decade ago. Sadly, the level of drug launches is not.

**Figure 2: Pipeline by development phase, 2018 versus 2017**



Source: Pharmaprojects®, January 2018

**Figure 3: Clinical phase trends, 2007–18**



Source: Pharmaprojects®, January 2018

## Top Companies

### Novartis is still top of the pops

Like the yearly best-selling records lists, one of the more hotly anticipated charts in the Pharma R&D Review is the list of companies with the biggest pipelines. In the music world, 2017's chart-topper, depending on your source and the formula used to calculate it, was either *Despacito*, an earworm latinopop ditty by Luis Fonsi and Daddy Yankee with an incredible over 4.6 billion YouTube views and 1.3 billion streams in the US alone, or the ubiquitous Ed Sheeran's *Shape of You*, which was the best performing track in the US and number one in 44 countries. No pharma company can claim such an extraordinary global reach, and it's to Switzerland that we look for our top company this year again. Novartis has cemented its position at the top with a second year heading the hit parade, though its pipeline size has shrunk by 28 drugs, meaning that it has only a narrow lead over its nearest rival this year. That distinction goes to Johnson & Johnson (J&J), which climbs up three places to claim the 2018 runner-up position and is one of only two Top 10 acts to actually increase the sizes of their portfolios (the other being Takeda). However, given that it acquired over 20 drugs by completing its takeover of Actelion, which

made its farewell tour in 2017, J&J's overall increase in pipeline size of two candidates feels somewhat less impressive. In fact, in an unprecedented scenario, only six of the Top 25 actually grew their pipelines at all. It would seem that 2017 saw its mainstream acts floundering somewhat (Table 1).

Despite this, AstraZeneca was also able to rise three places in the chart to claim third position, with Pfizer and Roche completing the Top Five. The latter ties with GlaxoSmith-Kline (GSK) and Merck & Co in terms of number of R&D products, but these companies are placed at six and seven, respectively, by considering the number of products which each company originated, rather than in-licensed. GSK posts the biggest fall within the Top 10, new CEO Emma Walmsley having implemented a radical refocusing of the company's pipeline during the year. Once again though, there have been no personnel changes within the Top 10, and no major mergers or acquisitions to form new pharma supergroups. There's just one new entry in the Top 25, as Gilead re-joins the band after a year out (Table 1).

**Table 1: Top 25 pharma companies by size of pipeline**

Position 2018 (2017)	Company	No of Drugs in Pipeline 2018 (2017)	No of Originated Drugs 2018
1 (1)	Novartis	223 (251)	138
2 (5)	Johnson & Johnson	216 (214)	116
3 (6)	AstraZeneca	205 (213)	117
4 (3)	Pfizer	192 (232)	126
5 (7)	Roche	191 (206)	114
6 (2)	GlaxoSmithKline	191 (250)	111
7 (4)	Merck & Co	191 (229)	109
8 (8)	Sanofi	179 (193)	78
9 (10)	Takeda	164 (141)	96
10 (9)	Bristol-Myers Squibb	134 (144)	96
11 (11)	Eli Lilly	121 (126)	84
12 (13)	Bayer	111 (112)	80

Position 2018 (2017)	Company	No of Drugs in Pipeline 2018 (2017)	No of Originated Drugs 2018
13 (12)	Allergan	108 (122)	49
14 (14)	Daiichi Sankyo	105 (105)	60
15 (16)	AbbVie	98 (102)	40
16 (19)	Boehringer Ingelheim	92 (88)	64
17 (15)	Astellas Pharma	92 (104)	48
18 (21)	Otsuka Pharmaceutical	89 (86)	47
19 (17)	Amgen	87 (94)	54
20 (23)	Celgene	85 (76)	32
21 (20)	Eisai	84 (87)	50
22 (18)	Shire	67 (93)	21
23 (27)	Gilead Sciences	66 (62)	46
24 (22)	Teva	66 (82)	30
25 (25)	Ligand	65 (66)	19

Source: Pharmaprojects®, January 2018

There may not have been any wholesale punk-style revolutions in pharma, and last year saw less acquisitive activity in general from the big 10. Aside from the aforementioned J&J/Actelion deal, notable M&A activity was seen at Novartis, which acquired Ziarco; Merck & Co col-

lected Rigontec; Sanofi took over Protein Sciences; Takeda absorbed Ariad; and Bristol-Myers Squibb gobbled up IFM Therapeutics. By no means a vintage year for mergers and acquisitions then, perhaps a sign of the effects of global political uncertainties.

## Top Therapies

### Could cancer's solo ambitions break up the band?

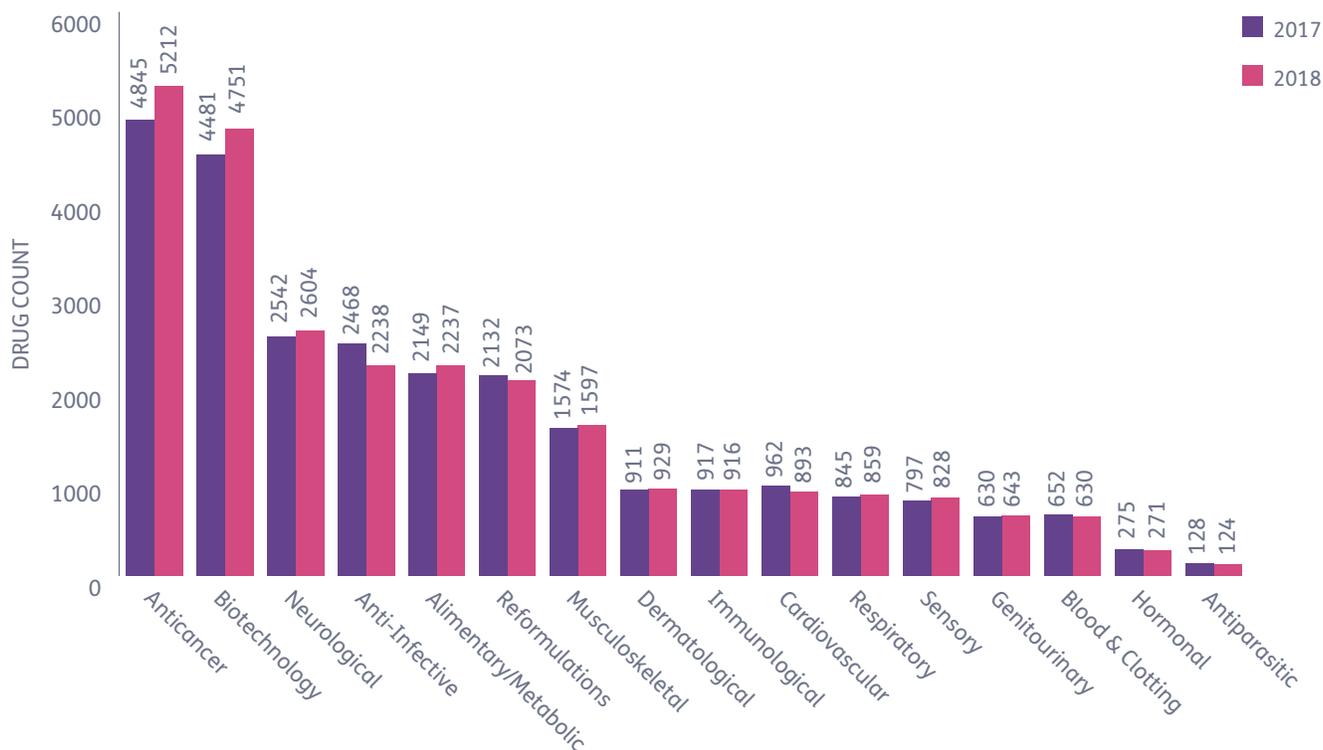
Pop or rock? Dance or metal? Country or indie? Music and its fans are obsessed by genres. Is it better to focus your energies on just one and get really into its minutiae, or to have a varied style-hopping collection? Does broad taste make you a dilettante, or narrow taste a trainspotter? Such issues have fuelled many a late-night debate, and no doubt fractured a few friendships. Something of a similar discussion has been underway in pharma for the past few years. Previously, it was not uncommon for a Top 10 pharma company to have interests spanning the whole gamut of therapeutic areas.

This is now becoming increasingly rare, as even the biggest companies have narrowed their focus to a handful of areas in medicine. Is this a good thing, or might it lead to a certain homogeneity of approach, where everything starts to sound the same?

To investigate this, let's first look at the numbers of pipeline drugs under development in each of the broad therapeutic areas – pharma's musical genres, if you will. Of course, just as a piece of music can fit into more than one category, many drugs are under development for diseases in more than one therapeutic area. Hence there can be 'double-counting' here: a drug under development for cancer and immunological indications will count towards both categories' totals.

Figure 4 presents both the 2018 and 2017 data for this metric, and is particularly interesting this year, because the lower overall growth rate now means that while growth is sustained in many therapeutic areas, several have seen actual declines this year.

