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**NOVEMBER 2017**
COMMERCIAL INSIGHTS FOR THE C-SUITE
VOLUME 37, NUMBER 11

*PHARM EXEC'S* 2018 PIPELINE REPORT

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# No Overnight Successes

**ONE OF MY SONS RECENTLY** said, after he watched a paper napkin drift from the table to the floor, "I wonder who was the first person to figure out that if you crumpled paper, it would just fall straight down because of density?" I said, "I don't know." His brother said, "Who cares?" Which one do you think is going into the sciences? My other son is gifted in other areas, but it's the people that question and keep looking for reasons or answers underlying the surface that probably excel in positions in research and science. I found myself thinking more about these people behind the scenes in pharmaceutical research, and none more so than reviewing this issue's annual pipeline report (see page 14).

**LISA HENDERSON**
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What is true of many people and companies, there is no such thing as an overnight success. In last year's report, we were highlighting some potential successes in Alzheimer's, but as contributing writer Josh Baxt notes in this year's report, high-profiles failures in this disease are leading researchers to question the scientific hypothesis around amyloid plaques.

With the first CAR-T therapies being approved in August and October—Kymriah and Yescarta in the blood cancers of leukemia and lymphoma, respectively—I did a cursory Internet search of chimeric antigen receptors. They went back to 2000. Since they probably were being hypothesized longer than the ability to post and quickly search on the Internet, an average of 20 years definitely falls into the overriding truth of the term overnight success. Factor in that studies around CAR were spurred by research into Epstein-Barr virus, discovered in 1964, and built on since then, truly scientific discoveries are a long-time effort in trial and error.

If you think about what actually is driving the current era of personalized medicine, preceded by the end of the blockbuster era, it is that scientists have found vaccines against deadly viruses; drugs that manage diseases affecting large populations; and effective cures for other diseases. That is what science has done. That science is now on the journey to rare diseases or those with unmet needs, is a testament to the research efforts into polio, rubella, statins, HIV/AIDS, and more.

Aside from the science advancing human health, regulatory authorities can positively affect getting the discoveries to patients. Specifically in the US, those pathways include orphan designation, breakthrough designation, priority review, and accelerated approvals. In 1983, the Orphan Drug Act was signed into law. Since then, over 600 drugs have been approved with the designation. A breakthrough therapy designation is for drugs intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate a substantial improvement over currently available therapies. Since 2013, 87 drugs received approvals under that designation.

Many drugs in this year's pipeline fall under orphan or rare disease categories. For example, Spark's gene therapy voretigene neparvovec (Luxturna) for inherited retinal disease will, if approved (it won a 16-0 advisory panel backing last month), be the first therapy to improve hereditary blindness, which is an orphan indication that affects around 6,000 people worldwide. Drugs approved this year that advance rare diseases are avelumab, the first FDA-approved treatment for metastatic merkel cell carcinoma; lesipasvir and sofosbuvir is the first HCV direct-acting antiviral approved for use in adolescents; cerliponase alfa is the first FDA-approved treatment for a form of Batten disease; ibrutinib for the treatment of chronic graft-versus-host disease (GVHD); and benznidazole is the first treatment approved in the US for Chagas disease.

Besides the fact that this month is the popular pipeline report, which would be enough for me to write this editor's letter around, I heard a radio commercial this morning for Penn Medicine's cancer services talking about its role in a recent gene therapy approval, and explained to the public how CAR-T worked and how they could consider Penn for cancer services. That, of course, was its role in the approval of Novartis' Kymriah.

Next month, we profile Ruud Dobber, President, AstraZeneca US, and Executive Vice President, North America, who earned a PhD in immunology and eventually became a researcher in the fields of aging and immunology. Dobber explained that as a scientist and a researcher, people learn to be resilient because there are so many failures. He says, "But if you are successful, you have that moment of 'Eureka' and that's phenomenal."

These are the times I'm thinking about those really resilient, curious, and dedicated scientists and researchers. I told my son he should go into the sciences. The other one? Maybe he can write about them.

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*By Josh Baxt*

Amid the constant battle with biology and new complexities in fighting disease, persistence seems to be paying off for drug developers. Major driving forces include the rise of CAR-T and other gene therapy, newly discovered cancer targets, better patient identification methods—and the realization that failures have their place in shaping the pipeline of tomorrow.

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# FDA Explores Flexible Drug Marketing Policies

## Agency leaders go slow in weighing changes to DTC ads and off-label marketing

FDA regulation of prescription drug and medical product promotion has come under fire in recent years, as federal courts have supported industry challenges to rules limiting communications of unapproved drug uses. But with little to show from two years of meetings and discussions about reconciling long-held promotion restrictions with legal decisions favoring greater protection of commercial speech, the arrival of Scott Gottlieb to helm the agency has raised expectations that a more flexible policy will emerge. While marketers maintain they can provide truthful information on drug uses without undermining product safety, no one expects radical change in the current political climate.

The deadly opioid epidemic, moreover, has prompted more intense examination of the role of drug marketing in encouraging excess prescribing of these dangerous medicines. Multiple states and local governments have filed suits against manufacturers for encouraging opioid overuse and abuse, and FDA's Office of Prescription Drug Promotion (OPDP) has issued enforcement letters citing violative promotion of pain medicines. Most recent is a warning to Cipher Pharmaceuticals for minimizing risk information in professional materials on combination extended release pain therapy ConZip. Another cites Pain Therapeutics and DURECT Corp. for touting its investigational opioid therapy Remoxy ER on its website, prior to approval.

The HHS inspector general (OIG) is scrutinizing how pharma marketing programs encourage such overprescribing, with an eye out for evidence of doctors receiving kickbacks from manufacturers, noted OIG senior counsel Mary Riordan at the advertising and promotion conference in September sponsored by the Food and Drug Law Institute (FDLI). The Justice Department recently collected more than $7 million from Galena Biopharma to settle allegations that the company paid kickbacks to doctors to boost prescriptions for pain drug Abstral, and the investigators are scrutinizing other cases (see sidebar on facing page).

### Signs of change

Just before the new administration took over in January, FDA issued a memorandum that largely defends agency restrictions on off-label communications. It also published a final rule that changed the definition of "intended use" of regulated products, prompting an outcry from industry that it requires manufacturers to revise labeling for additional uses even when the firm does not support that off-label use.

At the same time, FDA published two new draft guidances that set the stage for more flexible communications with payers and formulary committees on pricing issues and for permitting certain "out-of-label" communications that are "consistent with" FDA-required labeling (CFL). And in March, FDA delayed implementation of the controversial "intended use" rule for a year (until March 2018) and began the process of clarifying and finalizing the new guidances.

OPDP analysts sought to explain the intent and recommendations of the CFL guidance at the FDLI conference, as marketer comments on the proposal indicate a need for clearer examples of what is CFL and recommended disclosure strategies. FDA says it will permit communication of unapproved uses that provides truthful and non-misleading information on approved products and presents no harm to patients. CFL information may address the product's indication, intended population, dosing and directions for use and should be presented in an "appropriate context," with clear presentation of study results, claims, and limitations on data. OPDP staffers say they're ready to advise marketers on whether proposed promotional materials meet the new standard or imply new intended uses.

The new draft guidance on manufacturer communications with payers, formulary committees, and similar entities implements a provision in the 21st Century Cures legislation by outlining appropriate presentation of healthcare economic information (HCEI) on approved drugs. More surprising is a second section that describes a process for presenting similar infor-

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mation to payers regarding investigational drugs and devices prior to agency approval. The guidance aims to clarify what information qualifies as HCEI, who can deliver the information, and what type of claims fall outside this policy.

## Clarifying DTC

If FDA is going to make notable changes in promotion policy, it may start by revising the scope and format of risk information presented in DTC advertising. FDA is examining evidence that limiting warnings in TV commercials to severe, serious, or actionable side effects might be more informative than lengthy laundry lists of potential adverse events. The change reflects research indicating that more targeted presentation of risks actually may help consumers weigh potential side effects (see http://bit.ly/2l6oVpo).

Such a change is supported by OPDP analysis indicating that consumers may retain more risk information from targeted statements. A separate study by researchers at the London Business School found that consumers regard drugs as less risky when drug ads list all its side effects, and that they better understand warnings and side effects when only the most serious risks are presented.

If FDA is going to make notable changes in promotion policy, it may start by revising the scope and format of risk information presented in DTC advertising

Similarly, another OPDP study raises questions about the value of requiring disclosures about limitations on comparative price information in DTC and professional print ads because most consumers and physicians fail to notice or understand such caveats, even when prominently displayed. The analysts also are examining how larger size and clearer presentation of text running in TV commercials may be better understood and remembered by viewers; if animated TV ads improve understanding of risk information; and changes in DTC ad design for older and hearing impaired audiences.

OPDP has a long research agenda, which has drawn complaints from industry that many of its projects are redundant and not useful. But Gottlieb pointed to "FDA's own research on broadcast TV advertisements" in his comments posted in August suggesting that a more targeted method for delivering risk information "may lead to better retention of those risks." If the commissioner is going to alter TV commercial formats, he wants strong evidence that benefits clearly outweigh risks. As FDA officials move forward on DTC revisions and finalizing the two new draft guidances, they also will be reviewing the continuing debate over how marketers can respond to unsolicited requests and discuss scientific information. But there won't be any change in the basic requirement that all communications are truthful and not misleading, always. PE

## Enforcers eye drug pricing

In addition to off-label marketing, the HHS inspector general (OIG) remains concerned about drug pricing issues, noted Mary Riordan at the Food and Drug Law Institute (FDLI) conference last month, particularly Medicaid rebates and drug marketing activities that may drive up spending. A high-profile topic for the OIG is whether drug manufacturers reduce Medicaid rebates by erroneously classifying innovator products as multi-source generics, as seen in the Mylan EpiPen case. A related issue is how errors in labeling codes by manufacturers support Medicaid coverage of unapproved drugs.

Erroneous reporting of average sales price information to Medicare Part B is under scrutiny, as is how often and how accurately manufacturers make "reasonable assumptions" in calculating average manufacturer prices and best prices for Medicaid and Medicare. Riordan also cited continued OIG interest in violations related to pharma company speaker programs, particularly maneuvers designed to compensate high-prescribing physicians even when CME programs are cancelled or provide very little "education." An emerging issue, she added, is how well life sciences companies ensure protection of confidential patient identifiable information. The shift to personalized medicine and expanded use of Internet services that target messages to receptive consumers increases risks of patient data exposure.

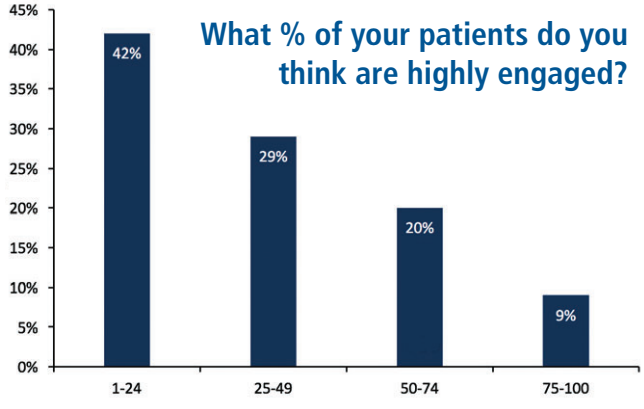
# Digital Engagement and Patient Support Programs

## How can technology be truly patient-centric?

Patient-centric care—care that prioritizes respect and dignity, information sharing, shared decision making, activation, and collaboration—is a critical area of focus for both healthcare and the biopharma industry. Patient experience is one of the core elements of patient-centric care, and has a positive[1] association with clinical effectiveness and patient safety across a wide range of disease areas, study designs, settings, population groups, and outcome measures. This close association means that the patient experience needs to be taken seriously as a quality measure in healthcare, both for care providers and for the companies developing drugs and devices.

Patient engagement, which has been defined by the Center for Advancing Health as "actions individuals must take to obtain the greatest benefit from the health care services available to them," is another key focus of care that is fundamental to driving patient outcomes. Recent research has shown that patients who are more engaged with their health care have better outcomes and care experiences, and that tailoring patient support to an individual patient's level of engagement increases their levels of activation through building skills and confidence.[2]

However, despite this data, evidence shows that there is a long way to go to optimize patient engagement in healthcare. In a 2016 New England Journal of Medicine Catalyst Insights Council survey—carried out in 340 US health care executives, clinician leaders, and clinicians—42% reported that under a quarter of their patients were highly engaged, and over 70% said that under half were highly engaged. Only a tenth of those questioned said that more than 75% of their patients were highly engaged.




Source: New England Journal of Medicine Catalyst Insights Council survey

### Improving patient experience and engagement

The goal of effective patient support programs is to build patient engagement, knowledge, and empowerment, leading to better medication adherence and outcomes. In an era where the search for healthcare information is the third most common online activity, and 59% of people turn to the internet for answers to medical questions, before friends, parents, spouses, or doctors, the provision of information and support through digital channels is a core element of many patient programs. As digital health becomes smarter and more advanced, we see a move towards leveraging the capabilities of digital to provide information and support that can be tailored to individuals, according to their health status, time since diagnosis, disease progression, educational status, and even the underlying beliefs and behavior.

Human interaction remains vital, however, providing consistency and credibility throughout what can be a complex and challenging patient journey through the healthcare system, to offer care, support, and clarity. In a study published in the New England Journal of Medicine Catalyst, when asked which were the two most effective patient engagement initiatives, 59% of the US executives, clinical leaders, and clinicians said 'having physicians, nurses, or other clinicians spend more time with patients,' followed by 54% who said 'shared decision-making.'

Within the context of support programs, as an 'in person' support resource for patients and carers, nurses bring a huge swathe of clinical and social expertize in supporting patients navigate their healthcare journey, and our experience shows that the relationships a patient develops with their care teams is the most valued component of any support strategy. This support is not just practical; it's the emotional support and engagement with patients and their families that can offer the most impactful sustained benefit and drive activation, confidence, and self-management.

### QuintilesIMS Patient Engagement Platform

Acknowledging the ever-increasing industry move towards digitally augmented, multi-channel support models in patient programs, and looking ahead at how QuintilesIMS can enhance its nurse-led, people and relationship focused patient support programs, work began on the QuintilesIMS Patient Engagement Platform in 2016.

One of the founding principles underpinning development of the platform

is that evidence increasingly shows that behavior change is not achieved through transactional one-dimensional technology solutions, such as reminders and alerts, and that sustainable outcomes are delivered through integrated, behaviorally-driven, personalized e-health interventions.[3]

Further, experience and academic literature supports the position that the most impactful programs are those that understand motivators and drivers of patient behavior, and deploy interventions that integrate high-touch healthcare professional-led support, with multi-channel digital and print support, matched to the individual's needs.[4,5,6]

The QuintilesIMS Patient Engagement Platform is developed from a behavior-change first, technology second approach, deploying five adaptable engagement modules that support the entire patient journey, all underpinned by validated behavioral methodology.

At its essence, the QuintilesIMS Patient Engagement Platform is an adaptable e-health support platform that enables personalized education, advice, tools and actions to be provided to a patient, in an engaging way, at the point in time which it is most needed. All designed to build on the trusting relationship that is established between patient and program nurses. The platform enables the patient and nurse to dynamically interact, and jointly craft a tailored action plan that meets the needs of the individual patient.

An adaptable measurement framework is woven into the base platform that allows for data to be leveraged to continuously improve and tailor the experience for the patient, whilst delivering a higher-level, long-term view of program impact and outcomes.

## Using digital platforms and personal contact to drive patient engagement

There are many different approaches to creating behavior change in patients. Different examples of these are validated in daily use by healthcare professionals, or through their integration into treatment guidelines, such as the inclusion of diet, exercise, and behavioral modification in the Endocrine Society guidelines on the treatment of obesity in 2015. The power of digital technologies, combined with personal interactions, allows companies to harness these approaches and create tools for patients that are tailored to their needs and support the nurse in uncovering and addressing behavior change opportunities, for example through action plans.

By tailoring the solution to the specific needs of an individual or group, patients can receive the content and tools that will allow them to gain knowledge about their condition and understand how they can work with healthcare professionals to manage their symptoms and treatment. It can be difficult to manage complex treatment regimens and juggle clinic visits, particularly for people who work, who are parents or carers, or who have a condition that makes thinking and planning difficult.

A key consideration for the US market is that a good nurse support and digital tool can help to simplify the patient's journey through the often-disparate support elements provided by drug manufacturers—they may be dealing with copay cards and assistance, a nurse call center, a web resource, all provided separately. The holy grail is to integrate all support into one resource for patients and, importantly, to collect joined up data about the performance of this suite of services.

## Supporting nursing staff and physicians

Digital platforms can support and empower nurses by providing training resources, scheduling tools, and background reading, both for nurses and for patients. They can also provide access to outcomes data, such as adherence and persistence; engagement, including satisfaction, completed activities and health activity feedback; and utilization of the platform. Outcomes data can be useful to physicians by helping them understand real-world outcomes of different prescribing decisions, allowing them to track patient enrolment, evaluate referral rates, and devise better patient management programs.

