How Patients Are Transforming Pharma R&D

Patient-centric R&D is imperative for pharma in delivering effective medicines and better outcomes. The push to implement it is challenging long-held biopharma business practices, including how clinical trials are designed, recruited and run – and what they measure.

BY MELANIE SENIOR

- Commercial, scientific, technological and regulatory forces are urging the pharma industry toward greater patient-centricity.
- This is impacting all stages of R&D, including clinical trial design, efficiency and endpoints.
- New technologies are enabling pharma's patient-centricity, offering tools to better understand disease and patients' experience thereof, and to improve outcomes.
- Several challenges remain, including which patient voices to incorporate into R&D decision-making, and how to do so systematically.
- Yet patient-centric R&D is a business imperative for pharma in helping deliver the outcomes the industry needs to survive.

The pharmaceutical industry is in the grip of "patient-centricity" – a vigorous, vocal effort to put patients at the center of what it does and the drugs it develops. New positions have been created, divisions re-named, patient declarations written and published. Efforts are underway to change cultures and mind-sets within pharma to focus first and foremost on patients' needs and priorities, rather than those of the health care professional, as has traditionally been the case.

The movement has a pleasingly ethical, feel-good aspect to it. But it's driven by commercial, scientific, technological and regulatory/legislative forces in the health care industry that leave pharmaceutical firms with little choice but to embrace patient-centricity. Budget constraints and the drive for cost-effective care, as decreed within the Affordable Care Act, are forcing payers and providers to focus on the outcomes that medicines deliver to patients in the everyday setting. Those outcomes depend on whether patients are given appropriate therapy that they perceive as beneficial – and with which they're motivated to remain compliant. Avoiding wasteful spending on ineffective treatment is a priority.

Science is evolving to focus on the individual, too. Advances in genomic tools and other "-omics" are driving the development of more personalized medicines, often tailored to individuals' genetic mutations or susceptibilities. These advances are also allowing scientists to sub-segment diseases into ever-narrower categories. Half of trials now collect DNA from patients to help develop biomarkers, according to the Personalized Medicines Coalition. Meanwhile, industry's focus on developing treatments for specialist, rare conditions continues.

If costs and science are compelling patient-centricity, digital technologies are helping enable it. They're offering new, richer, more convenient and perhaps more accurate sources of patient data, helping to understand patients' experiences but also the course of their disease. Improved data analytics and "big data" expertise are allowing scientists to extract new kinds of insights from huge numbers of patients – far more than a traditional clinical trial would

allow. These novel information sources – behavioral, social and environmental, for instance – are starting to inform the broader directions that R&D should take. Meanwhile, increasingly sophisticated wearable devices and sensors allow clinicians to track heart rate, blood pressure, movement, sleep and much more, over long periods. Technology has also empowered consumers, who are driving the growth and development of advocacy groups, and a louder and more organized patient "voice."

Regulators, too, are encouraging more patient involvement in the approval process. FDA is committed, under the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and on available therapies. It has led the way in engaging with patients and seeking to incorporate their views into the regulatory process, including by encouraging greater use of patient-reported outcomes (PROs). (*See sidebar, "Patient-Focused Regulators."*) PROs are measures captured directly by patients via a questionnaire or similar tool, and often pertain to aspects of treatment that matter to patients, such as how they feel and how a treatment is impacting their everyday lives and quality of life, rather than purely clinical endpoints used by physicians.

PATIENT-RELEVANT OUTCOMES

The pharma industry's newfound patient-centricity gurus explain that patient-centricity is a mind-set that must pervade all business functions. R&D is where its early impact is greatest, and most important, though: in helping design and shape a generation of therapies tailored to patients' needs and from which they are most likely to benefit.

With the exception of rare disease R&D, where the small patient numbers typically mean drug developers have no choice but to engage fully with patients and their families, most pharma firms haven't systematically involved patients in clinical trial design. Generating statistically robust data around clinically recognized and validated endpoints has been the priority. Patient experience, convenience and patient-relevant endpoints have taken a backseat.