Figure 4: The R&D pipeline by therapy group, 2017 and 2018

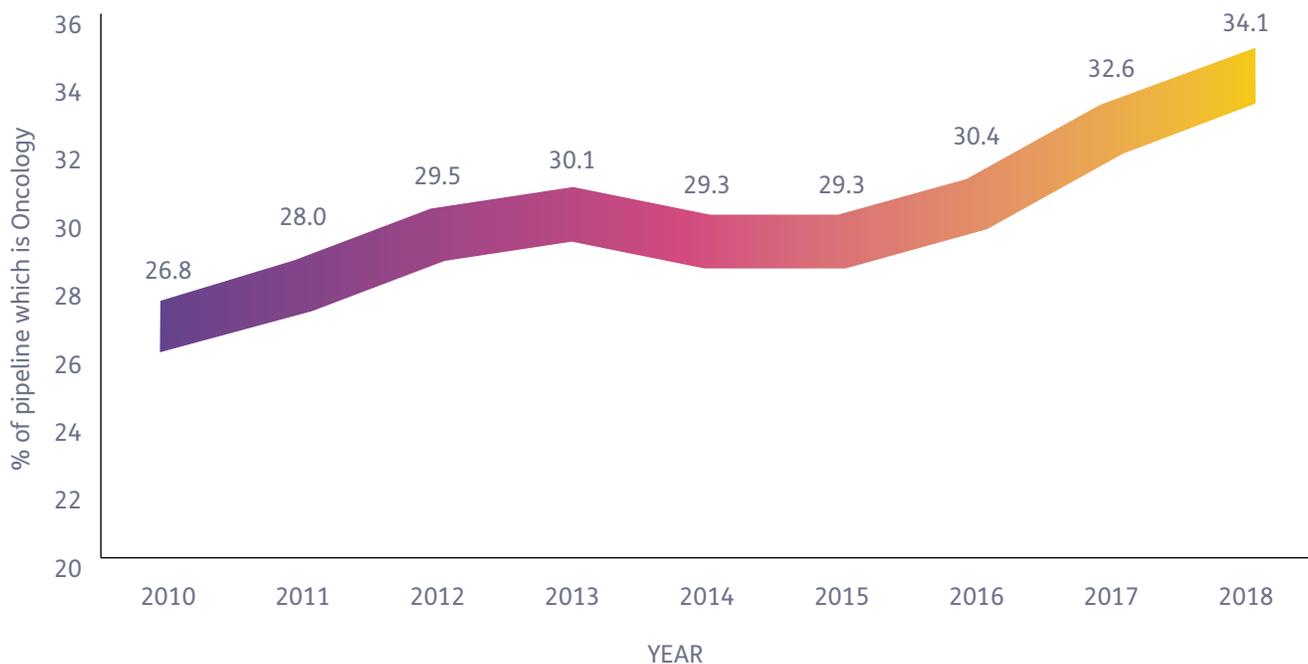


Source: Pharmaprojects®, January 2018

Still chart-topping, cancer posts a 7.6% increase in the number of candidates this year, a growth rate which is close to three times that of the overall pipeline. It's instructive to put this into the wider context of how its share is increasing year-on-year. In Figure 5, you can see that now, over a third of all drugs in development have at least one oncology indication attached to them, whereas it was just over a quarter at the decade's start. That is a fairly extraordinary statistic, and is akin to when the lead singer of a band starts to garner all the attention, usually producing general disgruntlement among the other members (US group Blondie famously started a 'Blondie is a band' campaign in the late 70s, after lead singer Debbie Harry started getting a disproportionate amount of the press coverage). So, if cancer is hogging the limelight, what is at the expense of?

Well, the biggest decline is seen in anti-infectives, which with 2,238 candidates reports a 9.3% shrinkage in its pipeline, at a time when, arguably, there has never been a greater need for new drugs in this area. This almost entirely reverses the big increase of 11.1% seen in this group of drugs in 2017. The other therapeutic area to majorly lose out was cardiovascular, down 7.2%, while immunological and blood & clotting also posted declines. For those worried that cancer's power within the band is becoming disproportionate, there was some comfort in that second-placed neurologicals also grew, at around the average rate of 2.4%. This is despite underperforming last year and no sign yet of the breakthroughs needed in Alzheimer's and other tough-to-crack CNS diseases (Figure 4).

**Figure 5: Proportion of the pipeline which is focused against cancer, 2010–18**



Source: Pharmaprojects®, January 2018

## Despite Inharmonious Times, Pharma Keeps on Rockin' and Rollin'

As 2017 fades out, should pharma be singing joyfully at the top of its voice like an X-Factor wannabe, or mumbling miserably like the late, great, Leonard Cohen? Whatever side of the debate you're on, few would disagree that political polarisation increased further through the year, and it can feel like the world is sounding more discordant than ever. The counterpoint to this is that, despite a seemingly never-ending chorus of disapproval, pharma seems to be doing OK – even if there is an element of it sticking its fingers in its ears and la la la-ing very loudly.

Record levels of new drug approvals in the US and continuing pipeline expansion last year, albeit at a lower rate, would seem to suggest that things are humming along nicely for the industry. And as our forthcoming NAS supplement to this report will reinforce, there were some genuinely innovative drugs brought to market last year. But not everything is moving along *brilliante*. There are fewer drugs in Phase III trials this year, most Big Pharma firms have smaller pipelines, and levels of innovation are not where they should be. Both the fragility of the EU as Brexit proceeds, and the unpredictable nature of the US administration – at the time of writing, the US government is in one of its periodic shutdowns while a budget cannot be agreed – are threatening to undermine confidence. Few pharma CEOs will be skipping to work whistling a happy tune.

The noise around drug pricing issues is likely to be moving towards a crescendo. One area where the pharma and music industries have markedly diverged is in the cost of their goods. Over the past 50 years, music has progressively become much cheaper, as manufacturing and distribution overheads all but disappeared with the move to digital delivery. I have many 12" singles in my collection in my spare room which cost £8.99 twenty years ago, whereas now, a track rarely costs more than 99p to download, to say nothing of the streaming services' subscription propositions.

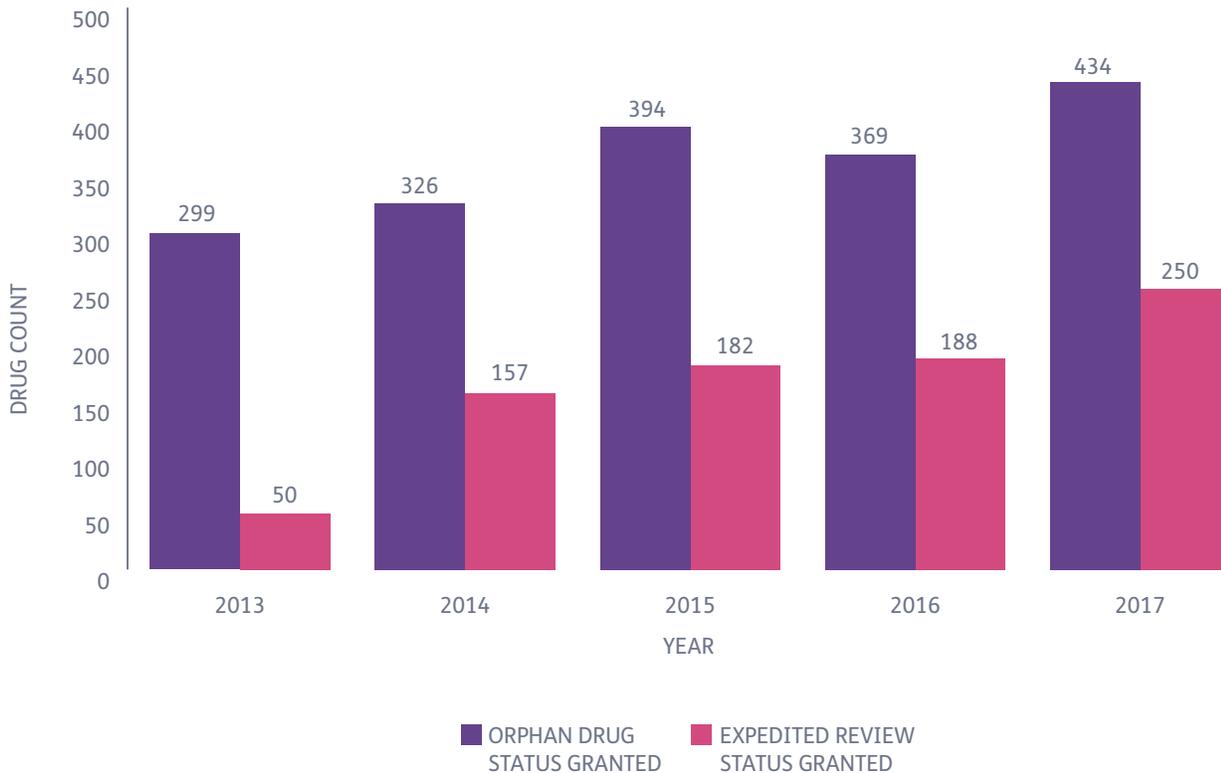
Paradoxically, the price crash has led many to not want to pay anything at all for music – hence the rise of illegal downloads. All of this has benefitted the consumer hugely, but made it much more difficult to make a living in the music business if you are an artist.

This is in sharp relief to the situation in pharma, where the expense of drug development has spiralled, leading to soaring prices facing payers, and ultimately consumers too. Whereas arguably the changes to the music industry have resulted in its democratization, the burgeoning costs, particularly of niche products and those for rare diseases, are increasingly restricting patients' access to the latest new releases. Payers are starting to push back, and the industry can expect to be held more and more accountable for its pricing strategy. Increasingly, we can expect questions to be asked as to whether drug prices are really so high because of their intrinsic development costs, or because Big Pharma simply isn't very efficient at doing what it does.