## Digital patient support: looking into the future

Modular, integrated patient support programs that combine high-touch nurse-led support with multi-channel digital solutions are likely to play an increasing role in healthcare, as the industry moves towards more intelligent and personalized strategies that allow for resources to be focused on those most at need, and work with the patient to empower them with the ability to self-manage and achieve more sustainable long-term health goals.

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**Rebecca Galbraith is Head of Communications, Market Access at QuintilesIMS.**

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# The Fine Line of Pharma & Patient Group Collaboration

## Can health stakeholders be friends without being captives?

A new attempt by European drug firms and patient organizations to chart a course between cooperation and cooption has highlighted the scale of the challenges that healthcare stakeholders face when they reach out to one another. "Any relationship between patient organizations and the pharmaceutical industry can be perceived as commercially motivated," concluded this exercise, conducted over recent months by the biggest European players on each side: the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Patients' Forum (EPF).

The paper they have produced, "Working together with patient groups," is couched in carefully controlled and diplomatically sanitized language, as is to be expected from two such sophisticated organizations, and it aims to present a practical and constructive take. But its proposed solutions are, nonetheless, tantamount to a recognition that the challenges it identifies are far from being met—patient groups still labor under the shadow of accusations of behaving as the drug industry's hired lap-dogs, and drug firms continue to be suspected of manipulating patient organizations like glove puppets, simply by scattering a few crumbs of their profits among them.

Continuing financial dependency "may lead some to assume there is undue or inappropriate influence of the industry on patient organizations and their decision-making," acknowledge EFPIA and EPF. The possible remedies run the familiar gamut of keeping everything clean and above board, ensuring collaborations aim at "clearly identified patient benefit," observing good governance principles and codes, communicating transparently and "proactively and publicly," and fuller disclosure of funding links.

### Relationship gains

There is much that can usefully come out of cooperation, they say. Patient organizations may collaborate with industry to co-create educational programs and take part in clinical development through working with regulatory authorities, ethics committees, investigators, and industry, or contributing to study design and the development of layperson summaries, or even provide input into recruitment and retention. Patients can provide researchers with insights into the challenges of living with a disease, enabling drug manufacturers to incorporate feedback directly into their R&D processes; and they play an increasing role in regulatory processes, and even in defining the value of medicines.

But the overall tone is defensive. "Collaboration between pharmaceutical companies and patient organizations fulfill a legitimate need for interactions identified in advance," the two groups say, subject to some of the reservations and conditions about "how these relationships are managed." They are at pains to underline the need for independence of patient organizations "in all aspects of their decision-making, development of policies, and external communications" to ensure credibility. But the overall impression from the conclusions is that despite all the efforts to dispel doubters' concerns, both sides are resigned, at least for the present, to being on the receiving end of persistent skepticism.

Paradoxically, closer collaboration between health stakeholders is these days being driven by a growing chorus of calls to bring coherence and new efficiencies to Europe's fragmented health systems. EFPIA and EPF themselves note that in the past, industry, academia, healthcare professionals, regulators, and patient organizations "largely worked in silos." Decisions about patients' care, medical research, health information, and service design "were taken without meaningful patient involvement," leading, they say, "to inefficiencies and low value in process and outcomes." Nowadays, companies have developed new ways "to incorporate patient insights and to collaborate with patients and patient organizations in a transparent and ethical way," resulting in "better trials, better engagement, better communication throughout the entire life cycle of medicines—and ultimately better patient outcomes."

### Ties questioned

But the shadows of suspicion are hard to dispel. It isn't just in the area of drug firms' direct funding of patient organizations that the attempt to hold hands but to stay

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at arm's length runs into trouble. A major project to train better-informed patient advocates over the last three years, known as the European Patients Academy, and drawing on patient organizations, academics, and regulatory authorities, was repeatedly accused of playing an industry game because part of its support came—in kind—from drug companies.

At the same time, on everything from drug pricing to drug research, and from cross-border care to assessing the performance of national health systems, the slogan is "work together." Just before the summer, more than 100 European health organizations wrote an open letter to the European Commission insisting that "EU health collaboration is crucial for Europe's future," and demanding that "voices from civil society—patients, consumers, health professionals, epidemiologists, and technical experts—are represented in policy dialogues that build on all available evidence and expertise." In October, a key recommendation from an EU panel of experts on developing new pricing models for innovative drugs was to "create dialogue platforms involving all relevant stakeholders."

The obvious impediment to this vision of utopian harmony among stakeholders is that not every stakeholder shares the view of the others. As George Bernard Shaw sagely advised: "Do not treat everyone as you would treat yourself. Their tastes may not be the same." So a warning bell immediately starts to ring when, for instance, a new report from the EU on its exploration of best practice in national health systems remarks that health service performance assessment "is a complex combination of activities" that includes at the top of its priorities "the involvement of stakeholders," and that sees a role for providing citizens "with the information of what they can and should expect from the health system." It envisions the collection and dissemination of information on the functioning of the health system as "a key element allowing patients to use broader knowledge for more educated choices." That, of course, depends on what is considered an "educated" choice—and raises the slightly chilling prospect of the Goliath of health systems deciding for each David what his or her educated choice should be, or of neutered patients compliantly abdicating all responsibility for their own decisions.

A degree of distrust is not only to be expected, it may be valuable in moving toward real rather than apparent solutions

## Conflict awareness

A degree of distrust is not only to be expected, it may be valuable in moving toward real rather than apparent solutions. Distrust featured prominently in the input from some civil society contributions to the EU debate on how to promote closer collaboration on health technology assessment (HTA) earlier this year. The European consumers association, BEUC, for instance, while in principle in favor of taking EU-level cooperation further among national HTA authorities to bring greater coherence to EU medicines provision, highlighted the risks of industry gaining undue leverage without tight safeguards. "The interests of industry and HTA can differ," it said in its response to the EU consultation on the future of HTA. Even if early dialogues among industry, drug regulators, and HTA organizations "can be beneficial," it is essential to take into account "the conflict of interest that might arise."

Similar warnings came from Prescrire, the non-profit group of health professionals that publishes independent information on drugs and therapeutic strategies. Prescrire flatly rejected the merits of early dialogue, which it sees as a backdoor allowing industry to stitch up drug pricing deals instead of presenting objective arguments for a drug's merits. It said that allowing industry access to early dialogues provides them with "a platform that can lead to regulatory capture and enable companies to influence pricing and reimbursement decisions."

## Careful consideraton

At a time when the pressure for collaboration and cooperation is increasingly strong—take, for instance, the gathering momentum of personalized medicine, or the influence of the so-called "roundtables" organized by leading drug firms and national health authorities in Europe over the last year, or the countless "joint actions" under the EU's health program, or the burgeoning public-private partnership of the Innovative Medicines Initiative—it may be time to pause and reflect for a moment on whether all forms of collaboration are as good as they purport to be, and whether everyone swept up in the headlong rush to join is going to benefit equally. PE


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# 2018 Pipeline Report: New Targets, Combinations, and Complexity

Analysis shows that persistence is paying off for drug developers, driven by the rise of CAR-T and other gene therapy, newly discovered cancer targets, better patient identification methods—and the realization that failures have their place in shaping the pipeline of tomorrow

*By Josh Baxt*

Tantalus had it rough. The character from Greek mythology was forced to spend eternity looking at water he could not drink and fruit he could not eat. Each time he reached out, the water would recede, the branches would rise away.

Pharmaceutical and biotechnology companies face similar problems. The targets are so enticing, the results often wanting. Consider checkpoint inhibitors. They are quasi-miracle drugs: incredibly powerful for the lucky responders, ineffective for others.

There are many variations on this theme. Following the success of cancer drug Gleevec, targeted therapies seemed like a sure thing. They've helped, but not as much as many had hoped. Pivoting to the central nervous system, the quest for effective Alzheimer's disease therapies has been fraught with failure. Ask Merck & Co., Lilly, Axovant, Accera, Lundbeck, etc.

Many articles, including this one—*Pharm Exec*'s 14th Annual Pipeline Report—offer competitive snapshots, which companies have the upper hand. But in the end, the competition is with biology, which seems to be saying: "Really, you thought it would be that easy?"

But adversity is good for people and companies. The race is on to match checkpoint inhibitors with other therapies to transform cold tumors into hot ones. Companies' researchers are reexamining their Alzheimer's strategies. New targets are being tested in multiple indications. It seems the best way to meet complexity is with more complexity.

## Skepticism with Alzheimer's

Bad news first. The Alzheimer's Association projects there may be 16 million people with the disease by 2050, a crushing load for patients, caregivers, and governments. Statistics like this are generating a lot of urgency. Unfortunately, the pipeline keeps coming up short.

"There have been a lot of high-profile failures for amyloid plaque," notes Joshua Pagliaro, partner in life science strategy at PwC. "I think a lot of people have had the question: Is this a sound scientific hypothesis?"

Pagliaro is not alone in his skepticism. "The amyloid theory may need some alterations," says Les Funtleyder, portfolio manager at E Squared Asset Management and *Pharm Exec* Editorial Advisory Board member. "We may need to go back to the drawing board there."

That's not comforting for companies with amyloid therapies in the pipeline. They've gone this far, invested this much, they need to believe their science is better—their trial design superior.

At present, Biogen's aducanumab is being tested in two international Phase III trials (EMERGE and ENGAGE). The therapy, which targets beta amyloid, has been fast-tracked by the FDA. Recent findings in an extension of an early-phase study have been positive, showing the antibody therapy reduced amyloid plaque levels in patients treated up to 36 months. Given favorable results and ultimate approval, EvaluatePharma puts aducanumab sales at $1.5 billion by 2022.

Biogen has a particularly robust Alzheimer's pipeline, including beta-secretase cleaving enzyme (BACE) inhibitor elenbecestat, which is being co-developed with Eisai. BACE inhibitors are designed to prevent amyloid plaques from accumulating. The drug has been granted fast-track designation in the US and is also in Phase III. Elenbecestat is projected to earn $296 million in 2022, mostly for Eisai.

In addition, Biogen is developing anti-amyloid antibody BAN2401, which is currently in Phase II trials. The company has a lot riding on the amyloid plaque hypothesis.

Amgen and Novartis have their own BACE inhibitor in the works, CNP520, a small molecule in Phase II, which has also been fast-tracked by the FDA.

AbbVie's anti-tau antibody, ABBV-8E12, began Phase II studies early this year for Alzheimer's and progressive supranuclear palsy. It has both fast-track and orphan-drug status in the latter indication.

Smaller vTv Therapeutics is in Phase III for its receptor for advanced glycation endproducts (RAGE) inhibitor, azeliragon. RAGE is upregulated in Alzheimer's and is thought to play a role in inflammation, amyloid buildup, and tau phosphorylation. Azeliragon has a long checkered history, but is now moving forward.

Farther down the pipeline, companies like Cognition Therapeutics are trying different approaches. The company's investigational drug CT1812, a small molecule that targets sigma-2 receptor complex on neuronal synapses to mitigate amyloid toxicity, was recently fast-tracked by the FDA.

These organizations may have better success with their Alzheimer's therapies, or the industry may have to rethink its strategies.

"Some of the challenges have been around patient recruitment," says Pagliaro. "We're recruiting patients who have early signs and symptoms already. Is that really the right time to treat? Should we be treating Alzheimer's prophylactically, like the way we treat cardiovascular disease?"

Given the development of accurate biomarkers, this could be a sound strategy. On the other hand, are private payers going to pay top dollar for prophylactic

### *FAST FOCUS*

» According to recent statistics cited by the Pharmaceutical Research and Manufacturers of America (PhRMA), 74% of medicines currently in clinical development are potentially first-in-class medicines, and 822 projects—defined as unique molecule-indication combinations—are designated by the FDA as orphan drugs.

» A range of novel scientific approaches are being pursued in the clinic, including cell and gene therapies, DNA and RNA therapeutics, and conjugated monoclonal antibodies.

» Checkpoint inhibitors have sparked pursuits in combination therapy in cancer, as pharma companies seek to maximize their benefits for more patients. Beyond the major combination groupings that have emerged, EvaluatePharma notes a sharp increase over the past two years of PD-L1 combinations involving cancer vaccines and oncolytic viruses.

» Along with research efforts in Alzheimer's disease focused on beta amyloid plaques and tau protein tangles, potential drugs are also targeting decreasing inflammation in the brain that is associated with Alzheimer's and enabling the immune system to fight the disease.

| TOP FIVE R&D ASSETS CNS | |
|---|---|
| DRUG NAME: | MultiStem |
| COMPANY | Athersys |
| PHASE | II |
| SALES PROJECTION (2022): | $1.977bn |

| | |
|---|---|
| DRUG NAME: | Aducanumab |
| COMPANY: | Biogen |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.536bn |

| | |
|---|---|
| DRUG NAME: | Intepirdine |
| COMPANY: | Axovant Sciences |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.116bn |

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|---|---|
| DRUG NAME: | Epidiolex |
| COMPANY: | GW Pharmaceuticals |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.015bn |

| | |
|---|---|
| DRUG NAME: | SAGE-547 |
| COMPANY: | SAGE Therapeutics |
| PHASE: | III |
| SALES PROJECTION (2022): | $962m |

**** Source for all tables:***
*EvaluatePharma®*
*September 2017, Evaluate Ltd,*
*www.evaluate.com*
*http://bit.ly/2hc6iMz*

therapies when Medicare reaps the ultimate financial rewards?

For now, companies with Alzheimer's therapeutics in late-stage trials are sweating it out. They've seen the carnage, are they next?

## MS and epilepsy

Multiple sclerosis (MS) therapeutics offer a brighter picture. And, yes, this is cheating, since MS can be considered more autoimmune than CNS disorder.

Celgene's ozanimod is one of the brighter spots in the pipeline. The oral, selective S1P 1 and 5 receptor modulator is in Phase III for relapsing MS, ulcerative colitis, and Crohn's disease. In May, Celgene announced positive results for the RADIANCE trial. The drug's safety profile may give it a leg up on Novartis' fingolimod. EvaluatePharma predicts ozanimod could produce $1.4 billion in sales by 2022.

Novartis is not blind to fingolimod's shortcomings and is working on its own next-generation S1P modulator, siponimod, which could generate fewer side effects. The drug is currently in a Phase III trial for patients with progressive MS. Evaluate estimates siponimod's 2022 sales at $915.6 million.

Actelion, now part of Johnson & Johnson, is testing its S1P drug ponesimod with Tecfidera for patients with relapsing MS. Tecfidera is approved to treat psoriasis.

Epilepsy is one of the specialty markets that is getting much attention. GW Pharmaceuticals leads the way with its cannabinoid product Epidiolex, which treats Dravet syndrome, Lennox-Gastaut syndrome, and other severe forms of epilepsy. Epidiolex is in Phase III for both indications, as well as tuberous sclerosis, and has received orphan designation from the European Medicines Agency (EMA). Evaluate estimates Epidiolex's 2022 sales at $1 billion. Despite delays, the drug seems poised for FDA approval.

GW's picture brightened when Sage Therapeutics' GABA modulator, SAGE-547, for super-refractory status epilepticus, failed recently in Phase III. The company continues to look for ways to move the drug forward, perhaps focusing on patient subgroups.

Zogenix recently announced positive Phase III results for its Dravet syndrome treatment, ZX008, which took some of the luster off GW. The drug is low-dose fenfluramine hydrochloride, a serotonin booster. It was both effective and well-tolerated. ZX008 has received orphan-drug designation from both the FDA and EMA. It has also been fast-tracked in the US for Dravet syndrome. Evaluate estimates sales of $219 million in 2022.

Another interesting specialty market is migraine. Novartis and Amgen are co-developing the monoclonal antibody erenumab (AMG 334 or Aimovig), which is in Phase III studies for episodic and chronic migraines. Erenumab targets the calcitonin gene-related peptide (CGRP) receptor to block pain. A recent analysis from Novartis showed the drug reduced the number of migraine days by as much as 50% for patients who failed previous preventive therapies. Amgen has exclusive commercialization rights in Japan; Novartis has exclusive rights everywhere else.

## Combo oncology

With the first CAR-T approval, checkpoint inhibitors aren't the big new thing in immunotherapy anymore. Still, they are opening up therapeutic doorways that have been closed for a long time.

"Checkpoint inhibitors have brought drug development into tumor types that haven't seen drug development in decades," says Madelyn Hanson, manager, oncology consulting services, clinical and scientific assessment, at Kantar Health. "The clear example was last year's approval of Tecentriq in bladder [cancer]. It was the first drug approved for metastatic bladder cancer in 34 years."

Checkpoint inhibitors are also driving combo-mania, as pharma companies try to maximize their benefits for more patients.

"The way pharma innovation seems to happen is you get a big change, and then you get iterations, and then you get another big change," says Funtleyder. "We've had the big change in the checkpoint inhibitors. Now we're trying to figure out how to incorporate them into clinical practice—after trying every drug under the sun with them."