There's no doubt that rare diseases are one sphere still setting the industry's pulses racing at an ever faster BPM. As of January 2018, 4,615 drugs, or just over 30% of the pipeline, are under development for at least one rare disease. The orphan drug status route is also continuing to gain traction, with Figure 6 showing that a record number of orphan designations were granted in 2017. Another issue with this approach is that developing drugs for orphan indications can be very first world-centric, since developing countries tend to focus their limited funds on diseases affecting the largest populations, and don't tend to have orphan drug programmes anyway. The graph also shows that the various schemes which the major territories have in place to fast-track approval for drugs where there is greatest need also showed higher uptake in the year just passed.

However, the issue of drug pricing may put a check on the headlong rush into rare diseases, and there are many common conditions which require urgent attention anyway. Successfully launching an Alzheimer's drug which actually reversed the course of the disease would be more lucrative than Britney Spears' just-concluded Vegas residency. The infectious disease area desperately needs new antibiotics, preferably before the last of the existing agents cease to work due to resistance. Despite all of the investment, cancer remains a major threat. And cardiovascular diseases, in the form of ischaemic heart disease and stroke, are still the world's biggest killers, egged on by poor lifestyle choices. There is much to be done. To solve these and myriad other problems, pharma must break out

**Figure 6: Rise in numbers of drugs receiving orphan drug status or an expedited review designation\* 2013-2017**



\*Data for 2013 not complete as we only began systematically recording the dates of these events mid-year.

Source: Pharmaprojects®, January 2018

of its rigid verse-chorus-verse-chorus-middle eight-chorus structure, and find ways to innovate and remix its familiar sound for a new generation.

So, the song remains the same for pharma this year, but there are so many counter-melodies and variations constantly competing for attention; that information remains key to decoding the message. As always, we here at

Pharmaprojects will be putting the needle on the record (ask your parents) and listening closely to every beat, note and crackle which emanates from the industry, not just in this annual review, but throughout the year. Rest assured, whether it be listening out for the fanfares of new drug launches or the funeral marches of discontinuations, Pharmaprojects and the rest of Informa’s Pharma Intelligence team will have our ears to the ground.

Excerpt from Citeline’s Pharmaprojects’ Pharma R&D Annual Review 2018 provided by Pharmaprojects. To access the full report go to: <https://pharmaintelligence.informa.com/resources/product-content/pharma-rd-annual-review-2018>

# Pharma R&D Annual Review 2018 Supplement: New Active Substances Launched During 2017

► By Ian Lloyd



## Introduction

Following on from our review of trends in the current pharmaceutical R&D pipeline, published in March 2018 (*visit <https://pharmaintelligence.informa.com/resources/product-content/pharma-rd-annual-review-2018> to download the report for free*), this supplement takes a look at the industry's success stories of 2017 – the drugs which were launched on to the market for the first time during the year. Our survey focuses exclusively on new active substances (NASs): new chemical or biological entities where the active ingredient had received no prior approval for human use. This will include vaccines with novel antigenic components. As such, this list represents a subset of all the first launches which Pharmaprojects reported during 2017, excluding the 60 new drug launches with reformulated or non-NAS moieties, or biosimilars. So to continue our musical theme this year, we will be favouriting the year's new hit original compositions on our mp3 player, while skipping past the remastered reissues (drug reformulations) and cover versions (generics and biosimilars).

A recent report from the consultancy Deloitte estimated that the financial return on drug R&D across 12 large cap biotechs and pharmas fell to just 3.2% in 2017.<sup>1</sup> No-one

can be in any doubt – developing drugs is difficult. Just as in the pop world, there is no formula to follow that can guarantee success. Surely world-dominating pop acts such as Adele, Beyoncé and Coldplay would agree that producing a hit is not as easy as A-B-C. I suspect that even the inescapable and seemingly unstoppable Ed Sheeran must wonder whether, as he sits down to pen a new song, that, just maybe, this one won't garner the usual 2 billion Spotify streams. The pharma industry's labs are littered with failures, just as the recording studio reverberates to rejected riffs and half-realised ideas. While drug development is less prone than music to be blown off-course by the vagaries of fashion, it is still something of an art, or at least a very inexact science.

But we are here to celebrate those that made it to the top of the charts, whether they be the global megahits, or are pushing forward the boundaries of the niche genres of rare diseases. Let's start by looking at the numbers. As our main report noted earlier this year, R&D pipeline sizes continue to expand, which is only a good thing if output does too. Well, this year, there are plenty of reasons for pharma execs to be whistling a happy tune.

<sup>1</sup> Deloitte (2017) *A new future for R&D? Measuring the return from pharmaceutical innovation 2017*. Available from: <https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/measuring-return-from-pharmaceutical-innovation.html> [Accessed 20 March 2018].

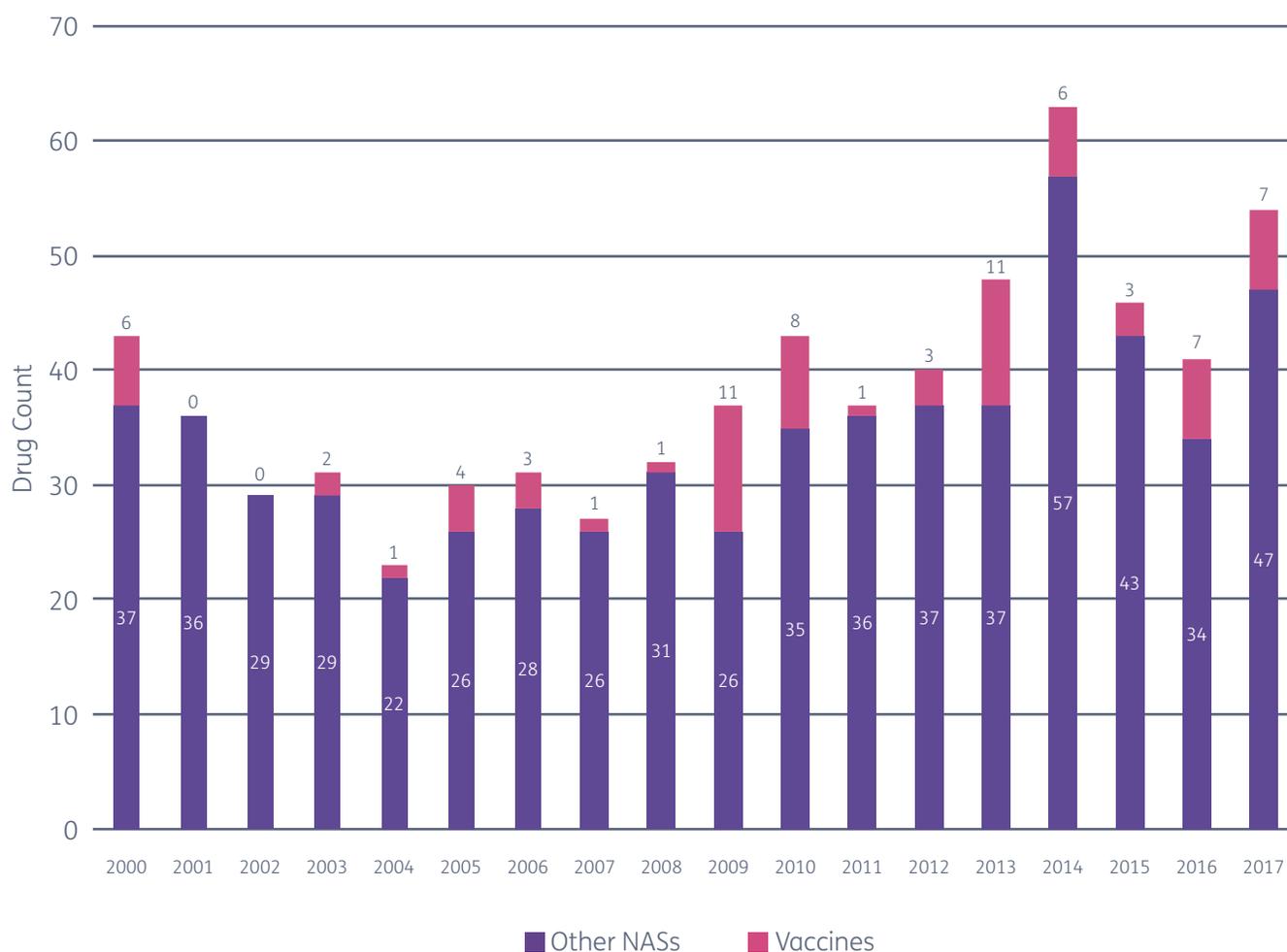
## 54 New Active Substance Launches

Now that's what I call music to pharma's ears

Figure 1 shows the number of new active substances launched by year for the millennium thus far. The graph demonstrates clearly why 2017's results are much more a polyphonic spree than plaintive solo: it was the second-best year we've seen, with a full 54 NAS launches. Only 2014's 63, which was fuelled by a profusion of new hepatitis C virus (HCV) therapies, beats them. This is an excellent result for the industry, especially following a notice-

able dip in productivity in 2016. The NASs in this year's veritable boxset of chart entries break down into 47 new chemical or biological entities, along with a further seven vaccines which incorporate novel components. The figures add to a picture of this decade being a considerable improvement on the noughties, where the average from 2000-09 was just 32 NASs. The mean from 2010-17 is up to just over 46.

Figure 1: Number of NAS launches by year, 2000-17, with numbers excluding vaccines also shown



Source: Pharmaprojects®, March 2018

As well as being a good year in general, it was a much better year for pharma's stadium acts, the Top 10 companies by pipeline size. 2016 had posted a somewhat woeful performance, with six of the Top 10 unable to deliver any drugs to the market at all. This state of affairs would surely have become unsustainable, so it's extremely good news to be

able to report that last year, all of them launched at least one NAS. Table 1 lists the top companies by number of NAS launches for all of these Top 10 companies, plus any other companies which were involved in the introduction of more than one therapeutic.

**Table 1: Top company NAS launch performance, 2017**

Company	Number of NAS launches 2017	Position by pipeline size in Top 100
Novartis	4	1
AstraZeneca	3	3
Pfizer	3	4
Merck & Co	3	7
Sanofi	3	8
Roche	2	5
Gilead	2	24
Kyowa Hakko Kirin	2	34
Regeneron	2	75
Johnson & Johnson	1	2
GlaxoSmithKline	1	6
Takeda	1	9
Bristol-Myers Squibb	1	10

*Source: Pharmaprojects®, March 2018*

The table shows that last year, not only did Novartis have the biggest pipeline, it managed to launch the most drugs, with four. It's interesting to take a deeper dive into how it came across these agents. It would seem that one was wholly originated at the Swiss firm (Rydapt), one came via an acquisition (Lutathera, from Advanced Accelerator), one was licensed-in (Kisqali, from Otsuka), and one was developed in-house but used technology licensed-in from a combination of an academic institution and a couple of small biotechs (Kymriah). This would certainly indicate that flexibility and a combination of approaches is key to success in today's industry.

Four other Top 10 companies were able to produce three releases apiece: AstraZeneca, Pfizer, Merck & Co, and Sanofi.

Of the four further companies which launched more than one NAS, the firm with the best NAS to pipeline size ratio was Regeneron, ranked at a lowly number 75 by R&D portfolio. In fact, both of its launches came via its long-standing collaboration on antibody development with Sanofi, which, prior to last year, had already delivered the PCSK9 inhibitor for high cholesterol, Praluent (alirocumab). However, Sanofi is winding the development partnership down now, having concluded that not only can it make its own antibodies, but also that it is keen to show it is not dependent on third parties to produce new drugs.

Only two other non-Top 10 companies generated more than one NAS. Japanese venture Kyowa Hakko Kirin beat all of its larger compatriots by launching two new agents:

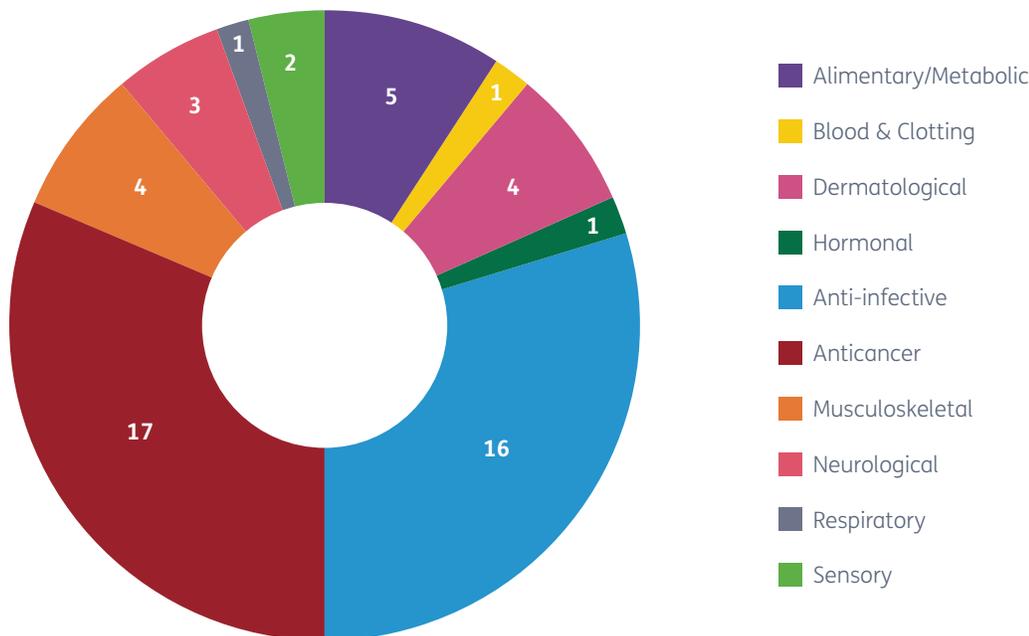
Fasenra for asthma and Fotivda for renal cell carcinoma. And Gilead completed its successful album of hepatitis C therapeutics with the triple combination drug Vosevi, which includes the NAS voxilaprevir; as well as launching the novel CAR-T cell therapy Yescarta – about which, more later.

When we slice up the NASs by the therapeutic area of their launched indication, as Figure 2 illustrates, the pre-eminence of cancer becomes clear. It led the way in 2017 with 17 NASs launched. At 31% of the total, cancer's NASs took up roughly the same proportion of the year's drug introductions as it did of the development pipeline as a whole. Anti-infectives came in a close second, with 16. Even leaving aside the fact that this includes seven vaccines, this is a more than respectable result for this category, bolstered primarily by antiviral introductions. Viral therapy has come a long way in the past

couple of decades, although the increasingly needed new antibacterials are still failing to materialize.

Elsewhere, the therapeutic area with the second- largest pipeline, neurologicals, fared less well, with just three launches. These were in multiple sclerosis, pain, and tardive dyskinesia, so there were no advances in the big, poorly served areas such as Alzheimer's disease or schizophrenia. And there was not a single NAS launch in one therapeutic area, cardiovascular, and just one in the related blood and clotting field. In terms of the types of drugs brought to the market, biological drugs accounted for 24 (44%) of the launches, again fairly close to the percentage in the overall pipeline. This breaks down into nine monoclonal antibodies, seven vaccines, four cell therapies, three recombinant proteins, and one antibody-drug conjugate.

**Figure 2: 2017 NAS launches by therapeutic group**



Source: Pharmaprojects®, March 2018

## The Novel NASs of 2017

### Pharma's musical palette broadens in a year of notable firsts

Based on the strict definition of novelty as being the first time a drug with a particular mechanism of action hits the market, 2017 produced 14 novel NASs, up from nine in 2016. But, like any good DJ, we are going to have to 'remix' our definition somewhat this year to keep up with the times. This is because two of the most significant launches of 2017 were the first two chimeric antigen receptor T-cell (CAR-T) therapies. CAR-T is effectively an ex vivo gene therapy, whereby T-cells are removed from the body and genetically modified to express a CAR, which will programme the cell to target antigens expressed on the surface of a tumour. This directs the T-cells, once they are introduced to the recipient, with the specificity seen with monoclonal antibodies. Both of the first two CAR-T cell therapies to reach the market use this approach to engineer a patient's own cells to target the CD19 molecule, which is expressed on a variety of tumours. While, strictly speaking, Amgen got there first in 2014 with the CD19-targeting monoclonal antibody Blincyto (blinatumomab), there can be no denying the intrinsic novelty of the CAR-T approach, so it feels right to include these two 'drugs' in the setlist of 2017's most innovative hits.

First to get the FDA nod was Novartis's Kymriah (tisagenlecleucel-t), which was approved in August before an October launch for paediatric acute lymphocytic leukaemia and for B-cell precursor acute lymphoblastic leukaemia in patients up to 25 years of age. The CAR-T song soon became a duet, being joined on the mic in October by Gilead Sciences' (via its Kite Pharma acquisition) Yescarta (axicabtagene ciloleucel), which gained approval in adult patients with relapsed or refractory large B-cell lymphoma for use after two or more lines of systemic therapy. Both drugs received orphan drug status, and both are expecting EU approvals in the first half of this year. This kind of ex vivo gene therapy holds great promise, and there are a further 68 such therapies in clinical trials at the time of writing.

On the subject of gene therapy, it also seems prudent to mention in passing a highly significant 2017 approval which didn't make our list, as its launch has been delayed to the first quarter of this year: Spark Therapeutics' Luxturna (voretigene neparvovec). This became the first ever US-approved in vivo gene therapy, targeting patients with the ophthalmological

genetic disorder, confirmed biallelic RPE65 mutation-associated retinal dystrophy. It will have to wait to take its applause after the encore in next year's report, but deserves props for its contribution to a year where some of the new therapeutic techniques certainly came of age.

A further cell therapy entrant is Holoclar, Holostem and Chiesi's autologous corneal epithelial cell transplant therapy. Being a non-genetically manipulated whole cell transplant consisting of cells expanded ex vivo, it doesn't have a specific mechanism of action as such, so once again doesn't count as novel by our traditional definition. However, it's undeniably innovative, being given the go-ahead in the EU back in 2015 for corneal injuries such as burns to the eye which result in limbal stem cell deficiency. The UK's health technology assessment agency, NICE, gave the green light for its use on the NHS in August 2017, but restricted its use to treating one eye, and in those who have already had a conjunctival limbal autograft or there is not enough tissue for a conjunctival limbal autograft (or it is contraindicated). It's another orphan drug launch.