Incyte's epacadostat, an ID01 enzyme inhibitor, has shown good results when combined with Merck's approved anti-PD-1 drug Keytruda against metastatic melanoma.

Epacadostat is also being tested with two other immunotherapies, Bristol-Myers Squibb's Yervoy and Opdivo, for other indications. With the ability to extend the efficacy of checkpoint inhibitors, epacadostat looks to have a bright future. Evaluate puts 2022 earnings at $1.9 billion.

Amgen is trying a slightly different strategy, combining their oncolytic viral therapy Imlygic with Yervoy. Phase II results were positive. The proportion of patients whose tumors shrank was much higher in the combo cohort compared to patients who received Yervoy alone. Tumor size may not be the best mark of success, but patients who received the combo had a median 8.2 months progression-free survival, compared to 6.4 months with just Yervoy. Imlygic could earn $271 million in 2022, forecasts estimate.

AstraZeneca has had less-than-stellar results with its durvalumab/tremelimumab combination. The combo recently failed to improve progression-free survival in non-small cell lung cancer (NSCLC) patients. Durvalumab (Imfinzi), a checkpoint inhibitor, fared equally poorly as a monotherapy against NSCLC.

On the bright side, the FDA granted accelerated approval for the monoclonal antibody against metastatic urothelial carcinoma, a common form of bladder cancer. AstraZeneca, which is partnering with Celgene, has high hopes for durvalumab and is testing it as a monotherapy or part of a combo in multiple clinical trials. Evaluate pegs durvalumab's 2022 overall sales for multiple cancers at around $2.6 billion.

Roche and AbbVie's venetoclax (Venclexta) has been approved for chronic lymphocytic leukemia (CLL) with 17p deletion or TP53 mutation, but it's also showing promise in combination against a broader range of CLLs when combined with Rituxan. A recent Phase III showed the combo increased progression-free survival for patients with relapsed/refractory CLL. The drug is also being tested against multiple myeloma, non-Hodgkin's lymphoma (NHL), and other malignancies and could earn $2.1 billion in 2022.

Janssen just submitted a new drug application (NDA) for its androgen receptor inhibitor apalutamide for non-metastatic, castration-resistant prostate cancer. The hope is the drug can prevent the disease from metastasizing. The company's SPARTAN study apparently produced good results, though those are not available at this writing. Apalutamide is also being combined with Zytiga in early phase trials against castration-resistant prostate cancer. Evaluate has apalutamide sales at $1.1 billion in 2022.

Verastem had good news to report for duvelisib, a dual-action phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma inhibitor for CLL, increasing progression-free survival from 9.9 months (with ofatumumab) to 13.3 months. The drug also showed efficacy against indolent NHL, and Verastem is planning an NDA sometime in 2018.

> "Now we're trying to figure out how to incorporate checkpoint inhibitors into clinical practice—after trying every drug under the sun with them."

One of the most interesting possibilities is the pan-cancer strategy, targeting mechanisms that drive cancers in multiple organs. We've seen this in checkpoint inhibitors, particularly Keytruda, which receive accelerated FDA approval for adult and pediatric solid tumors that have microsatellite instability or mismatch repair deficiency.

Loxo Oncology's larotrectinib (LOXO-101) announced a 76% objective response rate across tumor types at this year's American Society of Clinical Oncology (ASCO) meeting. Larotrectinib targets tropomyosin receptor kinase (TRK) fusions.

This is interesting new territory, but it's unclear how these broad-spectrum therapies will fare in the clinic.

"The FDA is willing to approve on a tumor-agnostic basis," says Hanson. "We will see how physicians handle that."

| ONCOLOGY | |
|---|---|
| DRUG NAME: | Epacadostat |
| COMPANY: | Incyte |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.973bn |

| | |
|---|---|
| DRUG NAME: | Axicabtagene Ciloleucel |
| COMPANY: | Kite Pharma |
| PHASE: | Filed |
| SALES PROJECTION (2022) | $1.780bn |

| | |
|---|---|
| DRUG NAME: | Abemaciclib |
| COMPANY: | Eli Lilly |
| PHASE: | Filed |
| SALES PROJECTION (2022): | $1.690bn |

| | |
|---|---|
| DRUG NAME: | Rova-T |
| COMPANY: | AbbVie |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.465bn |

| | |
|---|---|
| DRUG NAME: | Apalutamide |
| COMPANY: | J&J |
| PHASE: | III |
| SALES PROJECTION (2022): | $1.108bn |

| CELL/GENE THERAPY | |
|---|---|
| DRUG NAME: | MultiStem |
| COMPANY: | Athersys |
| PHASE: | II |
| SALES PROJECTION (2022): | $1.977bn |

| | |
|---|---|
| DRUG NAME: | Axicabtagene Ciloleucel |
| COMPANY: | Kite Pharma |
| PHASE: | Filed |
| SALES PROJECTION (2022): | $1.780bn |

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|---|---|
| DRUG NAME: | JCAR017 |
| COMPANY: | Juno Therapeutics |
| PHASE: | II |
| SALES PROJECTION (2022): | $669m |

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|---|---|
| DRUG NAME: | LentiGlobin |
| COMPANY: | Bluebird Bio |
| PHASE: | III |
| SALES PROJECTION (2022): | $589m |

| | |
|---|---|
| DRUG NAME: | AVXS-101 |
| COMPANY: | AveXis |
| PHASE: | I |
| SALES PROJECTION (2022): | $583m |

## The bright new world of CAR-T

CAR-T is a good segue from oncology into gene therapy. This is another area where high hopes have been softened by colossal failures. In March, Juno halted its acute lymphoblastic leukemia (ALL) trial for JCAR015 when three patients developed brain swelling and died. The causes are poorly understood, but Juno believes it may have been chemotherapy patients received to make the CAR-T more effective. Cellectis ran into similar, though not quite so severe, troubles with UCART123.

Despite setbacks, CAR-T is rolling forward. Novartis' Kymriah was approved in August to treat ALL. The price tag is steep at $475,000, but pretty much in line with a bone marrow transplant. In October, the FDA approved Kite's Yescarta for NHL.

CAR-T is a powerful and risky therapy and drug companies are responding to some of the more worrisome side effects. The FDA recently approved Genetech's tocilizumab (Actemra) to treat severe cytokine release syndrome (CRS), a potentially deadly side effect to CAR-T therapies. No doubt, drugs like these will be actively incorporated into clinical studies.

Kite, now part of Gilead, lost the first lap of the CAR-T race to Novartis but may end up a strong finisher. In results from two clinical trials for axicabtagene ciloleucel (KTE-C19) in refractory, aggressive B-cell NHL, more than half of patients demonstrated complete responses. Based on trial data, the FDA granted KTE-C19 priority review, and the therapy was approved by the agency last month. Evaluate puts sales at around $1.7 billion in 2022.

Juno is not giving up, either. The company is partnering with Celgene on early trials for its own CAR-T therapy for relapsed and refractory aggressive B-cell NHL, JCAR017. Early data from a Phase I trial (TRANSCEND) was encouraging. Half the patients had a complete response after three months and safety was reasonably good. Evaluate puts the therapy's 2022 earnings at $669 billion.

One of the issues with CAR-T is breadth—blood cancer but no success in solid tumors. That may be changing, however. In October, Poseida released positive preclinical results in prostate cancer for P-PSMA-101. Another study out of the University of Pennsylvania showed good results against melanoma and pancreatic tumor xenografts. Early days but worth watching.

## Gene and cell-based therapies

Gene therapy epitomizes the failure/renaissance model of drug development. Following a series of misteps nearly 20 years ago, scientists retreated to the lab to find better paths forward. UniQure's Glybera was approved in Europe in 2012, but the $1 million price tag has been prohibitive. Now we are poised to see a wide variety of gene therapies in oncology, ophthalmology, hemophilia and other inherited blood disease, sickle cell, cardiovascular disease, etc.

In October, an FDA advisory committee gave its blessing to Spark's gene therapy voretigene neparvovec (Luxturna) for inherited retinal disease. The vote was 16 to 0. The therapy targets RPE-65 mutations and will be the first drug to improve hereditary blindness. In the pivotal trial, 93% of patients showed some benefit. It's an orphan indication, the condition affecting around 6,000 people worldwide. Neparvovec should be approved by January. Spark has a number of early-stage therapies in the works for hemophilia, Batten disease, and Huntington's disease.

While it is still early in the trial process, Bluebird Bio received good news on elivaldogene tavalentivec (Lenti-D), its therapy for cerebral adrenoleukodystrophy (cALD), the disease depicted in the movie *Lorenzo's Oil*. In the Phase I/II trial, elivaldogene tavalentivec halted disease progression in 88% of the treated boys even two years after treatment. Most kids with cALD don't live past 10 years old.

Bluebird has also received breakthrough therapy designation from the FDA for LentiGlobin to treat beta thalassemia, and inherited blood disorder. The drug is also being tested against sickle cell disease. LentiGlobin has had problems in trials, with some patients responding and others not so much. As a result, the therapy has been reformulated. Evaluate puts the drug's sales at $589 million in 2022.

AveXis has received the go-ahead from the FDA to begin the pivotal trial for AVXS-101 for patients with spinal muscular atrophy (SMA) type 1, which causes muscle weakness and paralysis. The trial will measure the therapy's efficacy after a single dose. AVXS-101

seeks to mitigate the defective SMN1 gene. Evaluate estimates sales at $583 million in 2022.

Voyager Therapeutics also received good news for their advanced Parkinson's disease gene therapy, VY-AADC01, from its Phase Ib trial. Patients showed lasting improvements in motor function after a single dose.

Development partners Alnylam and Sanofi Genzyme announced promising Phase III results for their RNAi drug, patisiran, against hereditary ATTR amyloidosis with polyneuropathy, which affects multiple organs. Around 50,000 people suffer from the condition worldwide.

Alnylam is also partnering with The Medicines Company on the latter's Inclisiran, which inhibits PCSK9 synthesis through RNAi to lower cholesterol. Phase II results from the Orion-1 trial showed positive results for both safety and efficacy and Inclisiran is likely headed into Phase III trials. Evaluate estimates Inclisiran sales at $354 million by 2022.

Are big changes ahead for this field? Gene therapy is not just for biotechs anymore. Pfizer has pledged $100 million to build a gene therapy facility in North Carolina, expanding a plant it acquired after purchasing Bamboo Therapeutics. Pfizer is also collaborating with Sangamo and Spark, so the big pharma appears to have significant plans in the space.

On the cell-based therapy side, Athersys' MultiStem has received the FDA's new regenerative medicine advanced therapy (RMAT) designation. MultiStem is made from human stem cells derived from bone marrow and can be frozen and stored. Once administered, the cells are designed to produce beneficial factors that could help the body repair damage and reduce inflammation. The product has the potential to be an off-the-shelf cell therapy that could treat stroke, traumatic brain injury (TBI), neonatal hypoxic ischemia, and other conditions.

Athersys has had challenges moving MultiStem through a Phase III trial in Japan. The company recently partnered with Nikon CeLL to get past some of these manufacturing problems. Evaluate puts MultiStem sales potential at $1.9 billion in 2022.

## New antibiotics

Antibiotic resistance is a growing issue and a potential healthcare emergency. Without effective antibiotics, many of the treatments we've come to take for granted—chemotherapy, transplants, routine surgeries—would become incredibly risky, perhaps impossible.

Without effective antibiotics, many of the treatments we've come to take for granted—chemotherapy, transplants, routine surgeries—would become incredibly risky, perhaps impossible

Achaogen's plazomicin, which received breakthrough designation from the FDA this year, is being developed to treat carbapenem-resistant enterobacteriaceae (CRE) and other serious infections. Last year, Achaogen announced positive Phase III results for plazomicin against CRE and complex urinary tract infection (cUTI). In addition, the company recently presented five posters at IDWeek in San Diego, highlighting the antibiotic's potential. Plazomicin seems poised for approval. The drug could reach $436 million sales in 2022, according to Evaluate projections.

Cadazolid, from Actelion Pharmaceuticals, is in development to treat *Clostridium difficile*-associated diarrhea. The antibiotic is being tested against vancomycin in two Phase III trials (IMPACT 1 and 2). So far, cadazolid has met its primary goal—non-inferiority to vancomycin—in IMPACT 1 but not IMPACT 2. Evaluate puts potential 2022 revenue at $116 millon.

MicuRx Pharmaceuticals' MRX-1 has shown activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The drug is being developed to treat acute bacterial skin and skin structure infection (ABSSSI). MicuRx began enrolling 600 patients in China last year for a Phase III study.

Iclaprim was initially developed by Roche and has now moved to Motif Bio. An advanced

| CARDIOVASCULAR | |
|---|---|
| DRUG NAME: | LJPC-501 |
| COMPANY: | La Jolla Pharmaceutical |
| PHASE: | Filed |
| SALES PROJECTION (2022): | $490m |

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|---|---|
| DRUG NAME: | Bempedoic Acid |
| COMPANY: | Esperion Therapeutics |
| PHASE: | III |
| SALES PROJECTION (2022): | $466m |

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|---|---|
| DRUG NAME: | EG-1962 |
| COMPANY: | Edge Therapeutics |
| PHASE: | III |
| SALES PROJECTION (2022): | $46m |

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|---|---|
| DRUG NAME: | Inclisiran |
| COMPANY: | The Medicines Company |
| PHASE: | II |
| SALES PROJECTION (2022): | $354m |

| | |
|---|---|
| DRUG NAME: | Mavacamten |
| COMPANY: | MyoKardia |
| PHASE: | III |
| SALES PROJECTION (2022): | $283m |

**JOSH BAXT** is a freelance science and healthcare writer

dihydrofolate reductase inhibitor, iclaprim is designed to treat ABSSSI and hospital-acquired pneumonia (HAP). The drug has had its ups and downs but met its primary endpoint—non-inferiority to vancomycin—in a recent Phase III study (REVIVE-2). Iclaprim recently received orphan-drug designation from the FDA and is poised for approval. The drug could bring in $522 million between Motif and partners in 2022.

Circling back to combination treatments, Merck is combining relebactam, imipenem, and cilastatin to treat CRE. The therapy met endpoints in a Phase II study against cUTI. Two Phase III trials are ongoing.

Nabriva Therapeutics' lefamulin, initially developed by Roche, has shown potential against resistant gram-positive strains. Lefamulin showed strong results against community-acquire bacterial pneumonia (CABP) in a pivotal Phase III trial (LEAP-1). Evaluate estimates $293 million in 2022 sales between Roche and partners.

Omadacycline, from Paratek Pharmaceuticals, is a broad-spectrum antibiotic that has shown efficacy against gram-positive and gram-negative bacteria and is being tested against ABSSSI and CABP. The first Phase III trial (OASIS), compared omadacycline to linezolid for ABSSSI and met all endpoints. Another Phase III study (OPTIC) found omadacycline effective against CABP. Sales in 2022 could reach $93 million.

## Cardiovascular roundup

The cardiovascular space is in consolidation mode at the moment. There's little groundbreaking on the immediate horizon. However, there are always efforts to refine approaches to help more patients.

The FDA recently accepted La Jolla Pharmaceutical's NDA for LJPC-501 for patients with distributive or vasodilatory shock who do not respond to vasopressors. A Phase III study met blood pressure endpoints and showed a trend toward longer survival. Evaluate estimates 2022 sales at $490 million.

Esperion Therapeutics' bempedoic acid has shown the ability to reduce LDL when combined with ezetimibe and atorvastatin. Esperion recently completed enrollment in its pivotal Phase III trial and expect to file an NDA in the first quarter of 2019. Evaluate puts estimated sales at $466 million.

> Developing an effective drug, earning FDA approval, and getting payer buy-in are all so difficult. Still, persistence pays off

EG-1962, from Edge Therapeutics, is being developed to treat aneurysmal subarachnoid hemorrhage (aSAH), hoping to improve on nimodipine, the current standard of care. Edge is evaluating EG-1962 in two clinical studies, including a pivotal Phase III trial. Evaluate estimates $46 million in revenue by 2022.

MyoKardia recently reported positive results for mavacamten (MYK-461) in the Phase II PIONEER-HCM study in symptomatic, obstructive hypertrophic cardiomyopathy. Patients showed post-exercise peak left ventricular outflow tract. This would be the first new drug for this genetic condition in more than 40 years. Mavacamten received orphan-drug designation from the FDA in 2016. Evaluate estimates 2022 sales at $283 million.

## Within reach

Developing an effective drug, earning FDA approval, and getting payer buy-in are all so difficult; it's a testament to humanity's inherent stubbornness that these medicines get made at all. Still, persistence pays off. CAR-T and other gene therapies are poised to lift off. New oncology targets are being identified with regularity. Next-generation sequencing is helping identify responsive patient subgroups and streamlining trials. It's hard, but it's doable.

And failures have their place—they help illuminate the biology and lead to better, more effective approaches. This is encouraging for those working on Alzheimer's disease therapies, though less so for patients and caregivers who need the help now.

But if anything, the current pipeline shows persistence pays off. Given enough work, even the most intractable indications can crack. PE

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# Aligning Early Advice with Long-Term Planning

The five ways pharma developers can ensure their early engagement with payers and regulators will pay off when it's time to demonstrate commercial value

*By Bengt Anell, Sangeeta Budhia, and Richard Macaulay*

As regulators lower evidentiary requirements for marketing approval to speed the development and review of new drugs for unmet medical needs, payers are demanding more data for these drugs to justify price premiums. This divide has left drug developers in a difficult position as they try to satisfy both parties in their clinical and commercial evidence plans.

On one side, for severe diseases with unmet treatment need, regulators increasingly accept clinical trial packages that lack large Phase III comparative randomized controlled trial (RCT) data and use intermediate surrogate endpoints to demonstrate a positive benefit-risk profile.

On the other side, payers want to see that a new product delivers clinically meaningful benefits (i.e., improvement in quality-of-life and morbidity/mortality endpoints that are directly relevant to patients) in well-conducted Phase III trials versus a locally-relevant comparator, as well as in more diverse, real-world settings. And they want those benefits to be cost-effective, delivering value for money. Payers, therefore, are increasingly using—and demanding—real-world evidence (RWE) to inform their decision-making.

Recognizing the difficulty sponsors face in meeting their requirements, regulators and payers have developed programs to help pharmaceutical companies get early, formal advice and guidance on how to build an evidence generation plan that will provide the optimal data package for each.

However, developers who seek early advice and engagement often find it challenging to reconcile input from stakeholders with differing mandates and goals (see table on facing page). Meetings and discussions alone can't align these differing needs, and there's no such thing as a perfect evidence package because there are always trade-offs between time, costs, risks, and utility.

Therefore, companies need to be strategic in how they engage with regulators and payers to navigate these complexities, and to avoid duplicating work and creating unnecessary challenges for themselves.

## Regulatory approval without market access is a Pyrrhic victory

The industry's pipeline is increasingly dominated by transformational therapy classes: CAR-T cell treatments, immuno-oncology, and gene therapies. At the same time, the proliferation of accelerated regulatory pathways across the globe are offering streamlined and more flexible approaches to drug development. For example, if results warrant, it's now possible for a first-in-human trial of an experimental cancer drug to morph, without pause, into a pivotal efficacy trial.

Developers must seek advice on the regulatory requirements for these technologically advanced products, and novel, possibly curative (i.e., single-use) treatments. But regulatory approval does not necessarily confer commercial viability.

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» Studies have shown that regulatory guidance can boost product success rates and shorten clinical development timelines. For instance, in the US, marketing applications that are submitted utilizing a pre-investigational new drug meeting have reportedly experienced median clinical development durations almost two years shorter than those that didn't include the meetings.

» Europe is largely considered the key arena for early engagement with regulators and payers on product development. However, companies need to be strategic in their approach amid the fragmented European health technology assessment (HTA) landscape, which covers 77 different agencies in 29 countries.

» Developers should expect wide-ranging advice, concerns, and critiques from payers and prioritize feedback when creating evidence plans. For example, in Germany, comparative effectiveness research is a prized data channel, while in the UK, cost-effectiveness data is valued more.

**Stakeholder Input: Differing Needs**

| | Regulators | HTA Agencies/Payers |
|---|---|---|
| Mandate(s) | Product quality (i.e., purity, consistency)<br>Safety<br>Efficacy | Cost-effectiveness<br>Comparative clinical effectiveness<br>Budget optimization and affordability |
| Goal | Favorable risk-benefit ratio | Value for money<br>Proven benefit versus current treatments |
| Perspective(s) | Patients, providers | Patients, providers, payers, national healthcare systems, governments, society |
| Evidence types preferred/ accepted | Randomized controlled trials (RCTs); For rare and/or severe diseases with high unmet needs: immature single-arm trial data with no comparative data | Large Phase III trials demonstrating long-term (i.e., mature data), clinically meaningful improvements on patient-relevant endpoints, supported by robust health economics analyses. RWE that shows these outcomes will be seen in a real-world setting |
| Comparators preferred/ accepted | Placebo; usual or "traditional" standard of care (SOC); historical controls | Active controls; head-to-head comparisons with payer-chosen comparators; locally/nationally relevant SOC; currently reimbursed SOC; optimal ("best") SOC |
| Patient population of interest | Tightly defined (homogenous in terms of disease) set of patients receiving meticulously documented, identical care in a controlled setting | Patients with varying comorbidities and levels of compliance receiving average care of variable quality in diverse settings |
| Endpoints preferred/ accepted | Clinical, including biomarkers/surrogates (e.g., in oncology, tumor shrinkage, progression-free survival; in diabetes, HbA1C levels in the blood) | Patient-relevant (e.g., in oncology, morbidity, mortality, quality of life [QoL]; in diabetes, incidence of cardiovascular disease, vision loss, renal failure); robust data in relevant patient subgroups |
| * Health economics and outcomes research (HEOR) considered | None. (Note: The 21st Century Cures Act requires the FDA to develop a framework and guidance for using real-world evidence [RWE] to support some regulatory decisions in the future. Likewise, the EMA is actively promoting a gradation of evidence generation from clinical trials alone to a mix of evidence.) | RWE; Cost-utility (e.g., quality-adjusted life year [QALY]); cost-effectiveness (e.g., incremental cost-effectiveness ratio [ICER]); comparative effectiveness; budget impact; burden of disease impact |

Source: PAREXEL International

The divergent mandates and methods of regulatory and health technology assessment (HTA) agencies/payers.

* The many national, regional, and local payers in the EU each define HEOR and economic value differently. Some, such as the National Institute of Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) in the UK, focus on cost-effectiveness. Others, such as Haute Autorité de Santé (HAS) in France and the Federal Joint Commission (G-BA) in Germany, concentrate on comparative clinical effectiveness. Other HTAs, such as the Spanish and Italian regional authorities, are most concerned with budget optimization and affordability.

For example, Glybera, a gene therapy to treat a rare metabolic disease that triggers pancreatitis, was granted a five-year marketing authorization in the European Union (EU) in 2012 under the category "exceptional circumstances." But the manufacturer (uniQure N.V.) announced it would not renew the EU license when it expired last month. Why? At a cost of $1.1 million per treatment, and addressing a condition that affects only one in one million people (a total market of 150 to 200 people in the EU), Glybera had only been used commercially and paid for once as of mid-2016. Payers decided that the evidence did not justify its price tag.

Payers and value watchdog organizations, especially those in Europe, foresee further troubles for these novel drugs. In January 2017, the German health technology assessment (HTA) agency IQWiG (Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen), ruled that the "additional benefit" of Xalkori (crizotinib) for non-small cell lung cancer patients with a ROS1 mutation was "not proven." If this verdict is ratified, Xalkori would only qualify for reference pricing versus its generic chemotherapy comparators, rather than premium pricing.

In a press release announcing the verdict, Beate Wieseler, IQWiG's head of drug assessment observed, "The current dossier assessment shows what problems can arise for early benefit assessments if drugs are approved early on the basis of relatively few data—we often see this, particularly in rarer diseases. If the European Medicines Agency (EMA) were to implement their 'adaptive pathways' plan and in future were to approve even more drugs with even fewer data, then this problem could be further aggravated."

## Early engagement: Smart call, but be savvy

In the face of these ominous trends, the developer's goal must be to create a tailored, data-based

evidence plan that can reduce risk, guide rational development, support regulatory approval, and demonstrate product value to payers, prescribers, and patients in a timely (and affordable) manner.

Early engagement with regulators and payers is critical to such a plan, but it's not always easy to obtain, interpret, or utilize such advice effectively. Here are five ways to get the most out of regulatory and payer guidance:

### 1. Seek advice in the right places

There are multiple mechanisms for formal, early interaction with both regulators and HTA bodies. The most advanced of these mechanisms exist in the EU and the US. Data shows that regulatory advice can boost success rates and shorten clinical development time:

- An EMA study showed that between 2008 and 2012, 85% of marketing authorization applications (MAAs) that received and followed early scientific advice (SA) were approved, as opposed to only 41% that did not seek SA.
- Of 132 marketing applications submitted to the FDA between 2008 and 2012, the 49 which utilized a pre-investigational new drug (PIND) meeting had a median clinical development time (CDT) of 6.4 years; the 83 applications with no PIND meeting had a median CDT of 8.3 years.

For companies seeking advice on what payers want—a major factor in securing market access in many of the EU's single-payer systems—Europe is the key arena for early engagement. But developers must tread carefully across the fragmented European HTA landscape, which encompasses 77 different agencies in 29 countries.

It is important for pharma companies to start engaging in countries with the most established early HTA processes: the UK, France, Germany, Sweden, and Norway. Select target HTA bodies based on factors such as standard of care (SOC)/treatment pathway for the target disease, the track record of prior HTA results in the therapeutic area/indication, and the incidence rates of relevant conditions, which vary by country.

For example, Germany is Europe's biggest market for pharmaceuticals, but it also has some of the most stringent clinical evidentiary requirements for proving "added benefit," and for qualifying for potential price premiums. Recently, we advised a client to skip seeking advice (or reimbursement) from the G-BA, the main decision-making body of German physicians, dentists, hospitals, and health insurance funds, because there were very few patients with the relevant condition in Germany (while there were many in both the UK and Portugal).

More is not better when pursuing early engagement with regulators and payers; identify the best, most relevant sources of advice, and pursue those.

### 2. Understand the risks

Early advice can help optimize pivotal clinical trial designs, and enhance data packages with relevant RWE, but it also comes with risks, including:

- The advice is non-binding. Regulators and payers can change their minds, and their advice, years later, when official product assessments are underway.
- Obtaining and adhering to advice is no guarantee that regulators or HTAs will consider the clinical data or RWE successful or sufficient once they examine it closely.
- Sponsors can only meet with a small fraction of the payers and regulators that will ultimately review their data dossier, so the advice they receive will, perforce, be incomplete.
- Early advice won't protect against market changes five to 10 years down the road. For instance, if a blockbuster cure emerges that transforms an indication's treatment pathway and a drug's competitive landscape, all bets are off, regardless of the advice a sponsor has received.

Companies must perform due diligence and gather competitive intelligence to plan for many contingencies. Bringing suboptimal or poorly-prepared briefing documents to meetings could increase a sponsor's chance of an unwanted outcome. If meetings end without agreement on the development plan, the result could be delays and increased costs.

These and other risks can be mitigated if companies pursue early engagement with a full understanding of the potential pitfalls, and address them proactively.

### 3. Do your homework

Many organizations fail to appreciate that their role is not to be a passive recipient of information during meetings with regulatory authorities.

For example, too many companies wait for regulators to provide leadership and clarity on complex issues (e.g., biomarker validation) instead of developing their own approaches. The FDA and EMA look to pharma companies for leadership on novel technologies. And although regulators are properly cautious, they also are eager to break new ground, so

long as the science is sound, and the studies well designed. Companies need to show up with data, plans, and a compelling rationale for both. Even if a developer has a good scientific backstory, it's smart for them to introduce their ideas—backed by emerging data from their studies—as early as possible. Such an approach helps build mutual understanding with regulators.

It's important to be an active participant in meetings. Summarize the discussion, outline agreements, and list action items. Make sure all concerns and questions have been addressed before leaving a meeting. Review the agency's official meeting minutes (if it generates them), and notify regulators of any disconnects between the company's understanding and theirs. Ask for clarification.

Unless companies do their homework, they can't push back (politely) when regulators or HTAs suggest including an additional analysis or endpoint that adds, for example, three years to a clinical trial; a developer can't talk about feasibility and utility unless it knows its stuff thoroughly.

When it comes to nailing down what HTA agencies want from RWE, developers need to be well-prepared to get clarity on:

- Preferred comparator(s), patient-relevant outcomes of interest, whether surrogate endpoints will be considered, important patient subgroups to analyze, and any other design issues with high levels of uncertainty.
- How to mitigate payers' concerns about health economics modeling; that is, how to increase its credibility and reliability, making it more transparent and avoiding debatable assumptions and accusations that the data are being cherry picked.
- How to prospectively identify (and then fill) gaps in evidence.

**4. Right-size the advice you get**

Regulators and HTA agencies will proffer advice, but they won't make decisions for a sponsor. Companies must distinguish between nice-to-have and need-to-have advice and make judgment calls.

Payers have different perspectives. In Germany, for example, comparative clinical effectiveness is prized while cost-effectiveness rules in the UK. Therefore, companies should expect divergent advice, as well as concerns, warnings, and critiques; the key is to prioritize and leverage feedback to create better evidence plans.

**5. Justify your decisions**

Ultimately, sponsors are responsible for their development choices, including some that may not align with authorities' advice. When that happens, companies will have to be prepared to defend their decisions in their marketing and reimbursement applications.

Sponsors can justify well-reasoned decisions that are both scientifically sound and pragmatic with respect to what is possible to achieve in the real world. In the EU, the minutes from scientific advice sessions with regulators must be included in any future MAA.

Documentation of all engagements is crucial, even if the agencies don't provide a report. Sponsors need to substantiate advice given, and actions taken (or not taken). They should create records of all meetings and ask for confirmation even when it's not clear how much weight these documents will carry.

Commercial teams need to be at the table from the beginning to emphasize the risks of prioritizing a short-term development timeline over the longer-term prize of market access

## Merging clinical and commercial evidence

Integrating clinical and commercial evidence planning can create efficiencies and produce data that will promote both initial commercial success and sustained viability. But integration is no easy feat. For example, clinical teams may not want to wait for guidance from HTA agencies if they are intent on hitting development deadlines and if they fear that advice will be divergent anyway. That means commercial teams need to be at the table from the beginning to emphasize the risks of prioritizing a short-term development timeline over the longer-term prize of market access.

In the current complex environment of breakthrough medicines and treatments, and accelerated development pathways, companies with a strategic mindset that integrates clinical and commercial teams in early engagements with regulators and HTA agencies will benefit. Companies that pass up the opportunity, or come to these meetings insufficiently prepared, will likely struggle to succeed. PE

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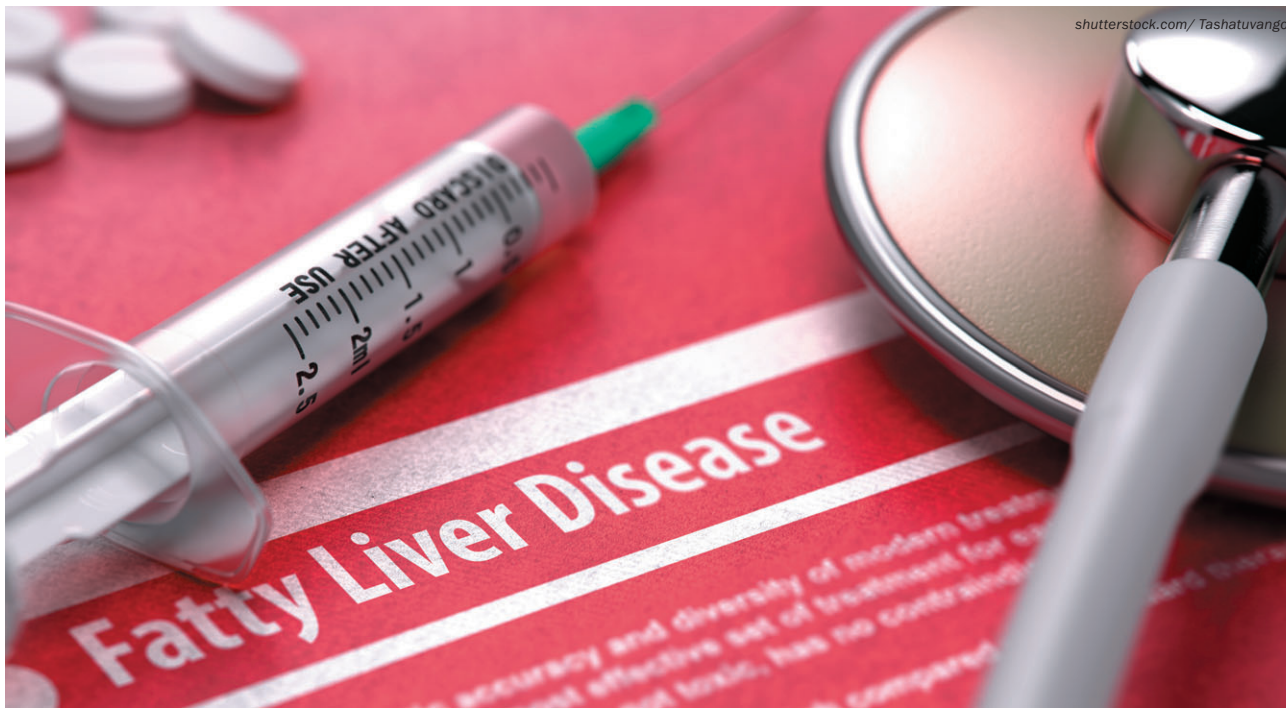

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# Strategies for Successful Access in the Untapped NASH Market

With no approved medicine yet for the liver-destroying condition, a potential rush of options on the horizon will require skillful navigation of this likely lucrative but uncharted market terrain

*By Jayachandra Reddy and Rishit Thakkar*

Non-alcoholic fatty liver disease (NAFLD) is the accumulation of triglycerides in the liver cells in the absence of any other specific liver disease. Non-alcoholic steatohepatitis (NASH) is the severest form of NAFLD, categorized by a buildup of fat in the liver exceeding 5% of its weight.