An additional ex vivo gene therapy was also launched, however, which manages to tick the boxes of being novel both in approach and via its assigned mechanism of action. TissueGene and Kolon Life Science's Invossa (tonogenchoncet-L) consists of primary chondrocytes infected with a retroviral vector expressing transforming growth factor beta 1 (TGF- $\beta$ 1), which are then injected intra-articularly into the patient. This technique using local delivery overcomes the t1/2 and side-effect limitations of systemically administered TGF- $\beta$ . This makes it the first drug of any kind to hit the market with the mechanism of TGF- $\beta$ 1 agonist, having been launched in South Korea for osteoarthritis of the knee.

This chorus of approval for cell and gene therapies has been matched in cancer by a further set of first-in-class drugs of the more established kinds. Whereas this year, there were no such new monoclonal antibodies, there was further activity in the small molecule kinase inhibitors space. Launched in July by Puma Biotechnology was Nerlynx (neratinib), which is approved for adult breast cancer patients with HER2-overexpressed/amplified disease. What makes this agent novel

though, is that as well as targeting ErbB-2 tyrosine kinase (HER2), it also hits the ERbB-4 kinase, or HER4.

Before we leave cancer, which, aside from the CAR-T therapies, accounts for only four of the novel NASs, there are a further two first-in-class orphan drugs which both debuted in August. Agios Pharmaceuticals and its collaborator, Celgene, premiered Idhifa (enasidenib), the first isocitrate dehydrogenase 2 (IDH2) inhibitor, which was greenlit specifically for patients suffering from relapsed or refractory acute myelogenous leukaemia with an IDH2 mutation. Finally, the combination of BioCryst and Mundipharma delivered the first purine nucleoside phosphorylase inhibitor in the form of Fodosine (forodesine hydrochloride). This drug is indicated for relapsed or refractory peripheral T-cell lymphoma and is another of the NASs starting its world tour in Japan.

Moving to this year's other success story, anti-infectives, unusually, there were two novel NASs in viral diseases in 2017 away from the usual HIV or HCV axis. Cytomegalovirus (CMV) is an infection which fell off the radar somewhat in recent years; it was a common opportunistic infection in AIDS, but is now rarely seen in the West due to the rarity of the syndrome as most HIV patients are successfully kept in good health by antiretrovirals. However, it can still pose a problem in other immunosuppressed populations, such as those who have undergone bone marrow transplants following chemotherapy. Thus, it's good to welcome AiCuris and Merck & Co's Prevmis (letermovir) to this year's rock 'n' roll hall of fame. It's the first example of a CMV terminase inhibitor, and was launched in the US at year-end for prophylactic use in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant. In Japan, we saw Maruho's Amenalief (amenamivir) introduced for varicella zoster virus infection (shingles). It's a DNA helicase inhibitor, and contributes to a banner year for shingles, with two new vaccines also reaching the market. One of these, GlaxoSmithKline's Shingrix, is expected to achieve blockbuster status.

Also novel in the bacterial infections world is Zinplava (bezlotoxumab), for the treatment of *Clostridium difficile* (*C. diff*) infections. This is not an antibiotic; rather, it is a monoclonal antibody specific for *C. diff*'s toxin B. It is this toxin which causes the diarrhoea associated with this intestinal infection. Originally under development by Medarex, Bristol-Myers Squibb acquired rights following its acquisition of that company, but licensed it out for development and

commercialization to Merck & Co. Its US launch in February was quickly followed by EU launches and a Japanese approval later in the year. A follow-up combination product adding actoxumab, which targets *C. diff*'s toxin A, is already in Phase III trials.

In the metabolic area, two new enzyme replacement therapies count as first-in-class. Late infantile neuronal ceroid lipofuscinosis type 2 may be more of an obscure indie band type of disease than a headline act, but is a severe and fatal childhood lysosomal storage disorder disease causing seizures, vision loss, and death usually before the age of 12. It is caused by defective lysosomal tripeptidyl peptidase I, something addressed by BioMarin's recombinant version of the enzyme, Brineura (cerliponase alfa). Similarly, Ultragenyx Pharmaceutical's Mepsevii (vestronidase alfa) is a recombinant form of beta-glucuronidase, the enzyme which is faulty in another lysosomal storage disorder, mucopolysaccharidosis type VII. Unsurprisingly as both of these drugs are for very rare metabolic disorders, both have orphan drug status.

Moving to autoimmune diseases, two novel monoclonal antibodies got their big break. The first interleukin-5 receptor antagonist (as opposed to the previously launched direct IL-5 antagonists, mepolizumab and reslizumab), Fasenna (benralizumab), was a codevelopment between AstraZeneca and the drug's originator, Japan's Kyowa Hakko Kirin, using the latter's proprietary Potelligent technology. The indication here is severe asthma in patients aged 12 years and older with an eosinophilic phenotype, and launch occurred in the US in November. Dupixent (dupilumab) is the first systemic therapy for atopic dermatitis to hit the market, along with being the first to have the mechanisms of interleukin-4 and -13 receptor antagonism. This drug is indicated for the difficult-to-treat population of adults with moderate-to-severe disease which is inadequately controlled with prescription topical therapies, or where such therapies are deemed not advisable. The drug's US launch has been followed by several in the EU, and developers Sanofi and Regeneron have already filed a follow-on application in the US for use in asthma, with an EU filing in this indication to come in 2018.

Antibodies are even finding their way into haemophilia, a disease more commonly associated with treatment via recombinant proteins. Hemlibra (emicizumab) is an asymmetric bispecific IgG antibody to factor IXa and factor X, which mimics the factor VIII cofactor function. It can thus

be used to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A with factor VIII inhibitors. It's also the first time we've seen factor IXa inhibition as a mechanism on an approved drug, and once again, the US is the first market to benefit, with the EU expected to be in harmony later this year. However, there is a note of dissonance to add to this refrain, as the drug's owner, Roche/Genentech, is facing patent challenges from its competitor Shire.

Our final novel NAS, Xermelo (telotristat ethyl), is for yet another orphan disease – diarrhoea associated with carcinoid syndrome, for use in combination with somatostatin analogues where the latter alone proved inadequate. This syndrome is found to occur in about 5% of patients with carcinoid tumours, a slow-growing form of neuroendocrine tumour, and can include intense diarrhoea, abdominal pain, and flushing of the skin, caused by endogenous secretion of serotonin and kallikrein. As the world's first tryptophan hydroxylase inhibitor, the agent works by inhibiting the former's production. It's a new release from the duo of Lexicon Pharmaceuticals and Ipsen.

A few other 2017 debuts deserve a sleeve note credit, despite not being strictly-speaking novel. Roche and Biogen's Ocrevus (ocrelizumab) for the relapsing-remitting and primary progressive forms of multiple sclerosis distinguished itself by booking almost a billion US dollars-worth of sales in the nine months it was on the market – a record for recent introductions. Also in the autoimmune area, Regeneron and Sanofi's Kevzara (sarilumab) is set to make

a noise in rheumatoid arthritis (RA). It will need to pump up the volume to make itself heard in a crowded market, which is dominated by Roche's Actemra (tocilizumab), but the RA market is sizeable, and patient response with therapies variable, so any chunk which it can grab will reap rewards. Also entering a competitive arena is MorphoSys and Johnson & Johnson's monoclonal for plaque psoriasis, Tremfya (guselkumab). It is the first product to be launched based on the German biotech's proprietary HuCAL antibody library technology, and is rolling out in Europe now too, following a July US first launch.

But, like a 70s concept album, let's bookend our discussion with a reprisal to where we began, as it was indisputably cancer's year. They may not be the New Kids On The Block anymore, but the immuno-oncology strategies had another good year, with PD-L1 antagonists having successful follow-ups to Roche/Genentech's 2016 hit Tecentriq (atezolizumab) in the form of both AstraZeneca's Imfinzi (durvalumab) and Merck KGaA and Pfizer's Bavencio (avelumab). Both were launched in May for urothelial cancer, with the latter also being launched a little earlier in the year for Merkel cell carcinoma. And the more established small molecule kinase inhibitors keep on rockin' too, with a whole host of new agents. The supergroup here had AstraZeneca also bringing Calquence (acalabrutinib) to the party, along with Otsuka and Novartis's Kisqali (ribociclib), Eli Lilly's Verzenio (abemaciclib), Bayer's Aliqopa (copanlisib), and Kyowa Hakko Kirin, AVEO and EUSA Pharma's Fotivda (tivozanib). 2017's NAS list was truly music to the ears of oncologists in their ongoing battle with this devastating area of disease.

## Good Vibrations for Pharma as it Enjoys a Second Summer of Love But no room for complacency if a punk-style backlash is to be avoided

It would seem that the *Good Times* are back for the pharma industry, based on the combined analyses of this year's Pharma R&D Report and this NAS Supplement. The industry continues to grow, with more drugs in the pipeline than ever before, which seems to be delivering a healthy output of new therapeutics and some major advances for patients. But history teaches us that trends tend to be cyclical. So let's draw one final analogy from the world of popular music before we close, to sound a note of caution.

In the late sixties, a flowering of creativity and seismic societal changes led to the so-called Summer Of Love. There was a feeling that anything was possible. But disillusionment soon set in, fuelled by the Vietnam war, and the hippie ideal and flowers in the hair soon wilted. Seventies prog rock grew self-important, bloated and complacent. Inevitably, revolution was scented on the air. The twin blitzkriegs of punk and disco shook up the late seventies, leading to another creative flowering and

the so-called second summer of love in the late eighties, as rave culture burst through. This time, the riot of innovation fell to the corporate takeover, as big business moved in and created the superclubs and the bombastic sounds of EDM. Arguably, we are now in an era of unsurpassed musical blandness and homogeneity, but, in reality, innovation has just returned to the underground. It's all one big *Circle Of Life*.