NAFLD is a major potential threat to public health and a huge market access concern. Globally, one out of four is suffering from NAFLD, with the highest prevalence in the Middle East and South America, and the lowest in Africa.

The prevalence of NASH in the US is between 3% to 5%, and it increases with the presence of metabolic disorders. NASH is expected to become the leading cause of liver transplantation by 2020 in the US.

Most NAFLD/NASH patients are asymptomatic or have nonspecific symptoms, such as fatigue. The well-known primary causes of NAFLD are obesity, type II diabetes, dyslipidaemia, and insulin resistance. However, diseases other than metabolic disorders also cause NAFLD. These include disorders

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» Therapies to treat NASH have, for the most part, proven to be ineffective or unappealing due to their long-term side effects. In addition, the majority of patients cannot achieve or sustain targeted weight loss goals.

» The prevalence of NASH in the US is between 3% to 5%, and with the growing epidemic of obesity globally, NASH could potentially become the most common cause of advanced liver disease.

» According to reports, among the seven major markets of the US, France, Germany, Italy, Spain, the UK, and Japan, the field for NASH treatments is predicted to grow from $618 million in 2016 to $25.3 billion in 2026.

of lipid metabolism (hypobetalipoproteinaemia, lipodystrophy), nutritional causes (total parenteral nutrition, starvation), medications (anti-HIV medications), and other causes (environmental toxicity). NASH can lead to other severe liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma. NASH patients are also at an increased risk of cardiovascular diseases.

Though liver biopsy is the gold standard to diagnose and stage NASH, it has limitations when it comes to patient care. It is an invasive method, it comes at a high cost, and there are chances of sampling errors. There are also risks like bleeding, pain, perforation, infection, and even (on occasion) death. Several studies are currently underway to identify the biomarkers of NAFLD/NASH and non-invasive diagnostic techniques.

## Treatment and management options

There is no approved treatment available for NAFLD/NASH. Lifestyle modification is the initial therapeutic option. Pharmacological treatment is considered for biopsy-proven NASH. Bariatric surgery is considered the last option to manage NASH. The current treatment and management options are as follows:

### Lifestyle modification

Lifestyle modification (diet and regular exercise) is the main standard of care for NAFLD, and is the initial step to manage NASH.

### Pharmacological therapy

- **Anti-obesity drugs:** Some studies on anti-obesity drugs have shown that they may improve NASH symptoms. In a small study on obese patients, Orlistat (inhibitor of fat absorption) caused weight loss and thereby improved NASH symptoms. However, long-term study data on the efficacy of these drugs on liver-related outcomes is not available, and some drugs may have serious central nervous system-related side-effects.
- **Insulin-sensitizing agents:** Several anti-diabetic drugs were studied for efficacy in NASH, considering insulin sensitivity is reduced in these patients. Though these drugs increase the insulin sensitivity, none of them were significantly beneficial in improving liver histology.

### Lipid lowering agents

- **Statins:** Statins reduce cholesterol biosynthesis, mainly in the liver, and modulate lipid metabolism through the inhibition of the enzyme HMG-CoA reductase. Statins are used to treat NAFLD as dyslipidemia frequently coexists with NAFLD/NASH, and there is an increased cardiovascular risk in these patients. However, there is limited real-world data on statin efficacy in these patients.
- **Omega-3 fatty acids:** These drugs are assumed to have multiple beneficial effects in NAFLD patients, the important reason being the alteration in the hepatic gene expression, thereby increasing fatty acid oxidation and catabolism. They are also known to improve insulin sensitivity, are anti-inflammatory, and reduce tumor necrosis factor-a levels, thus offering several potential therapeutic mechanisms. However, in a large population-based study, ethyl-eicosapentaenoic acid did not show any

Though liver biopsy is the gold standard to diagnose and stage NASH, it has limitations when it comes to patient care

**NASH Pipeline Projects**

| Drug name | Company | Mechanism of action | Phase of development | Special designation (FDA) |
|---|---|---|---|---|
| Obeticholic acid | Intercept Pharmaceuticals | FXR agonist | III | Breakthrough therapy |
| Elafibranor (GFT505) | Genfit | PPAR alpha/delta agonist | III | Fast track |
| Cenicriviroc | Allerga/Tobira | Dual CCR2/CC5 antagonist | III | Fast track |
| Selonsertib (GS-4997) | Gilead Sciences | ASK-1 inhibitor | III | - |
| Aramchol | Galmed Pharma | SCD1 inhibitor | II/III | Fast track |
| NGM282 | NGM Biopharmaceuticals | FGF19 hormone modulator | II | - |
| TRO19622 | Roche | Apoptosis inhibitor | II | - |
| BMS-986036 (PEG-FGF21) | Bristol-Myers Squibb | FGF agonist | II | - |
| GR-MD-02 | Galectin | Galectin-3 inhibitor | II | Fast track |
| Volixibat (SHP626) | Shire | ASBT inhibitor | II | Fast track |
| MGL-3196 | Madrigal Pharma | THR-β agonist | II | - |
| Solithromycin | Cempra | Macrolide antibiotic | II | - |
| GS-0976 | Gilead Sciences | ACC inhibitor | II | - |
| IMM-124E | Immuron | Immunomodulator | II | - |
| GS-9674 | Gilead Sciences | FXR agonist | II | - |
| LJN452 | Novartis | FXR agonist | II | Fast track |
| LMB763 | Novartis | Not available | II | Fast track |
| Emricasan | Conatus/Novartis | Caspase protease inhibitor | II | Fast track |
| IVA337 | Inventiva Pharma | PPAR agonist | II | - |
| MT-3995 | Mitsubishi Tanabe | Selective mineralocorticoid receptor antagonist | II | - |
| Semaglutide | Novo Nordisk | GLP-1 agonist | II | - |
| MN-001 (tipelukast) | MediciNova | LT antagonist/PDE inhibitor/5-LO inhibitor | II | Fast track |
| DS102 | Afimmune | Anti-inflammatory and antifibrotic lipid | II | Fast track |
| Saroglitazar | Zydus Cadila | PPAR agonist | II | - |
| CF102 | Can-Fite Biopharma | Adenosine A3 receptor agonist | II | - |

***Mechanism guide —*** *ACC: Acetyl-CoA carboxylase; ASBT: apical sodium dependent bile acid transporter; ASK-1: Apoptosis signal-regulating kinase 1; CCR: Chemokine receptor; FGF-19: Fibroblast growth factor; FXR: Farnesoid X receptor; LO: Lipoxygenase; LOXL2: Lysyl Oxidase: like protein 2; LT: Leukotriene; PDE: Phosphodiesterase E; PPAR: Peroxisome proliferator-activated receptor; SCD1: Stearoyl Coenzyme A Desaturase 1; THR-β: Thyroid Hormone Receptor* β

Drug candidates currently in late-stage development to treat non-alcoholic steatohepatitis.

significant effects on NASH symptoms.

» **Antioxidants:** Oxidative stress is an important step in the pathogenesis of NASH and its progression. Vitamin E has antioxidant properties, and is vastly studied as a potential treatment for NASH. Though Vitamin E demonstrated improvement in steatosis in a clinical study, it failed to improve the necro-inflammatory activity or alanine aminotransferase levels.

### Bariatric surgery

Bariatric surgery causes massive weight loss and remarkable histological improvement, including partial reversal of cirrhosis. In morbidly obese patients, bariatric surgery improves the histology, including resolution of NASH in 75% of cases and reduction of fibrosis in 34% of cases after a long follow-up. Massive weight loss associated with the surgery reduces pro-inflammatory mediators, thereby improving the hepatic insulin resistance and inhibiting the hepatic inflammation.

## Challenges for early market entrants

### Drug pricing

Payers may be reluctant to cover highly-priced NASH drugs, since the medicine has to be taken for a longer duration. So, the price fixed by the early entrants will play a major role in market success. Payers may also be reluctant to cover potentially expensive drugs, in part because lifestyle modification is often the first-line treatment for NASH.

### Physician acceptance

Since lifestyle modification is the initial step to manage NASH, physicians might be reluctant to prescribe the drugs for the disorder. Hence, targeting and educating physicians will be crucial for the successful market access of products in this space.

### Patients' unwillingness to undergo diagnosis

Although the prevalence of NASH and NAFLD are high, the diagnosis rate is low since liver biopsy is the gold standard to identify the disease. Since liver biopsy is a painful procedure, some patients may opt out of diagnosis, leading to a low diagnosis rate. Hence, patient education on the long-term ill effects of this largely unknown disease is vital for the success of early market entrants.

### Diagnosis, staging of NASH

Liver biopsy is the only method available to diagnose and stage

NASH. However, this is an expensive and invasive procedure, causing patient discomfort and potential side effects, which can even lead to death. Non-invasive methods are under development. Discovery of easily identifiable biomarkers, as in patients with diabetes (serum/urine glucose, HbA1c tests), will help monitor/stage the disease, as well as in dose adjustment of the drug thereafter.

### Future competition

Many competitors are vying to garner a major share of the untapped NASH market. Considering the unmet needs in this area, regulators are also promoting the development of promising drugs by providing special designations. A thorough understanding of the strengths and weaknesses of the late-stage product pipeline or next entrants, and their impact on potential sales will help in strategizing for the sustained commercial success of NASH treatments.

### Combination therapy

There are a variety of drugs with different mechanism of actions in late-stage clinical trials to treat NASH (see table on facing page). Since NASH is a multifactorial disease, it is most likely that a multifaceted combination therapy will be needed to successfully and effectively treat the condition. Hence, the collaboration/acquisition of other effective drugs in the pipeline, and testing combination therapies earlier could be a significant strategy for early entrants.

## Prime opportunity

The prevalence of metabolic disorders such as NASH is increasing at an alarming rate, and the untapped NASH market, worth billions, is predicted to be the next big market to emerge in this segment.

Several big pharma companies, including Novartis, Gilead, and Allergan, as well as smaller players in the space, such as Intercept and Genfit, are betting big on NASH therapy, considering the large-scale unmet needs and potential financial benefits achievable by being the first entrant in the market.

Some important questions for potential new product entrants are:

- What should be the optimal price for the first drug to convince payers, and make it a blockbuster as well?
- How can physician acceptance be increased?
- How can the diagnosis rate be increased to get more patients to treat?
- Are collaborations necessary to develop combination products?

Patient education on the long-term ill effects of this largely unknown disease is vital for the success of early market entrants

The first companies to usher in new treatments to the NASH market should find answers to these questions, which will eventually help them grab a major portion of the potential market. Different market access solutions, such as forecasting, pricing strategies, business development/licensing evaluation, and go-to market strategies, would help the early entrants achieve easier access, and increase the potential of their products. Competent partners who have the industry know-how and relevant expertise in this arena can help drugmakers strategize better and identify potential avenues to reap gains in this increasingly critical market. PE

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# When HIPAA Doesn't Apply

## Navigating Data Privacy and Security Considerations

Outlining the common data transactions between life sciences companies and the HIPAA-regulated stakeholders they deal with daily—and steps pharma can take to secure and protect its own data

*By Jennifer S. Geetter and Shelby Buettner*

### *FAST FOCUS*

» Absent a HIPAA standard to guide their privacy and security decisions, biopharma companies should develop their own benchmarks—informed by US FTC principles and state law—to mitigate potential data liability.

» Life sciences companies, though not directly regulated by HIPAA, usually structure their transactions, projects, and internal data programs in a HIPAA-compliant way due to their dealings with healthcare providers, payers, patients, and other groups who have such obligations.

» Whether a small or large organization, implementation of a comprehensive privacy program can be resource-intensive. Bolstering data privacy compliance, however, is widely considered an industry differentiator because it helps preserve and maintain relationships with HIPAA-covered entities.

From research and development through postmarketing approval activities, data continues to inform and drive decision making in the life sciences industry. Consequently, there are multiple data protection and integrity considerations throughout a drug or medical device product's lifecycle—many of which are highly scrutinized. Under the current privacy framework in the US, a single piece of information may weave in and out of a regulatory framework based on the type of data or of the entity receiving or disclosing it. As a result, data privacy and security considerations can become complicated and nuanced in the absence of a mandated baseline or regulatory standard, like the Health Insurance Portability and Accountability Act (HIPAA), to govern the data transaction.

In most cases, pharmaceutical and biotech companies are not directly regulated by HIPAA, although there are exceptions. More typically, such companies are indirectly impacted by HIPAA in their interactions with providers, payers, patients, and others that have HIPAA compliance obligations and/or HIPAA-granted rights. Absent a HIPAA benchmark for their privacy and security choices, drug companies must develop their own standards informed by US Federal Trade Commission (FTC) principles and state law. In some instances, this flexibility is welcome, but it is not without the potential challenge related to the lack of a clear regulatory safe harbor. Compliance with certain baseline expectations borrowed from existing frameworks is advised to protect against potential liability, especially in light of the FTC's more opened-ended privacy expectations and enforcement. This article illustrates common data transactions between drug companies and HIPAA-regulated entities and provides an initial checklist that stakeholders may wish to use to begin an internal dialogue about data privacy and security issues.

## Historic and current regulatory oversight: How did we get here?

For historical reasons underpinned by changes in health insurance coverage, HIPAA was drafted and ratified with a focus on inclusion of stakeholders within the reimbursement corridor (providers and plans) rather than the life sciences industry. At the time of the act's passage, HIPAA included forward-looking provisions that moved the goalposts on a number of privacy and security benchmarks; for example, minimum security program requirements and the inclusion of limitations on uses—not just disclosures—of data.

In addition, by enumerating permitted uses and disclosure of protected health information (PHI) where a patient/beneficiary's written authorization was not required, HIPAA contributed to the public's reasonable expectations with regard to the balancing of public benefit and personal privacy. More than 20 years later, however, HIPAA increasingly reflects common sense, basic security measures, and not aggressive, best-in-class requirements. And it has shaped, even set, a data use and disclosure framework even when the parties to the data transaction are not HIPAA regulated. It is not uncommon to see companies describing themselves as "HIPAA compliant" even when they are not subject to HIPAA; HIPAA has become a marketing strategy and a privacy compliance shorthand.

[Pharma's] compliance with certain baseline expectations borrowed from existing frameworks is advised to protect against potential liability, especially in light of the FTC's more opened-ended privacy expectations and enforcement

The FTC, on the other hand, can be a source of direct enforcement for commercial entities regardless of whether they are HIPAA regulated. It describes itself as the country's primary privacy and security enforcer of consumer data in support of its mission to prohibit firms from engaging in deceptive or unfair acts or practices. Fair information practices (FIPs) are internationally deployed information privacy standards disseminated by numerous government entities,

| Pharma Data Privacy Checklist |
|---|
| ☐ Assess the current limits, guardrails, and risks associated with enterprise data privacy and security<br>• What types of data does the company touch and when?<br>• Does the data currently exist or will it be created?<br>• What is the purpose of the data use or disclosure? |
| ☐ Review (and implement) global internal data privacy and security policies and procedures<br>• Adhere to the practices, processes, and standards of the HIPAA pathway that a regulated entity would need to follow<br>• Ensure consistency with HIPAA's administrative, physical, and technical safeguards<br>• Integrate the FTC's fair information practices principles that govern collection limitation, data quality, purpose specification, use limitation, security safeguards, openness, individual participation, and accountability<br>• Conduct and document training annually and upon hire<br>• Regularly audit the effectiveness of the data privacy and security program |
| ☐ Implement a third-party supplier and vendor (e.g., cloud-based data storage centers) qualification process to: (1) ensure that your data privacy and security policies and procedures align with the third party and any contractual obligations, and (2) confirm that the third party has an appropriate data privacy and security program |
| ☐ Review existing contractual requirements for data privacy and security provisions<br>• Determine whether your current data privacy and security program meets the requirements |
| ☐ Review and, as necessary, modify authorization and informed consent forms; develop template future use language to be used in authorizations |
| ☐ Review the fees paid to vendors for marketing-related services covered by HIPAA<br>• Assess reasonableness and fair market value considerations |
| ☐ Develop checklists and decision tree to accurately categorize different types of use and disclosures |
| ☐ Develop prospective standards for de-identification |

including the FTC, as well as trade groups. Although compliance with FIPs is advised as a best practice, FIPs are only principles, unlike the HIPAA Privacy and Security Rule's mandatory enumerated requirements. The FTC does not have corresponding regulations and adds additional layers of compliance requirements and complexity in making the determination when a life sciences company has "complied enough."

## Data exchanges & HIPAA interactions

### Contracting

Usually, life sciences companies are not directly regulated by HIPAA as a covered entity (CE) or business associate (BA), but often must structure their transactions, projects, and internal data programs in a HIPAA-compliant way to ensure partnering CEs and BAs meet their data obligations. CEs and BAs frequently attempt to mitigate the potential for downstream non-compliance and typically mandate HIPAA and other data privacy and security compliance provisions in contracts with life sciences companies. In our experience, however, privacy, security, and data protection programs may be siloed within an organization's divisions and significant inconsistencies in the complexity of these programs exist across and within the life sciences industry. Absent an analogous baseline HIPAA standard, the checklist above may be useful to life sciences companies seeking to build their privacy and security infrastructures.

### Written authorizations

Life sciences companies analyze research data for a variety of purposes—to develop new drugs, broaden the intended use of existing drugs, conduct real-world evidence and comparative effectiveness analyses, compete against biosimilars, and undertake targeted product surveillance to identify trends. In some cases, life sciences companies will need PHI for these activities, some of which will require that the individual execute a HIPAA written authorization for the disclosure of PHI to the company. The authorization must be written in plain language and include a specific and meaningful description of the data, the purpose of the requested use or disclosure, the identities of the disclosing and receiving parties, the process for revocation, an expiration date, and a signature.

### Excluding activities

HIPAA permits the use and disclosure of PHI when expressly authorized by a patient/beneficiary or when such use or disclosure is expressly permitted without authorization by the Privacy Rule. In certain circumstances, a life sciences organization may play a direct role in patient care, serving as a non-covered entity healthcare provider. For example, when a device company uses PHI to counsel a surgeon to determine the appropriate size, type, or other specifications of a prosthetic device for use in a surgery, the company is providing "treatment." Under HIPAA, this disclosure of PHI to a medical device company for the covered provider's own treatment purposes is permitted without the patient's authorization.

Although the particular agency guidance concerns a medical device example, as the guidance was sought by that industry, it would seem that the same logic would apply in those cases where a non-device life sciences company received PHI to assist with treatment. The public disclosure pathway also allows the disclosure of PHI to a drug company without an authorization when, for example, a CE makes an adverse event report to the manufacturer of an FDA-regulated product.

Determinations of whether HIPAA applies to other biopharma activities have occurred incrementally through agency guidance, Q&A, and other interpretive activities. Life sciences companies would benefit from thoughtfully and regularly monitoring data

privacy and security guidance and enforcement activities to preserve compliance with evolving standards.

### Future use

Research data is typically collected by a CE and provided to a drug developer for a particular study. Years later, when the company seeks to use or disclose this same data for an unanticipated purpose, it can be less clear what the firm can or should do. At the time of drafting the authorization, sponsors and researchers may be unable to anticipate all future possible uses and disclosures of data derived from a single clinical trial.

Today, legal and normative considerations are implicated as drug companies analyze whether an authorization's scope as originally drafted was appropriately broad and included the new proposed use. One other consideration should be to manage subjects' expectations within the authorization to ensure it appropriately describes downstream use of their PHI and whether the data will be protected under the same HIPAA requirements that apply to the original CE.

### De-indentification

Drug companies use de-identified data to track surveillance, prescribing, and other patient trends. HIPAA de-identified data is not deemed PHI under HIPAA and may be used or disclosed by a CE without authorization. When a life sciences company's activities are not regulated under HIPAA's two de-identification pathways, there is no clear regulatory standard or trustworthy best practice to determine when data becomes identifiable. The risk of re-identification of believed-to-be-de-identified data continues to evolve due, in part, to technological advancement coupled with an always-growing quantity of data. Big data and analytical capabilities exacerbate this issue by attributing single data points of health information to a particular individual, thereby rendering the data identifiable. The industry is left to resolve when data is de-identified. The implementation of prospective internal guardrails may decrease or mitigate the risk of re-identification.

### Customer communications

Communication with current customers, for example, related to a new formulation of a currently-prescribed drug is another activity where a drug company or its vendor may be subject to HIPAA. Written authorization is necessary before PHI may be used or disclosed for marketing purposes by HIPAA-regulated entities, but is not required for every communication with a customer. Generally, life sciences companies should keep in mind that the characterization of a communication as treatment, a healthcare operation, or marketing is imperative to analyzing whether a written authorization is required or an exception is appropriately met (e.g., refill reminders).

## Checklist tool

In the absence of a clear regulatory standard, drug companies still have opportunities to implement best practices to mitigate potential data liability and enforcement. Basic privacy literacy is vital to protecting companies from liability, negative publicity, and steep enforcement actions by minimizing human error and maximizing aligned public expectations. Regardless of the size of a company, there is often a demonstrated need for implementation of a comprehensive privacy program designed for all emerging data-driven activities that the industry leverages. Although this implementation may be resource intensive, bolstering data privacy compliance is an industry differentiator that simultaneously preserves and maintains relationships with CEs. PE

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# Interpreting UK's Post-Brexit Life Sciences Strategy

## Examining the access outlook and implications from the UK's recently unveiled blueprint as it prepares for secession

*By Neil Grubert*

### FAST FOCUS

» The life sciences sector in the UK reportedly generated £64 billion ($85 billion) in revenue in 2016, employing more than 233,000 scientists and staff. The global life sciences industry is expected to reach more than $2 trillion in gross value by 2023.

» UK's life sciences strategy post-Brexit proposes a program to address future healthcare challenges in the UK, called HARP—the Health Advanced Research Program. Its aim is for NHS and UK-based industries to partner in creating new ways to deliver sustainable healthcare; for example, working with NHS Scotland, Scottish Universities, and Scottish Industry.

» The biggest hurdle to wholesale implementation of the UK strategy may be funding, as despite recently launched initiatives in advanced therapies, advanced medicines, and vaccines development and manufacturing, it's uncertain if the government will be willing to commit the resources required to support the full range of proposals in the report.

The eagerly awaited life sciences strategy commissioned by the UK government avowedly "places an emphasis on putting the UK in a world-leading position to take advantage of the health technology trends of the next 20 years." The report, prepared by eminent geneticist Prof. Sir John Bell, and released in August, is the product of consultation with a range of stakeholders, including the National Health Service (NHS), the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA), the devolved administrations in Scotland, Wales, and Northern Ireland, a range of manufacturers, and charities.

### Five key themes

The strategy covers five broad themes: the UK's science base, growth and infrastructure, collabo-

ration between the NHS and industry, the digitalization of healthcare, and ensuring access to the skills needed to support a flourishing life sciences industry. Table 1 summarizes the core recommendations and strategic goals in each of these five areas.

## Regulation

Curiously, regulation is not one of the key themes of the life sciences strategy. Nevertheless, the report does include a short section devoted to this subject, with a focus on the implications of Brexit for the future regulatory environment in the UK.

The strategy notes that, "given the UK market size at around 3% of global pharmaceutical sales, a wholly free-standing system would likely be high cost—both in terms of efficiency and attractiveness to companies who typically apply to the largest markets first. Industry's view is that the UK and the MHRA (Medicines and Healthcare Products Regulatory Agency) should therefore seek to continue to work closely with the EMA (European Medicines Agency) to deliver the best regulatory service for patients across the EU and UK." The report recommends different approaches for the various elements of regulation:

- For clinical trials, pharmacovigilance, and other activities in which larger patient populations improve the quality of evidence for decision-making, the UK and the EU should pursue continued collaboration. The UK should also seek continued participation in mutual recognition agreements, such as the FDA/EMA agreement with regard to manufacturing inspections.
- For pharmaceutical licensing, continued participation of the MHRA in the EMA's dossier reviews and joint scientific deliberations would be beneficial to patients in both the UK and EU. If the UK did not wish to be involved in the EU voting system, it could make its own "sovereign decision" based on the shared information and deliberations.
- For medical devices, it would be advantageous for the UK to continue to use the CE marking system, which applies not just in the EU, but also in Israel, Norway, and Turkey.

The strategy is cautious about talk of the UK pioneering an innovative regulatory approach to emerging technologies, such as cell and gene therapies, algorithms, and digital medicines. Within the current EU regulatory system, the MHRA has been a leading advocate of reform (e.g., adaptive licensing), but a post-Brexit UK would need to ensure that any pursuit of new approaches to regulation did not jeopardize its involvement in EU systems and processes.

The report does identify a couple of areas of regulation in which the UK might usefully distance itself from practice in the EU. The strategy recommends that the UK continue its relatively liberal approach to the regulation of stem cell research. The General Data Protection Regulation (GDPR), due to be implemented in May 2018, will make data sharing more onerous in the EU. The strategy recommends that, following Brexit, the UK should "attempt to maintain the current balanced approach to

**Strategy Overview**

| Focus | Core recommendations | Strategic goals |
|---|---|---|
| Science base | Establish the Health Advanced Research Program (HARP) to undertake large research infrastructure projects and high-risk "moonshot programs" | Over the next decade, create two to three entirely new industries in fields such as genomics, diagnostics, digital health technology, artificial intelligence, and healthy ageing |
| | Increase funding for basic science to ensure the UK is in the upper quartile of OECD R&D investment | Attract 2,000 new discovery scientists from around the world |
| | Enhance UK clinical trial capabilities | Over the next five years, increase by 50% the number of clinical trials and raise the proportion of change-of-practice studies and trials with novel methodologies |
| Growth and infrastructure | Ensure the tax environment supports growth | Over the next decade, create four UK-based companies with a market capitalization of > £20 billion |
| | Boost investment in manufacture and export of high-value health technologies | Over the next five years, attract 10 large (£50 million-250 million capital investment) and 10 smaller (£10 million-50 million capital investment) life sciences manufacturing facilities |
| NHS collaboration | Adopt the Accelerated Access Review's recommendations to create streamlined national market access routes for health technologies | Over the next five years, the NHS should undertake 50 collaborative programs in late-stage clinical trials, real-world data collection, or the evaluation of medical devices or diagnostics. By 2023, the UK should be in the top quartile of comparator countries for speed of adoption and overall uptake of innovative, cost-effective products |
| Data | Establish digital innovation hubs that each provide data across regions of three to five million people | Set up two to five digital innovation hubs |
| Skills | Develop a skills action plan | Build a migration system that facilitates recruitment of the best talent from around the world |

**Source:** *Life Sciences Industrial Strategy – A report to the Government from the life sciences sector; http://bit.ly/2h3ephr*

**Table 1.** The core recommendations and strategic goals in the UK's life sciences strategy report.

The strategy is cautious about talk of the UK pioneering an innovative regulatory approach to emerging technologies, such as cell and gene therapies, algorithms, and digital medicines

data sharing regulations," with a view to creating an integrated digital environment that will attract manufacturers and benefit patients. However, even companies that are based outside the EU but provide goods or services to individuals in the EU, or monitor their behavior, will be required to comply with the terms of the GDPR.

## Market access

Although the strategy document term does not explicitly mention "market access," it does contain numerous proposals related to this subject. The report asserts that "the country's strength in clinical trials puts it in an enviable position, but the UK commercial environment needs improving, with the NHS working more effectively with industry. To assure the future of the UK life sciences sector, it is necessary to improve the relationship between the healthcare system and industry, and for these partners to work more coherently together to deliver better patient outcomes and create economic growth."

The life sciences strategy broadly supports the adoption of the Accelerated Access Review (AAR), published in October 2016, which the UK government commissioned to find ways to make innovative health technologies available to patients sooner. However, the report also proposes numerous market access measures that go beyond the AAR's recommendations. Table 2 (see facing page) provides an overview of the strategy's proposals in relation to market access.

## Accelerating new drug development

The life sciences strategy endorses the AAR's call for a more-coherent national horizon scanning system and the creation of an Accelerated Access Pathway to speed up access to the most promising new drugs by up to four years. However, only five to 10 technologies—not just drugs, but also diagnostics, medical devices, and digital products—are expected to be granted transformative innovation status each year. Furthermore, not all of these technologies would necessarily complete the Accelerated Access Pathway—some might drop out at various points along the way. In addition, the pharmaceutical industry will be skeptical of the benefit of transformative innovation status without a commitment to additional funding for these privileged products.

Drug manufacturers would welcome a forum for early engagement with the NHS, the National Institute for Health and Care Excellence (NICE), and the MHRA, provided that stakeholders uphold the conclusions reached in these discussions, and do not subsequently change their minds without good cause—a recurring criticism made by pharma companies of early dialogue elsewhere.

## Improving the drug appraisal process

Parallel assessment of drugs by the MHRA and NICE, and the proposed requirement to publish final appraisal guidance within 90 days of either marketing authorization or the date of product release in the UK, could significantly expedite NHS reimbursement of new medicines. However, such a reform would require NICE to radically alter its working methods and be prepared to accept possible data limitations at launch.

The recommendation that NICE appraise all new medicines, as well as selected devices and diagnostics, would increase the institute's workload, and presumably require an expansion of its capacity.

The pharma industry would support the suggested use of more-flexible criteria in value assessments. Similarly, drug manufacturers would welcome a longer-term perspective in value assessment.

## Boosting the uptake of innovative medicines

One of the life sciences industry's greatest frustrations with the UK pharmaceutical market is its relatively slow uptake of new medicines. The life sciences strategy seeks to tackle this problem through a range of policies to assess the potential impact on the NHS of new therapies, provide guidance on the adaptation of clinical pathways, incentivize uptake, and measure adoption. Granting a new medicine conditional reimbursement approval as soon as it achieves specified licensing and value

milestones would also expedite uptake. Linking the monitoring of adoption and diffusion of new technologies to evaluation of patient outcomes would similarly give payers and providers reassurance that the impact of these innovations on the NHS will be accurately measured, presumably with a view to refining policy based on the evidence gathered.

All of these measures will likely be necessary if the NHS is to achieve the strategic goal that the UK should rank in the top quartile of comparator countries for speed of adoption and overall uptake of innovative, cost-effective products by 2023.

## Exploring new approaches to pricing

The current Pharmaceutical Price Regulation Scheme (PPRS) is due to expire at the end of 2018. The strategy document does not mention the PPRS explicitly, but it does report that the life sciences industry favors replacing the existing arrangements for drug pricing with a new long-term voluntary framework agreement by the beginning of 2019. The industry would like a new system to "balance patient access to new medicines, value for money for the NHS, and the need to incentivize industry to invest in research and development for the next generation of innovative products."

In addition, the life sciences strategy echoes the AAR in identifying a future role for a variety of commercial arrangements, including volume-based pricing, outcomes-based pricing, indication-specific pricing, and methods that leverage NHS assets other than price (e.g., time, data, access). Such arrangements would be the exception, reserved for products that are expected to have a significant impact on the NHS budget.

**Market Access Objectives**

| Objective | Proposed measures |
|---|---|
| Accelerate the development of promising new drugs | • Build a coherent national horizon scanning system to identify promising pipeline drugs.*<br>• Give the most strategically important new health technologies "transformative innovation" status.*<br>• Create an Accelerated Access Pathway to speed up access to the most promising new drugs by up to four years.*<br>• Create a forum for early engagement between manufacturers, the NHS, and "arms-length" bodies such as NICE and the MHRA. |
| Improve the drug appraisal process | • Introduce parallel assessment of drugs by the MHRA and NICE.<br>• Establish a single, value-led appraisal process, managed by NICE, for all new medicines and selected devices and diagnostics. This process could involve NHS England and manufacturers in discussions regarding commercial access agreements and flexible funding and reimbursement vehicles.<br>• Use more-flexible criteria in value assessments, including QALY-based cost-effectiveness, burden of illness, unmet need, and therapeutic breakthrough impact.<br>• Develop value assessments to take account of patient outcome measures, affordability, and cost management data beyond one-year timeframes.<br>• Publish final appraisal guidance within 90 days of either marketing authorization or the date of product release in the UK.<br>• Ensure that any new fees charged by NICE (as proposed in the AAR) are "reasonable," and offer SMEs a "special fee structure." |
| Boost the uptake of innovative medicines | • Include a resource impact assessment and clinical pathway change analysis in the appraisal process, and publish an NHS adoption plan and guidance on the clinical pathway change required for implementation.<br>• Grant conditional reimbursement approval as soon as licensing and value milestones are achieved.<br>• Use NICE analyses to calculate uptake projections, which would be approved by a committee of representatives of NICE, NHS England, and manufacturers.<br>• Establish a uniform system of national and local routes for granting access to new health technologies.*<br>• Introduce incentives for local adoption of innovations.*<br>• Use audited reports from healthcare providers to ensure that adoption levels meet NICE's definition of universal uptake.<br>• Measure trust boards and clinical commissioning groups on their uptake of "value-proven innovations," and include targets in the Care Quality Commission's regulatory framework.<br>• Link independent monitoring of the adoption and diffusion of new technologies to evaluation of patient outcomes, with a view to accurately measuring the impact of these innovations within the NHS. |
| Explore new approaches to pricing | • Replace the current Pharmaceutical Price Regulation Scheme (PPRS) with a new long-term voluntary framework agreement that would "balance patient access to new medicines, value for money for the NHS, and the need to incentivize industry to invest in research and development for the next generation of innovative products."<br>• Explore the potential of commercial arrangements such as volume-based pricing, outcomes-based pricing, indication-specific pricing, and methods that leverage NHS assets other than price (e.g., time, data, access). |
| Capitalize on the NHS's unique data resources | • Develop a national system to efficiently conduct studies generating real-world data that are accessible to researchers.<br>• Introduce mandatory e-prescribing in hospitals.<br>• Streamline the legal and ethical approval process for access to national data sets.<br>• Establish a new regulatory, health technology assessment (HTA), and commercial framework to capture the value to the UK of algorithms based on NHS data.<br>• Set up national therapy-area-specific registries coordinated by relevant charities. |

* Recommendation from the Accelerated Access Review.