How does this relate to pharma's fortunes? Like Prince, it certainly had a purple patch in the late eighties and nineties, when there were high levels of NAS introductions, and it seemed that emerging technologies were also leading to a new dawn and a new day, which would leave the industry *Feeling Good*. But it turned out to be a case of *Don't Believe The Hype*. The promised efficiencies to the R&D process didn't really materialize, with little discernible improvement in attrition rates or drug development times. The industry turned to the megamerger to solve its problems in the noughties, but this didn't seem to work either, and productivity went into something of a slump. A change of tactics was needed. The past decade has seen Big Pharma narrow its focus to fewer therapeutic areas, and seize on rare diseases as a route to enlightenment. Instead of miring itself in huge corporate mergers and acquisitions, it is looking to bolster its pipelines via targeted in-licensing and takeovers of smaller, more agile companies where innovation has prospered. As a result, pharma seems to be enjoying something of a second summer of love of its own.

But history teaches us the prudence of injecting a few cautionary notes. As previously outlined, the somewhat arbitrary nature of taking a snapshot by calendar year can serve to flatter one year at the expense of the next. So a year of fanfare can very easily be followed by a funeral dirge the next. Secondly, you never know when

the intrinsic complexities of biological systems themselves might throw a spanner in the works. There are many examples of drug class effects which only show up in late-stage development, or even worse, after launch. It would only take an unexpected problem to arise in a hot area, such as immuno-oncology or CAR-T, to change the industry's mood from *Ready For The Weekend* to *Blue Monday*. In the political arena, for those Born In The USA, the capricious nature of the country's president ensures that few are clear as to whether he is the industry's *Friend Or Foe*. And will instability in Europe, and in particular Britain following the latter's Brexit, lead to *Anarchy In The UK*? Many fear so. In a survey conducted by Informa Pharma Intelligence's *Scrip* publication, fewer than one in six pharma executives surveyed thought that drug development in the UK would not be impacted by Brexit, and 73% thought that the UK will be a later market for new product launches – sobering stuff. Plus, novelty rates remain fragile, and will need bolstering if the industry is to stay relevant and not fall back on relying on drug tribute acts. So certainly, there is no shortage of reasons why pharma's apparent progress this year could easily be blown off course.

But to end in a major key, 2018 is looking potentially exciting. Among the pending approvals we expect to be highlighting next year are: three new anti-CGRP monoclonals (a new class of drugs for the prophylaxis of migraine); an endometriosis and uterine fibroids therapy predicted to be ablockbuster; a new therapy for moderate-to-severe psoriasis; and further agents in the exciting CAR-T and immuno-oncology franchises. Pharmaprojects and the rest of Informa Pharma Intelligence will continue to watch for new breakout successes, because as in the music industry, there is no such thing as a dead cert. But with the pipeline currently busting with hot new talent, it could well be that some of pharma's *Greatest Hits* are still to come.

*Pharma R&D Annual Review 2018 Supplement: New Active Substances Launched During 2017 excerpt provided by Pharmaprojects. Download now at:*

<https://pharmaintelligence.informa.com/resources/product-content/pharma-rd-annual-review-2018-supplement>

## 2017 Completed Trials: Status Quo Or No?

► By Christine Blazynski, PhD and Laura Runkel

### Introduction

A completed clinical trial landscape provides a more granular view of how companies are progressing their pipelines and the disease strategies they are pursuing, compared to static pipeline snapshots. Company pipeline depictions lack the underlying intelligence that illustrates just how a candidate progressed, or perhaps disappeared altogether from a disease pipeline. As Informa Pharma Intelligence has done for the past three years, this analysis examines the landscape of industry-sponsored clinical trials completed during 2017<sup>1</sup>, of which there were a total of 3,534 Phase I through Phase III/IV. The nearly 700 trials termi-

nated in 2017 were not included in this analysis.

This year's metric is comparable to what was reported for 2016 completions (3,420 trials) and for 2015 (3,028 trials). At the therapeutic area level, 2017 completed trials in oncology again dominated, with 910 trials, and type 2 diabetes was the disease with the largest number of completed trials, at 171. Roche was the top sponsor in 2017 – surpassing the previous year's leader, Novartis, and as was reported for the previous year, 2017 also saw a significant volume of industry partnering for trials.

### Topline Trial Landscape Metrics

Across the nine therapeutic areas (TAs) included in Trial-trove, the rank order with respect to numbers of completed trials remained unchanged between 2016 and 2017 (Table 1). The top three TAs remain Oncology, Autoimmune/Inflammation (A/I), and CNS. In terms of absolute num-

bers, just over 80 more oncology trials completed in 2017 compared to 2016. The other TAs with more trials in 2017 include CNS, Cardiovascular, Vaccines, Ophthalmology, and Genitourinary.

**Table 1. Therapeutic area ranking for completed, industry-sponsored trials**

Therapeutic Area	Ranking			Trial Count <sup>a</sup>		
	2017	2016	2015	2017	2016	2015
Oncology	1	1	1	910	826	764
Autoimmune/Inflammation	2	2	3	656	677	542
CNS	3	3	2	582	547	562
Metabolic/Endocrinology	4	4	4	484	516	495
Infectious Diseases <sup>b</sup>	5	5	5	401	435	453
Cardiovascular	6	6	6	309	249	247
Vaccines	7	7	7	157	149	178
Ophthalmology	8	8	8	82	80	93
Genitourinary	9	9	9	78	72	70

<sup>a</sup> Trials may span multiple therapeutic areas

<sup>b</sup> Does not include Vaccines trials

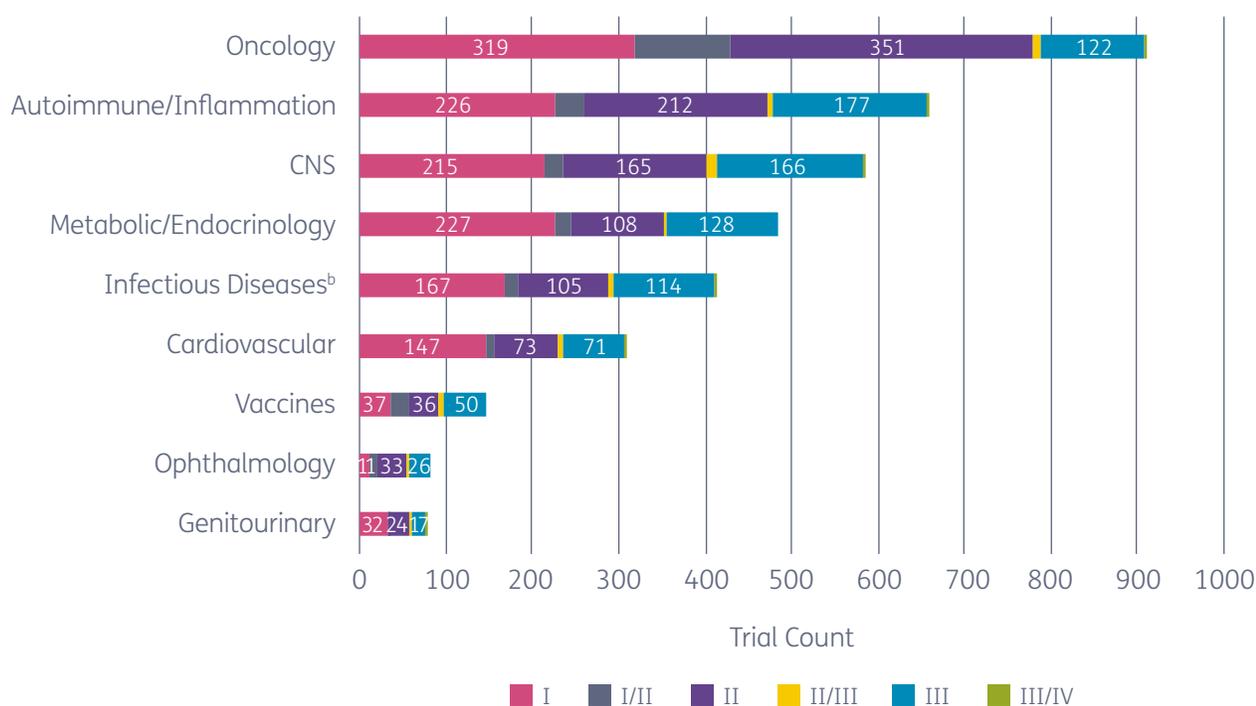
Source: Trial-trove®, February 2018

<sup>1</sup> Clinical trials were exported from Informa Pharma Intelligence's Trial-trove on 13 February 2018. The search was limited to industry-sponsored trials with primary completion dates, or primary endpoints reported dates between 1 January 2017 and 31 December 2017.

While Oncology, A/I, and CNS again led in terms of total number of trials, a view of the distribution of trials by phase reveals a few surprises (Figure 1). For absolute counts of Phase III trials, Metabolic/ Endocrinology slightly edged out Oncology for third place, while A/I and CNS ranked first and second, respectively. Relative to each TA's total completed

trials, Phase III Oncology trials accounted for 13%, while Phase III comprised 32% for Ophthalmology and Vaccines each. But Oncology's 351 Phase II trials (37% of all its trials) suggest that, should most of these programs progress to the next phase, 2018's completed trials ranking by phase may be different.

**Figure 1: Distribution of industry-sponsored trials completed in 2017 by therapy area<sup>a</sup> and phase**



<sup>a</sup> Trials may span multiple therapeutic areas

<sup>b</sup> Does not include Vaccines trials

Source: *Trialtrove*®, February 2018

Within each TA, Table 2 compares the top 10 diseases with completed trials in 2017 with the prior three years. The sum of trials for these diseases was highest in 2017, and apart from trials assessing efficacy in hepatitis C virus (HCV), the absolute numbers of trials for 2017 were close to, exceeded

the 2016 counts. Yet, for most of 2017's top disease completions, the watermarks reported for 2014 remain the highest<sup>2</sup> (type 2 diabetes [T2D], breast cancer, respiratory infections, non-small cell lung cancer [NSCLC], nociceptive pain, HIV, rheumatoid arthritis [RA], and hypertension).

<sup>2</sup> Data for 2014 are higher due to a three week later snapshot date.

**Table 2: Top 10 diseases with trials completed in 2017 and comparison to prior three years**

Disease	2017	2016	2015	2014*
Type 2 diabetes	171	190	180	315
Breast cancer	167	119	98	208
Respiratory infections	163	184	122	196
Non-small cell lung cancer	125	122	110	200
Nociceptive Pain	119	103	93	183
HIV	113	90	86	124
Psoriasis	108	82	67	106
Rheumatoid Arthritis	105	114	95	173
Hepatitis C virus	88	162	127	215
Hypertension	87	68	51	128

\*Data snapshot for 2014 was taken in March compared to February snapshot for later years.

Source: *Trialtrove*®, February 2018

Trialtrove analysts assign a trial outcome to completed trials, when that information becomes available in the public domain. Across all phases and diseases, the success rate (defined as numbers of trials attaining primary endpoint divided by total trials) was 31%. The success rate varied by phase, with Phase I trials having the lowest, at 12.4%. However, reporting of results for Phase I trials is often unavailable<sup>3</sup>. For Phase II and III, the overall success rates

were 39.6% and 43.0%, respectively.

The diseases with 25 or more trials that attained primary outcome(s) were led by breast cancer, with a total of 58 trials, which accounted for 34.7% of all completed trials (Table 3). The top-ranked disease, multiple myeloma, had 26 of its 45 trials hit endpoint.

## Completed Trials Landscape: Sponsor Assessment

13 sponsors completed over 70 trials in 2017. The top five sponsors (Table 4) showed some movement compared to the prior three years, with Roche moving to the top of the leaderboard, Merck & Co slipping to seventh place, and AstraZeneca emerging into the top five rankings.

The more telling metric is that of the top sponsors whose trials hit their primary endpoint(s). For those sponsors with more than 70 completed trials (Table 5), the overall success rates varied between a low of 15% (Boehringer Ingelheim [BI]) to a high of 40% (Novartis).

<sup>3</sup> Within *Trialtrove*, Phase I trials are only tagged with outcomes provided they have efficacy or efficacy biomarker outcomes. Low percentage of reporting reflects low availability in part due to the absence of these endpoints in trials.

**Table 3: Diseases with ≥25 trials\* attaining primary endpoints by disease and phase**

Disease	# Trials Attaining Primary Endpoint(s)						% of All Trials	Rank#
	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Total†		
Breast cancer	14	5	22	--	17	58	34.7%	6
Vaccines	16	6	10	2	19	53	33.8%	8
Colorectal cancer	17	8	14	1	5	45	45.5%	3
Non-small cell lung cancer	18	7	10	--	8	43	34.4%	7
Type 2 diabetes	5	2	15	--	20	42	24.6%	12
Pain (nociceptive)	6	2	15	--	16	39	32.8%	9
Non-Hodgkin's lymphoma	6	7	16	1	8	38	45.2%	4
Respiratory infections	4	6	10	--	15	35	21.5%	13
Melanoma	13	5	10	--	3	31	52.5%	2
HIV	5	2	7	1	16	31	27.4%	11
Multiple myeloma	5	2	14	--	5	26	57.8%	1
Liver cancer	12	5	7	--	1	25	38.5%	5
Prostate cancer	13	2	6	--	4	25	32.5%	10

\* Trials may include multiple diseases.

† No Phase III/IV trials among these top diseases completed, or if completed, attained primary endpoint.

# Rank based on percentage of trials attaining primary outcome per disease.

Source: *Trialtrove*®, February 2018

**Table 4: Top five sponsors\* completing trials in 2017**

Sponsor	2017 (rank)	2016 (rank)	2015 (rank)	2014 (rank)
Roche	160 (1)	160 (2)	123 (3)	244 (2)
GlaxoSmithKline	155 (2)	158 (3)	119 (4)	239 (3)
Novartis	152 (3)	165 (1)	147 (1)	265 (1)
AstraZeneca†	138 (4)	--	--	--
Pfizer	135 (5)	140 (4)	120 (5)	225 (4)
Merck & Co#	110 (7)	134 (5)	127 (2)	203 (5)

\* Trial count includes co-sponsored trials.

† AstraZeneca's prior metrics unavailable since prior analyses were limited to top five sponsors.

# Merck & Co ranked seventh, behind Eli Lilly in 2017.

Source: *Trialtrove*®, February 2018

**Table 5: Top sponsors with trials attaining primary endpoint(s)**

Sponsor	# Trials Attaining Primary Endpoint(s)						Total Completed Trials (rank)	Overall Success Rate (rank)
	I	I/II	II	II/III	III	Total		
Roche	8	2	29	3	13	55	160 (1)	32.5% (5)
GlaxoSmithKline	4	4	12	2	15	37	155 (2)	23.9% (10)
Novartis	8	2	24	1	26	61	152 (3)	40.1% (1)
AstraZeneca	6	3	11	1	22	43	139 (4)	31.2% (6)
Pfizer	5	1	14	--	19	39*	135 (5)	28.9% (8)
Eli Lilly	4	1	4	--	14	23	117 (6)	20.2% (12)
Merck	6	1	8	--	13	29	113 (7)	24.5% (9)
Bristol-Myers Squibb	4	2	12	--	9	27	88 (8)	31.0% (7)
Sanofi	3	3	9	1	13	29	85 (9)	34.5% (3)
Gilead	2	5	1	--	10	18	84 (10)	21.4% (11)
AbbVie	2	8	1	--	17	28	84 (10)	33.3% (4)
Takeda	1	2	15	2	8	28	76 (11)	37.3% (2)
Boehringer Ingelheim	1	--	2	--	8	11	72 (12)	15.2% (13)

\*Pfizer had one Phase III/IV trial that hit endpoint.

Source: *Trialtrove*®, February 2018

When Phase I trials are ignored, the success rates increase with a range from 28.6% (Gilead) to 52.9% (Takeda). The sponsors with the five highest success rates for Phase II through Phase III were: Takeda (52.9%), Pfizer (47.2%), Bristol-Myers Squibb [BMS] (45.8%), Novartis (44.5%), and AstraZeneca (40.7%).

### Co-sponsor trial activity

Nearly 90% of the completed industry-sponsored trials involved only a single top 20 pharma (by pharma sales<sup>4</sup>) or a single other pharma company (all other pharma [AOP]). Fewer than 4% of the trials involved two top 20 sponsors, and only 3% of trials were powered by two AOP sponsors. A total of 420 trials had some combination of co-sponsors (Table 6).

**Table 6: Distribution of co-sponsored trials**

# Sponsors	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase III/IV	Total
1 Top 20	557	57	403	18	377	2	1414
2 Top 20	40	4	48	2	42	1	137
3 Top 20	1	1	2	--	2	--	6
1 AOP	641	138	539	29	321	3	1671
2 AOP	36	10	25	2	32	--	105
3 AOP	4	1	3	7	1	--	16
7 AOP	--	--	--	--	1	--	1
1 Top 20 / 1 AOP	47	14	30	1	53	1	146
1 Top 20 / 2+ AOP	--	--	1	--	1	--	2
2 Top 20 / 1 AOP	1	--	1	1	3	--	6
3 Top 20 / 1 AOP	--	--	--	--	1	--	1

Abbreviations used in table: AOP = All other pharma

Source: *Trialtrove*®, February 2018

## Top Three Therapeutic Areas: Success Assessment by Disease and Sponsor

Across all TAs, the overall success rate was 30.9%; when Phase I trials are not included, the success rate rose to 41.4%. Across Oncology, the overall success rate was higher than the overall average, at 39.5%; when Phase I trials are excluded, the rate rose to 47.4%. For A/I, the overall success rate is 29.9%; it rises to 40.5% when Phase I trials are excluded. CNS trails in success rate, at 27.0% across all phases, while for Phases II and III it jumps to 38.4% (data not shown).

### Oncology

The five cancer indications with the largest numbers of trials that met primary endpoint(s) were breast cancer (58), colorectal cancer (44), NSCLC (43), non-Hodgkin's lymphoma (NHL; 36), and melanoma (31) (data not shown). Roche and Novartis outpaced all other sponsors, with 38 and 34 trials hitting endpoints, respectively. Besides these top two sponsors, those with 10 or more trials that attained primary endpoints included AstraZeneca, GlaxoSmithKline (GSK), Pfizer, BMS, and Celgene (Table 7). Relative success rates, however, reveal that Takeda and Celgene were the top performers last year.