QALY = quality-adjusted life year; SMEs = small and medium-sized enterprises

**Source:** *Life Sciences Industrial Strategy – A report to the Government from the life sciences sector; http://bit.ly/2h3ephr*

**Table 2.** Key objectives and proposed measures related to market access in the UK's life sciences strategy.

## Capitalizing on the NHS's unique data resources

According to the life sciences strategy, "one of the most important resources held by the UK health system is the data generated by the 65 million people covered within it." Developing platforms to facilitate the use of anonymized patient data in the R&D of new health technologies could potentially help manufacturers, improve the quality of care for patients, and—importantly—save the NHS money. The strategy document suggests that "the ability to demonstrate the true value of products on an ongoing basis should allow a reduction in the cost and time to bring new treatments to patients, with the same data enabling healthcare systems to procure

more effectively by, for example, rewarding outcomes or targeting treatments to those groups where they will work best."

The report sees a need to establish a new regulatory, health technology assessment (HTA), and commercial framework "to capture for the UK the value in algorithms generated using NHS data." This statement refers primarily to opportunities to apply lessons learned in local initiatives at a national level, thereby disseminating best practice. However, the strategy document may also be alluding to opportunities for the UK to use the value of algorithms based on NHS data as a bargaining chip when negotiating prices with manufacturers; the inference is that companies could apply what they learn in the UK to other comparable markets.

The call for the creation of national therapy-area-specific registries is interesting. Over the past decade, Italy has pioneered the development of a national network of Web-based registries, which underpin that country's extensive managed entry program. Given that both the AAR and the life sciences strategy advocate an expansion of managed entry agreements in the UK, a new network of registries would presumably play an important role in that process.

## Outlook, implications for pharma industry

Historically, the UK has been a major player in the EU regulatory environment, not least as the home of the EMA and one of the most active national agencies in centralized and decentralized approval procedures. However, with the EMA set to leave London as a consequence of Brexit, there will inevitably be a decline in UK influence, not just in decision making on individual drugs, but also shaping the overall approach to pharmaceutical regulation in Europe.

The life sciences strategy seeks to minimize the regulatory impact of Brexit by advocating continued collaboration between the MHRA and the EMA. Given the relatively small size of the UK market in global terms, continued alignment with the EU regulatory system would likely help to reduce the risk that manufacturers will delay launching new medicines in the UK. However, even if the UK government accepts the strategy's recommendations in this area, it remains to be seen if the EU will be happy for the UK to continue to play an active role in its regulatory system.

The strategy's broad endorsement of the AAR is good news for the handful of health technologies that will be fortunate to qualify for "transformative innovation" status, but it could impose unwelcome new burdens on a wider range of technologies (e.g., disinvestment in products and procedures that are deemed to be outdated or not cost-effective, new NICE fees, a budget impact threshold of £20 million [$26.5 million]).

The industry must also be concerned that the government has yet to formally respond to, let alone begin implementing, the AAR—more than 10 months (as of this writing) after its publication. Companies certainly hope the government will be quicker to act on the life sciences strategy's recommendations. However, the strategy presents the danger of a paradox: it is intended to bolster the UK's success in life sciences in a post-Brexit world, yet the government's preoccupation with negotiating—and then implementing—Brexit may limit its capacity to embrace the radical change proposed in the strategy.

Drug manufacturers would generally support the strategy's proposed changes to the HTA process, especially much earlier publication of appraisals, greater flexibility in the choice of appraisal criteria, and a longer-term perspective on the assessment of value.

Measures to boost the uptake of innovative medicines would be even more beneficial to drug manufacturers. The pharma industry has long been frustrated that NHS decision-makers have been quick to implement negative appraisals from NICE, but much slower to adopt positive recommendations (despite a statutory obligation to do so within 90 days of publication of a judgment). Manufacturers have also been highly critical of pronounced geographic variations in the uptake of new medicines—the so-called "postcode lottery."

The life sciences strategy's proposals for providing guidance on the adaptation of clinical pathways, incentivizing uptake, and measuring adoption should help to increase the use of novel health technologies in the UK. Nevertheless, the strategic goal for the UK to rank in the top quartile of comparator countries for speed of adoption and overall uptake of innovative, cost-effective products by 2023 may be somewhat ambitious.

The industry's call for a new pricing system to replace the PPRS from 2019 onward is not surprising. The life sciences strategy's recommendation that

a new system should "balance patient access to new medicines, value for money for the NHS, and the need to incentivize industry to invest in research and development for the next generation of innovative products" would keep all stakeholders happy, but it is somewhat vague as a blueprint for reform.

The proposal that the NHS should explore a wider variety of commercial arrangements for products that are expected to have a significant budget impact is interesting. To date, the overwhelming majority of patient access schemes in the UK have been simple discounts—a reflection of the resistance to the administrative cost and burden associated with more-complex types of managed entry agreement. The suggested creation of a network of national registries could play a significant role in a future shift toward performance-based agreements.

The life sciences strategy certainly identifies the NHS's unique data resources as a very significant asset in terms of attracting pharma companies to the UK market and strengthening the healthcare system's hand in negotiating with manufacturers. The report also appears to imply that manufacturers might be expected to offer the UK more-favorable pricing in return for access to NHS data that they could apply to launches in other markets.

A key question that is not thoroughly addressed by the life sciences strategy is how its recommendations will apply to all the countries that make up the UK Although the UK is extremely proud of its *National* Health Service—to the point of featuring it prominently in the opening ceremony of the 2012 Olympic Games—it is now more accurate to speak of four National Health Services, given that responsibility for healthcare is devolved to each of the constituent nations of the UK.

The most crucial question of all will be whether industry and government can agree on how to implement the key recommendations as a matter of urgency

The life sciences strategy describes itself as a "framework for the improvement of the life sciences sector for the whole of UK," but it is written from the perspective of England, which accounts for 84% of the UK population. It is unclear how references to essentially English institutions such as NICE, NHS England, the Care Quality Commission, and clinical commissioning groups will be adapted to the three other home countries.

One of the greatest obstacles to wholesale implementation of the life sciences strategy is likely to be funding. The report suggests that, "if the NHS is to be a partner of the life sciences sector, then it is appropriate that economic gains made through the life sciences strategy and the resulting efficiency benefits in the NHS should be recognized and directly used to support additional government investment back into the sector. This would create a virtuous cycle whereby the success of the UK's life sciences sector yields sustainable, increased investment in medicines and technologies which benefit patients."

At the publication of the life sciences strategy, the government announced £160 million ($207 million) of funding for new initiatives: £146 million ($189 million) for five major projects in the field of advanced therapies, advanced medicines, and vaccines development and manufacturing, and a further £14 million ($18 million) for 11 medical technology research centers to promote collaboration between the NHS and industry. It remains to be seen if the government will be willing to commit the resources required to implement the report's full range of proposals.

## Real action awaits

The life sciences strategy undoubtedly presents some exciting new opportunities for collaboration between the NHS and industry, but the report arguably raises at least as many questions as it answers. The strategy document states that it "should start the conversation between industry and government as to what both parties can invest, in order to achieve the ambitious vision set out and reap the benefits in the UK of improved health and a strong economy." The most crucial question of all will be whether industry and government can agree on how to implement the life sciences strategy's key recommendations as a matter of urgency. PE

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## A Hidden Champion

Austria's glorious history is inexorable. Vienna bursts forth with classical architecture and an abundance of double-headed eagles dot the capital serving as a constant reminder of the once mighty Austro-Hungarian Empire. Now, as the global reputation of neighboring pharma giants, Switzerland and Germany, continues to soar, Austria too is on the move, with the ambition of becoming a real driver and shaper of global medical innovation rather than merely just a link in the chain.

Nowadays a prospering local life sciences industry employs around 63,000 people and counts some 823 companies active in the combined fields of biotechnology, pharmaceuticals and medical devices. This contributes a full 9.6 billion EUR gross added value to the country's wealth, around 2.8 percent of national GDP, highlighting the economic value of a thriving life science ecosystem. Moreover, the government's newly unveiled strategy for research, development and innovation aims even higher: "to render Austria a tier-one innovation pioneer within the European Union and to raise the share of R&D investment to as much as 3.76% of GDP by 2020."

At the centerpiece of this thrust lies the capital, Vienna. "Austria has always enjoyed a strong scientific tradition with 4 Nobel prize winners since the beginning of the 20th century, but it is really in the last 25 years that life sciences and ICT have become the strongholds of the Viennese economy," recalls Gerhard Hirczi, managing director of the Vienna Business Agency. "We have matured into a medical biotech city and pioneer in niche areas such as oncology, immunotherapy, plasma and disease modifying allergy therapeutics where there are companies based here operating right at the bleeding-edge of scientific discovery."

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"There can be no denying that Vienna today represents a global pharmaceutical players' darling. Each and every one of the global top-10 ranked companies in annual sales maintains a strong presence in the Austrian capital. The same goes for the top 5 worldwide medical device developers," points out Peter Halwachs, managing director of LISAVienna. Indeed many of these multinationals run not only sales and distribution unities but also have established healthy R&D footprints as well.

According to Thomson Reuter's Sciencewatch the relative impact of clinical medicine in Austria is 58 percent above the world average. "We have been witnessing significant investments in clinical trials. Last year alone, we saw some 5000 patients taking part in Austrian trials with an especially high presence in certain specific therapeutic areas such oncology," confirms Jan Oliver Huber, secretary general of the Association of the Austrian Pharmaceutical Industry (PHARMIG).

Nor should it been forgotten that Vienna today constitutes one of most preferred European meeting spots for the international life sciences community with more than 150 medical conventions and congresses taking place every year involving the participation of literally thousands of physicians, clinicians and medical experts.

## R&D FRIENDLY

Much of the country's innovative fizz in medical science has its roots in the strong bonds forged between academia and industry when, in 1991, Austria became home to the world-renowned Vienna Biocenter (VBC). "The VBC today proudly encompasses four leading academic research institutions – the Research Institute of Molecular Pathology (IMP), the Institute of Molecular Biotechnology (IMBA), the Gregor Mendel Institute of Molecular Plant Biology (GMI) and the Max F. Perutz Laboratories (MFPL) – which, in total, play host to as many as 86 different research groups," enthuses VBC chairman, Harald Isemann.

**Alexander Biach, chairman, Hauptverband (Main Association of Austrian Social Security Institutions)**

**Jan Oliver Huber, secretary general, Association of the Austrian Pharmaceutical Industry (PHARMIG)**

The numbers are certainly intriguing. Vienna boasts almost 200,000 students making it the largest university city not only across the entire CEE, but also anywhere in the German speaking world. Impressively 36,000 of these students study in life science related meaning that approximately every 6th student encountered has a life-sciences background

What's more, the Austrian government has systematically and unerringly backed R&D activity through a welter of research grants. "Initial incentives for life science firms to invest in R&D started with a rebate of ten percent and this ratio been increased over the years so that on the 1st of January 2018 this will be raised to an impressive 14 percent," points out Phillip von Lattorff, country managing director of Boehringer Ingelheim's Regional Centre Vienna (RCV).

These initiatives have, in turn, spurred on the proliferation of countless innovation-orientated SMEs and a healthy domestic biotech scene that has really helped Austria to consolidate its position on the global life sciences map. "Vienna housed around 35 companies in life science R&D back in the 1990s and now we have 160 such companies and are witnessing a growth rate of 6-10 new players ever year," laughs Peter Halwachs.

## Eyes on the Prize

**Christa Wirthumer-Hoche, head, Austrian Medicines and Medical Devices Agency (AGES); chairwoman, EMA Management Board, Austria**

As the European Medicines Agency (EMA) seeks a new home post-Brexit, Vienna is firmly pressing its candidacy as a viable host. "Vienna fulfills all the necessary criteria for the new seat of the Agency so we are looking forward with great hope and optimism to the final decision due mid-November," confides Christina Wurthumer-Hoche, EMA chairwoman and head of the Austrian Medicines and Medical Device Agency. Gerhard Hirczi, managing director of the Vienna Business Agency is even more optimistic. "It's absolutely crucial that a large proportion of the existing staff follow the EMA to their new home and Vienna, having been elected the most liveable city in the world eight times in a row, is well placed to lure them and their families. Combined with a lively life sciences scene and a very proactive local agency committed to smoothing the repatriation process, we would also provide a purpose-built facility wholly tailor-made to the organization's needs, deftly integrating both conference and office spaces."

**TOP 10 PHARMA COMPANIES (RETAIL + HOSPITAL SALES)**
**AUG 2016- AUG 2017**

| | |
|---|---|
| 1 | ROCHE |
| 2 | NOVARTIS PHARMA |
| 3 | PFIZER |
| 4 | SANOFI |
| 5 | MERCK SHARP DOHME |
| 6 | FRESENIUS KABI |
| 7 | BAYER |
| 8 | JANSSEN |
| 9 | SANDOZ |
| 10 | RATIOPHARM |

*Source: QuintilesIMS*

## A MANUFACTURING POWERHOUSE IN THE MAKING

Where Austria most definitely does stand apart, is for its prowess in pharmaceutical manufacturing. The country distinguishes itself within Central Europe for the profusion and quality of its pharmaceutical activity and has therefore been able to attract many large multinationals to position their production capabilities there. "Austria is world reputed to be a stable, reliable, predictable country, both economically and politically, allowing operations to always run smoothly and that counts for a lot," explains Karl-Heinz Hofbauer, site lead of Shire's Vienna production.

This stable setting has thus allowed Shire to maintain significant operations after the company's 32 billion USD acquisition of Baxalta, taking over the Vienna production site and seven nationwide plasma plants that distribute to over 100 countries.

**Barbara Rangetiner, general manager, Octapharma**

**Josef Weinberger, corporate quality and compliance officer, Octapharma**

The company has now formulated "a plan to produce additional products in Austria, from the company's existing portfolio that are manufactured at other sites, and equally from the global pipeline that is aided by the company's large R&D investments," reveals Hofbauer.

The transition of medical science towards biologics provides yet another departure point for local manufacturing to take off, as multinationals search for high quality and consistent production bases that can appropriately handle increasingly sensitive formulations. Austria's entry into biologics production has been driven for decades by market leader, Novartis, which has committed to investing as much as one billion USD in Austrian manufacturing plants between 2010 and 2020. This decision, according to country president, Ard van der Meij, derives from the fact that "pharmaceutical production is clearly a process that is not easy to replicate and multiply into several locations" and the company has "been able to build on our long history and experience in penicillin production to now move into biologics; a hugely complex process." Thus far the company maintains 3 sites in Western Austria, stimulated by a decision on the part of the global management board for the company to be responsible for their own biosimilar production, rather than resorting to external contract manufacturing organizations (CMOs).

The largest announcement in recent years has been Boehringer Ingelheim (BI)'s commitment to build an 820 million USD biopharmaceutical plant in the heart of Vienna to be completed in 2021, the largest single investment in the German company's history. "Vienna thus far has ticked all the boxes, and we have shown the capability to build at the same speed and cost as anywhere else, with exactly the same commitment from the local and state government as you would find in Germany," explains Philipp von Lattorff, managing director of BI's regional center Vienna.

Yet another actor making big-ticket investments in bolstering their local manufacturing footprint is Swiss plasma pioneer, Octapharma. "To give you a sense of the Austrian affiliate's strategic relevance and importance, we possess a staff of 1,068, which constitutes around one sixth of Octapharma's global workforce. Moreover some one third of our manufacturing personnel are based out of Vienna," proudly reveals Josef Weinberger of the global management board. Indeed the Austrian capital actually constitutes the site of the firm's first ever production facility and very much remains a flagship asset today.

**Manuel Reiberg, former president, Association of the Research & Development based Pharmaceutical Industry in Austria (FOPI)**

**Karl Heinz Hofbauer, managing director & site lead Vienna, Shire**

**Robin Rumler, country manager, Pfizer**

**Mogens Guldberg, general manager, Novo Nordisk**

"Over the years we have continued to invest heavily in expanding this facility and ensuring that our capabilities keep pace with scientific advancements in plasma-derived products. The original complex has been upgraded, latest-generation production and laboratory technologies have been installed and entire new buildings have been constructed. The plant's annual fractionation capacity, for example, has increased seven-fold since 1989 and the size of the premises has more than tripled to 80,000 m², some 22,000 m² of which were purchased only last year," details Barbara Rangetiner, general manager of pharmaceutical production.