When considering only Phase III trials, Pfizer's success rate led at 81.1% (9 of 11 trials), followed by Eli Lilly at 71.4% (5 of 7 trials), and AstraZeneca (5 of 8 trials). The top sponsor by relative success for completed Phase II trials was Takeda, with 9 of 12 trials attaining primary endpoints (75.0%).

### Oncology: To partner or not

For trials that were co-sponsored solely by top 20 pharma, 23 of 53 (43%) attained primary endpoints. Five of the completed oncology trials involved three top 20 pharma sponsors. Amgen, Bayer, and Sanofi completed two of these trials: a Phase I/II pancreatic cancer trial and a Phase I acute myelogenous leukemia trial. 48 trials involved two top 20 sponsors, with 21 trials meeting primary endpoints (43.8%). 19 of these trials were co-sponsored by GSK and Novartis, with eight hitting primary endpoints. The next most frequent sponsor pairings were Astellas/Pfizer with five trials; AbbVie/Roche, and Johnson & Johnson/Roche completed four trials each (and both co-sponsor pairs had two trials meet primary endpoints). Trials sponsored by a sole top 20 sponsor totaled 405, with 150 attaining primary endpoint for a lower overall success rate of 37% (data not shown).

**Table 7: Top sponsors with completed oncology trials, and success rate**

	Negative Outcome	Outcome Indeterminate	Outcome Unknown	Positive Outcome	N/A	Total Trials (rank)	Success Rate
Takeda	--	--	6	12	4	22 (9)	54.5%
Celgene	4	5	8	18	2	37 (5)	48.6%
BMS	4	4	11	17	3	39 (4)	43.6%
Novartis	6	8	23	34	9	80 (2)	42.5%
AstraZeneca	5	4	8	17	7	41 (3)	41.5%
Bayer	2	1	11	12	3	29 (8)	41.4%
GSK	5	4	9	16	5	39 (4)	41.0%
Pfizer	2	3	11	16	7	39 (4)	41.0%
Roche	13	8	28	38	8	95 (1)	40.0%
Sanofi	3	3	13	12	--	31 (7)	38.7%
Eli Lilly	5	4	9	11	6	35 (6)	31.4%

Note: Indeterminate designation is assigned to trials when the outcome is neither clearly positive or negative. Unknown is assigned to trials that have yet to report full results for primary endpoint(s). N/A indicates trials with no results available in the public domain.

Source: *Trialtrove*®, February 2018

Trials sponsored by a sole AOP company numbered 358, with 146 attaining primary endpoint (40.7%) for a slightly higher overall success rate compared to top 20 sponsors. Notably, Celgene completed 27 trials (44.4% success); Otsuma had eight of its fourteen trials meet endpoint (57.1%); and Merck KGaA held third place with 11 trials, of which only three hit endpoint (27.2%). There was far less collaboration among AOP sponsors, with only 29 trials having two sponsors in this group (41.4% meeting endpoints) and seven trials having three AOP sponsors (57.1% success). A small number of trials were sponsored by both top 20 and AOP; of these 57 trials, 23 met primary endpoint – a 40.3% success rate (data not shown).

Autoimmune/Inflammation Across the diseases in this therapeutic area included in *Trialtrove*'s coverage, five diseases had 50 or more completed trials: rheumatoid arthritis (RA; 105 trials), psoriasis (108), asthma (81), chronic obstructive pulmonary disease (COPD; 66), and osteoarthritis

(OA; 54) (data not shown). But, when looking at percentage of trials by disease that attained primary endpoint, the top five diseases are: transplantation/graft versus host disease (GVHD; 66.7%), other inflammatory arthritis (62.5%), Crohn's disease and pulmonary fibrosis (57.1%), and allergic rhinitis (52.2%). For the top five diseases, RA had a success rate of 16.2%, psoriasis 21.3%, asthma 14.8%, COPD 47%, and OA 30.2%. If Phase I trials are excluded from the group, the success rates change to 33.3%, 34.4%, 8.7%, 45.2%, and 30.2%, respectively.

AstraZeneca completed the largest numbers of trials last year, but ranked third by the metric of success. As observed for the Oncology area, rank by volume differs from rank by success rate (Table 8). When Phase I trials are excluded, the top three companies by volume also finish in the top three rank by success, although the rank order differs: AstraZeneca (26 trials; 46.2% success), Novartis (24; 75.0%), AbbVie (26; 42.9%) (data not shown).

**Table 8: Top sponsors with completed Autoimmune/Inflammation trials, and success rate**

	Negative Outcome	Outcome Indeterminate	Outcome Unknown	Positive Outcome	N/A	Total Trials (rank)	Success Rate
Novartis	1	--	7	13	7	28 (4)	46.4%
AbbVie	4	3	9	11	3	30 (3)	36.7%
AstraZeneca	3	1	12	13	16	45 (1)	28.9%
GlaxoSmithKline	2	3	15	8	11	39 (2)	20.5%
Boehringer Ingelheim	--	2	9	5	9	25 (6)	20.0%
Roche	--	8	4	5	8	25 (6)	18.5%
Merck	--	--	3	1	2	6 (9)	16.7%
Pfizer	1	7	5	4	10	27 (5)	14.8%
Astellas	--	1	3	1	2	7 (8)	14.3%
Bristol-Myers Squibb	--	1	1	2	11	15 (7)	13.3%
Eli Lilly	1	--	2	2	20	25 (6)	8.0%

Source: *Trialtrove*®, February 2018

### Autoimmune/Inflammation co-sponsorship activity

A total of 280 trials were run solely by a single top 20 sponsor; of these, 59 reported success (21.1% success). A small number of trials (23) had two top 20 sponsors, and 11 of these hit endpoint (52.3% success). The partnered AbbVie/BI trials accounted for 10 of these trials (five of which attained endpoints). 309 trials were sponsored solely by one AOP company; 107 reported attaining primary endpoints (34.6%). Only 20 trials were sponsored by two AOP companies (40% success). 19 trials were sponsored by a single top 20 and single AOP company; seven of these trials involved Regeneron and Sanofi (data not shown).

### CNS

The 10 diseases with the most trial completions ranged from a high of 118 for nociceptive pain, to migraine and multiple sclerosis, which tied with 34 each. When trials

from each phase are included in the success rate calculation, not one of these top 10 diseases came close to even 50% success. Parkinson's disease had the highest overall rate of 36.4%. When Phase I trials are excluded, schizophrenia's success rate rose from 18.2% to 87.5%, migraine from 29.4% to 60%, and Parkinson's disease moved from 36.4% to 50% success (data not shown).

Eli Lilly topped the sponsors with 25 completed trials, followed by Johnson & Johnson (J&J) with 21, and Lundbeck (19) (Table 9). Otsuka's 18 completed trials had the highest overall success rate – 50.0%.

When Phase I trials are excluded, Otsuka's success fell slightly to 46.7%, while Eli Lilly, Pfizer, and BI hit 50% each. UCB's five successful trials yielded a success rate (sans Phase I trials) of 55.6%, making this sponsor the overall leader.

**Table 9: Top sponsors with completed CNS trials, and success rate**

	Negative Outcome	Outcome Indeterminate	Outcome Unknown	Positive Outcome	N/A	Total Trials (rank)	Success Rate
Otsuka	1	--	6	7	4	18 (4)	50.0%
Lundbeck	3	1	7	6	2	19 (3)	46.2%
Allergan	--	1	5	7	3	16 (5)	38.9%
UCB	--	1	3	5	5	14 (7)	35.7%
Pfizer	--	1	5	6	3	14(7)	31.6%
Eli Lilly	1	--	12	5	7	25 (1)	31.3%
Johnson & Johnson	--	--	9	4	8	21 (2)	23.5%
Daiichi Sankyo	1	--	5	3	4	13 (8)	21.4%
Boehringer Ingelheim	3	--	3	--	8	14(7)	21.4%
Novartis	--	--	4	2	1	7 (10)	18.2%
Biogen	3	3	3	1	7	17 (6)	14.3%
Eisai	1	--	4	1	5	11 (9)	9.1%

Source: *Trialtrove*®, February 2018

## Closing Thoughts

Sponsors saw slightly lower success rates in 2017 compared to 2016. Novo Nordisk’s 46% success rate for 2016 was higher than Novartis’s success rate of 40.1% for 2017. 16 pharma sponsors had 25% or higher success rates in 2016, compared to eight in 2017. Trying to assign any reason for this decline, other than slow trial outcome reporting, would be highly speculative.

The analysis performed last year indicated a significant degree of co-sponsorship of trials, and of these, a higher percentage of these trials attaining primary endpoints compared to single-sponsored trials. However, no strong

co-sponsor pairings emerged in the 2017 dataset (compared to 2016’s Sanofi/Regeneron 13 trials in Autoimmune/Inflammation with 38.5% success, or the Lundbeck/Otsuka pair with 5 of 9 trials in CNS hitting endpoints). Whether or not the small number of partnered trials represents a true return to “going it alone” remains to be seen with our analysis of 2018 completed trials.

Overall, the top sponsors and trial volumes reflect the prior years’ status quo, year-over-year for completed trials activity; but the individual successes from 2017 demonstrate that there was ample shifting and evolution during 2017.

2017 Completed Trials: Status Quo Or No? excerpt provided by *Trialtrove*. Download the full whitepaper from: <https://pharmaintelligence.informa.com/resources/product-content/2017-completed-trials>

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