Number one pull-factor seems to be the supporting ecosystem and the ready availability of top-notch talent. "The human resource pool in Vienna is really well matched to the sorts of technical functions that our business requires. The Austrian education system is another plus factor with its very strong mid-level colleges where students tend to be able to develop their technical abilities. The local work ethic is also an invaluable asset. Not only do Austrians tend to be well educated, but the national mentality is to be ambitious, to take the initiative and to have a very high work rate in which you take great pride in the activity you are carrying out. This is perfect for a family-run, versatile, entrepreneurial outfit like Octapharma where employees are empowered to be creative and take responsibility," recounts Rangetiner.

## PUBLIC HEALTH: GREAT EXPECTATIONS

On the healthcare side of the equation, Austria has much to be proud about as well. World-class care has long been an expectation of the Austrian population. "OECD studies demonstrate that Austrians enjoy the highest public health coverage of citizens of any country in Europe and we are also one of the countries with the lowest unmet medical needs which means that residents have access



## Blazing New Trails in Neuroscience

**Astrid Müller, country director, Biogen**

For many multinationals, Austria's scientific human capital catchment pool, reliable infrastructure and understanding of importance of innovation make it a reasonable place for introducing cutting-edge therapies. The example of Biogen is very much a case in point. "Innovative drug developers are investing in clinical trials here because Austria stands at the forefront of scientific advancement in many therapeutic areas with key experts and opinion leaders readily available," reflects the company's country director, Astrid Müller. "Because we don't have in-country production people might think that we're just a marketing and sales affiliate, but actually we're doing quite a lot on the clinical research side," she discloses. "Right now, we have one of the most extensive pipelines in Multiple Sclerosis (MS), Alzheimer's Disease and other neurological diseases like Parkinson´s Disease. We have been (or will be) conducting studies at first-class centres around the country."

Moreover, the company, which is striving to establish itself as a global leader in neuroscience has been highly active in launching novel, first-of-a-kind treatments on the local market. "Our traditional strength without doubt, is in MS treatment, where we are the uncontested market leader possessing the broadest portfolio. We offer high-quality products from base therapy all the way up to a highly active stage of the end disease, and we are now building and capitalizing on this core foundation to enter other business areas," says Müller.

One example would be spinal muscular atrophy, where their product has been on the Austrian market since July and represents the first disease modifying drug in this field. "There was nothing available before, and now you have something that, though not a cure, can really have a massive impact on the quality of everyday life of patients and their families. We were the first to invest in this area and other companies will follow. Being pioneers in this field makes us very proud," she concludes.

to the best medical benefits by simply presenting their electronic card," affirms Alexander Biach, freshly elected chairman of the Hauptverband, main social security apparatus. "Moreover the rate of trust in the country's national health system is one of the highest in Europe: If someone has an accident or falls ill abroad, they always want to come back to be treated in Austria," he elaborates.

One big problem on the horizon, however, relates to the financing of such a well-loved system in an era of rising drug costs and surging demand for treatment as life expectancies are prolonged. Ominously, with 11.1 percent of the nation's annual GDP expenditure dedicated to healthcare, Austria already ranks as one of Europe's highest public health spenders.

Biach, himself, is committed to cutting the fat and crafting what he calls an "efficient, fast, uncomplicated, equitable, modern insurance system that offers real value for money" and intends to achieve this through a welter of reforms touching upon coordinated tendering, harmonized procurement and better prescribing behaviors that prioritize use of generics and biosimilars.

## STRUCTURAL COMPLICATIONS

In Austria, the ability for products to gain market access is directly associated to the perennial wrestling match between rising innovative drug prices and healthcare budgets, a common dynamic in most developed markets. Despite the country's reputation for traditionally being well disposed to facilitating the access and reimbursement of latest generation therapies, Mogens Guldberg, country manager of Novo Nordisk perceives certain complications arising from a tendency towards a decentralization of decision-making with regards to payers and sick funds, which in turn risks jeopardizing the long-term financial sustainability of the nation's healthcare apparatus. "Austria has a defined political structure with a long history based around the nine federal states being each individually given a health care budget. This can create a lack of fund allocation transparency in the system, not allowing us to fully understand how innovative drugs can help establish a more cost-efficient system," he warns.

"Most of the fundamentals are in place and, as the fourth largest European country in terms of GDP per capita, we should be able to properly and effectively reward innovation, however, the structural set up of our healthcare system is not helping us…

## MoNo: Riding the Momentum

**Bernhard Wittmann, managing director, Sigmapharm and MoNo**

A strong domestic production market is quintessential to any local healthcare scene, and Austria is blessed with a plethora of home grown players looking to take the next giant leap of growth, none more so than MoNo, an ambitious Austrian outfit that has just invested 24 million USD into a new plant in Burgenland, south of Vienna.

MoNo's origins can be traced back to the early 2000s when the manufacturing department of indigenous, local pharma outfit, Sigmapharm, was spun-off to create an independent CMO capbable of performing contract manufacturing also for external third parties. "Our core competence is products for Ear-Nose-Throat applications. MoNo manufactures non-sterile liquid products such as high viscosity, watery and oily solutions. Furthermore, we undertake aseptic production of sterile liquid products, without parenteral administration, such as eye drops and non-preservative containing throat and nasal treatments," explains Bernhard Wittmann, managing director of both companies.

This site "will offer a tenfold increase of our contract manufacturing capacity and will enable us to considerably expand our product portfolio. Moreover it's an entirely greenfield project, thus allowing capacity to further grow the site in conjunction with the future development of company… This year, in June, we presented our new plant to our partners and customers and the interest has been highly encouraging," enthuses Wittmann.



**Clemens Schödl, general manager, Gilead; Peter Wimmer, country manager, Angelini; Rudolf Wessely, CEO and founder, Gynial**

all too often, decision-making is being conducted in silos and thus there is a lack of a single holistic vision," laments Clemens Schodl, country manager of Gilead.

One underlying by-product of an inappropriately structured public healthcare system is the lack of transparency that exists within the two-tier finance system relating to primary and hospital care. "What I notice is that a lot of resources seem to be channeled towards the wrong sorts of areas," perceives Wolfgang Herrer, Chiesi regional manager for Central and Eastern Europe. "For instance, hospitals are managed at the regional level. Every regional politician wants to invest heavily in hospitals; therefore, Austria has an oversupply of hospitals and this area of healthcare is inefficient. At the same time, Austria lacks centers of excellence for specific therapeutic areas, that would contribute to decreased spending in the sector," he elaborates.

Robin Rumler, country manager of Pfizer very much concurs. "In Austria, there are as many as 22 different sick funds. From my perspective, this is an overly complicated system involving far too many different actors. Steps should be taken to centralize and rationalize these funding structures so we can gain greater understanding about how exactly this money is being spent… Right now, there are some 7.6 hospital beds per 1,000 inhabitants, which is an unnecessarily high ratio. We would surely do much better to remove departments in hospitals that are not underutilized and instead create specialist centers in the areas of oncology, cardiovascular diseases, pain and surgery. This would not only generate considerable cost saving, but also deliver patients an enhanced quality of care," he reasons.

In short, many pharma industry stakeholders feel that their businesses are being unjustly subjected to cost cutting whereas much more effective savings could be made elsewhere. "Austrian pharmaceutical and medication spending is only 12 percent of the overall healthcare expenditure. There are a large number of other areas where the government could leverage savings such as the domain covering ambulances and hospitals, which is, at present, being run in an extremely cost inefficient manner," argues Manuel Reiberg, president of the Association of the Research and Development based Pharmaceutical Industry in Austria (FOPI).



## SUSTAINABILITY AND ACCESS: A BALANCING ACT

Herwig Ostermann, executive director of the Austrian Public Health Institute, a neutral voice in the space between the government and industry, is keen to stress Austria's comparatively friendly approach to easing market access for innovative therapies. "When devising the budget cap, [the launch of innovative drugs] is most definitely taken into account, and technological progress has been incorporated in the original financing model," he notes. Yet, despite Austrian budget healthcare caps being readjusted every four years, Ostermann admits concern that, "highly expensive therapies, as observed in recent years, pose challenges to the fiscal sustainability of the entire system."

Emblematic of the prevailing challenges of financing latest generation innovations was Gilead's launch of the revolutionary, but expensive HCV drug, Sovaldi® resulting in the local pharma industry having to collectively pay a EUR 125 million solidarity payment back to the Austrian government in 2015. Meanwhile many in the industry are unhappy at recent price slashing reforms as the social security authorities struggle to keep the reimbursement budgets in the black. "Unfortunately recent reforms have included severe cost containment measures such as the introduction of fixed price bands for generics so that new drugs entering the market cannot be priced 30 percent more than the cheapest product, notes Reiberg.

PHARMIG's Jan Oliver Huber sheds light on the prevailing pricing scenario. "Austrian product prices are based on the

## Integrating the Healthcare Enterprise (IHE)

IHE is an initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information. Martin Tiani, CEO and founder of Tiani Spirit, a company at the vanguard of e-health speaks out about his firm's contribution to this new phenomenon.

**Martin Tiani, CEO and founder, Tiani Spirit**

**What was your vision when you founded Tiani Spirit?**

When encompassing an e-health record you must combine a huge range of 40 to 50 standards; IHE is able to select those standards in an extremely sensitive manner. IHE profiles the situation, then specifies what standards should be put in place, allowing all parties involved to have a specific tailored product while, in the meantime, ensuring they are connected at all times. The goal of Tiani Spirit was always to be number one in IHE globally, and for the last nine years we have achieved this objective. Our aim now is to connect as many stakeholders as possible.

**What are the next innovative steps for the company in expanding your IHE services?**

We are heavily working on a new component called clinical data repository; allowing discreet information, such as allergies or key figures, to be derived from documentation. This data can then be stored in a clinical data repository for public health, analytic and big data. Using this technology, we extract the discreet data and report the analytics so organizations can use this information for future endeavors

**What recommendations would you give to others looking to join the digital revolution?**

Tiani Spirit was lucky enough to have Cisco on board, and now we are one of only a handful of companies on their global price list. This partnership has given us credibility when going abroad. Furthermore, Cisco, like us, has a global vision of ensuring interoperability, and in the future, we will be able to diversify our electronic health information exchange technology into other sectors. Tiani Spirit is ready to be the catalyst to stimulate this technological revolution.

European average of 28 nations spread across the entire continent. More prosperous member states are part of the first launch wave, but the price of a product continues to be reviewed subsequent to placement on the reimbursement list, generally at 18 month intervals and, as less affluent member states are incorporated into the calculation, the average price tends to get driven down at each new review," he recounts. "Our worry would be that companies get fed up with these diminishing returns and instead start turning to alternative markets to conduct their drug launches."

To compliment the 2015 industry solidarity payment, reimbursement authorities implemented a hotly discussed reimbursement box-system whereby drugs are classified in "boxes" and their innovation value evaluated based on a comparison to drugs on the market. Robert Sauermann, head of the Department of Pharmaceutical Affairs of the Hauptverband, is open to discussing sustainable pricing "just so as long as [industry] can provide sufficient evidence to back up their therapeutic and financial claims."

This system requires companies to attack the market and attain access deploying differing methods. Peter-Karl Schwarz, general manager of LEO Pharma claims to be very much on-board with the system: "Our interactions with the reimbursement authority have been pretty constructive." His team has proved able to gain first wave status in LEO Pharma's global launches because "they have been successful in providing real scientific evidence on how we benefit our patients over and above improved clinical efficiency through increased adherence and compliance for long term treatment." "We are really differentiating ourselves from our competition with our holistic approach that is very patient centric and are reaping the rewards in reimbursement decision making," he reveals.

**Karl Peter Schwarz, general manager, LEO Pharma**

Other companies in other therapeutic areas, however, find it rather less easy to secure automatic reimbursement in a climate of increasing cost control and so have resorted to hybrid strategies to better assert themselves within the market. Peter Wimmer, country manager of Angelini Austria and Germany utilizes "a three-pillar system; Rx, OTC and private business.

We are able to manage the dynamics between the areas by establishing partnerships." This stable approach has allowed the company to gain a foothold in Austria, and are now conducting German operations from the Vienna offices.

## WELCOMING IN BIOSIMILARS

One approach to curbing rising innovative healthcare costs has been to open the doors to an influx of generics and biosimilars. On April 1st, 2017 a new regulation was introduced to differentiate these two cost-efficient treatments, building on the 4 percent biopharmaceutical volume growth Austria experienced in 2016. Country president of Novartis Group Austria, Ard van der Meij sees this as a positive step forward because he believes that "the pricing model for biosimilars was initially too aggressive," leading to many companies questioning whether a launch in Austria was financially viable. "Biosimilars are at the infancy stage and, as a community, all stakeholders have a responsibility to adapt to the evolution of the market so that we can better relieve stress on the entire healthcare budget," he declares.

**Philipp von Lattorff, country manager, Boehringer Ingelheim regional center Vienna**

**Ard van de Meij, country president, Novartis Group**

This mirrors the assessment of Sabine Möritz-Kaisergruber, co-founder of the Biosimilars Association and CEO of Astro Pharma which, in partnership with Hospira, is notable for having become the second firm to have managed to launch a biosimilar on the local market. "Previously, biosimilars more or less, fell under the same basket of regulations as generics so if you were not the first or second biosimilar on the market, there was really no clear incentive to be present in Austria at all," she explains.

"As it stands, the latest reform now places Austria more in line with other European countries in allowing companies to launch biosimilars and will be welcome news to the industry," analyses Martin Spatz, country manager of QuintilesIMS.

Indeed. "Looking at the originator drugs coming off patent and what effects biosimilars coming into the market will have on the public health landscape. The numbers show that within the next five years, the Austrian healthcare system will generate savings to the tune of 300 million EUR (352 million USD),"reaffirms Möritz-Kaisergruber.

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# Taiwan's Biotech Boom

## With its convergence of healthcare talent and tech, the nation is turning into a prime destination for innovative startups

Move over Silicon Valley, there is a new biotech hotspot looking to attract the best and brightest—and it's not in the US.

George Yeh, president of Taiwan Liposome Company.

Taiwan is beginning to attract technology and healthcare talent from inside and outside the region, as the small island nation is quickly becoming home to innovative healthcare care startups, such as Taiwan Liposome Company (TLC).

"It's trying to be a much more knowledge-based type of economy," says George Yeh, president of TLC, a specialty biopharma based in Taipei, Taiwan.

*Pharm Exec* recently sat down with Yeh to talk about his company and Taiwan's courting of the biotech industry. Using its proprietary drug delivery technologies, TLC's focus is on lipid-based formulation and scale-up to improve the safety and efficacy of injectable drugs—and thus prolong their product lifecycle.

TLC has been a long-time supporter of the Taiwan economy. Dr. Keelung Hong founded the company in 1997 after serving as a consultant to a number of biotechs, including Nycomed, Salutar, Onyx, and Sequus.

Yeh has been with TLC since 2002, following a stint as vice president of AsiaWired Group, where he was responsible for procuring corporate funding, strategic planning, and integration of high-level management and financial resources for startup companies.

Having offices and working in both the Taiwan and San Francisco areas, as well as his previous experience evaluating funding for startups, Yeh has his pulse on the emerging biotech space. His business connections to some of the top political figures in Taiwan also gives him insight into the economic development the country is leaning toward.

As Yeh explains it, Taiwan's economy is currently geared toward more IT-based businesses, and less on science-based fields—but there is a push to change that. In addition, doctors and medical professionals are well respected in Taiwan, Yeh says, and as more people with medical degrees run for and are elected to political offices, the higher support there will be on broadening the economy to bring in more biotech presence.

Take Taipei, for example. The city's mayor, Ko Wen-je, was a doctor at the National Taiwan University Hospital before being elected in 2014. According to his office's website, he held numerous positions at the university, including assistant professor, associate professor, and professor at the College of Medicine, as well as chairman of the department of traumatology. In Wen-je's Twitter biography, he refers to himself as a "truly independent political entrepreneur." Entrepreneurs, specifically those in the biotech industry, are exactly who the country, and city, are trying to attract.

The number's back up Yeh's comments.

According to a report published last year in *Taiwan Today*, the country's biotechnology sector is expected to reach $120.4 billion in production by 2025.

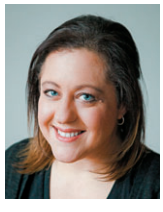
Taiwan's IT-based industries are a draw for many biotechs, Yeh explains. He predicts that in five to 10 years, we will see a lot of traditional IT companies cross over into the biotech and pharma space.

"We will see a lot more [pharma] technology start coming from Asia," notes Yeh.

Yeh, who earned a B.A. from the University of California at Berkeley and a master's degree from the University of Michigan at Ann Arbor, says that he is observing more and more people returning to Taiwan after their schooling.

"Talent has been educated and working in the US, and now they are starting to come back and build out technology [in Taiwan]," he says. "These are very entrepreneurial people who have a different type of technological ability. The culture there lends itself to becoming the next wave of the biotech talent pool."

The combination of technological savvy thinkers, plus entrepreneurs, plus pharmaceutical knowledge is the perfect storm to create the foundation for a lively and active biotech community in Taiwan. PE



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