That's changing. "It [patient input] is now formally part of the [trial design] process," reported Murray Stewart, MD, chief medical officer at **GlaxoSmithKline PLC**, during the *Financial Times Global Pharmaceutical and BiotechnologyConference* held in London in November 2015. This is particularly important in chronic conditions that patients have to live with day in, day out – and where medication adherence is most likely to go awry. "Understanding what patients are experiencing every day, and how they define the value of their treatments, are fundamental to our ability to push the boundaries of science in developing the next generation of medicines," declared **AstraZeneca PLC**'s development chief and chief medical officer Briggs Morrison, MD, early in 2015. (He has since moved on to run a biotech firm, Syndax Pharmaceuticals Inc.)

But even before seeking to push the boundaries of science, patient-centricity is about remembering the basics, insists Martin Coulter, CEO of **PatientsLikeMe Inc.** (PLM), a data-sharing network of over 400,000 patients and caregivers. "It's about understanding the patient journey better than we do. I don't think either side [pharma or providers] understands that well. The health care world sees a clinical dataset and whatever is in the medical record. But what's not necessarily being captured is the experience of the patient around elements of what makes us human: basic functioning such as mobility, cognition, pain, sleep and sex-drive." (*See "PatientsLikeMe Pioneers Social Medicine"* — START-UP, *October 2015*.)

Indeed, the early days of pharma's patient-centric era have revealed several examples of where clinicians have been capturing symptoms or measures that matter less to patients. In rheumatoid arthritis, fatigue matters more to patients than whether or not they can get dressed. In psoriasis, itchiness is much more important than lesion size or redness. Parkinson's patients care as much about better sleep, avoiding constipation and being able to function, as about the telltale motor symptoms such as tremor or limb rigidity that are typically measured.

Why should this matter to pharma R&D? Because if pharma develops treatments that help patients feel better, those patients are more likely to take those medicines properly and improve. Better outcomes means better reimbursement. Companies such as **Roche**, AstraZeneca and **Biogen Inc.** have all partnered with PLM to help address that patient-relevant data gap. At dermatology-focused **LEO Pharma AS**, which has re-written its entire strategy to put patients first, "we won't run a clinical trial without a PRO," says Kim Kjøller, MD, EVP, global R&D. In psoriasis, "normally we ask physicians to look at the surface area of scaling, and its redness. but we don't ask them to capture "Does it itch?" – even though that's what matters most to nine out of 10 patients."

Among the challenges facing wider use of PROs like itchiness is turning an inherently subjective assessment into a validated, standardized measure that's recognized by

PATIENT-FOCUSED REGULATORS

FDA has been the most active in embracing the patient voice: it has held over 20 "patient-focused drug development" meetings with patients and representatives from various therapy areas, which it uses to better understand disease severity and the adequacy of current treatments. Patient representatives meeting appropriate criteria can participate in FDA advisory panels. FDA also supports greater use of patient-reported outcomes (PROs) in clinical trials, and has set standards for their development and use.

The European Medicines Agency also wants to incorporate patient views into the assessment of medicines. Patients can't, as yet, directly participate in Committee for Medicinal Products for Human Use (CHMP) evaluation meetings, but the agency is on a strategic course toward greater patient consultation. In late 2014 it began a pilot study, around a rare disease medication, of how feasible patient involvement might be in the assessment process. Meanwhile, individual CHMP members from the various European countries are increasingly engaging with patients at their national level. In the Netherlands, for instance, scientific evaluation committees now include a patient representative. Patients are also included as part of the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC), on its Orphan Medicinal Products Committee (OMPC), as experts within scientific advisory groups and as members of the Patients' and Consumers' Working Party, which recommends to the CHMP and other committees on matters of interest to patients.

Exhibit 1

Selected Patient-Centric Pharma Programs

COMPANY	THERAPEUTIC FOCUS	ACTIVITIES	LIFECYCLE STAGE/RESULTS
Actelion	Pulmonary arterial hypertension, oncology	Patient-focused heritage of work to raise awareness of PAH. Patients invited to share their stories among company employees. Establishing novel clinical trial measures	Development/Clinical Trials Establishing patient relevant trial measures in rare T-cell lymphoma using PatientsLikeMe's Open Research Exchange
AstraZeneca	Respiratory, diabetes, oncology, lupus	Five-year research alliance with PatientsLikeMe to help shape future medicines development. Patient feedback on trial design in lupus. Internal competition to identify best patient-centric initiatives	R&D Implemented majority of patient-suggested improvements to lupus trial design and communication. Improved and shortened informed consent materials.
LEO Pharma	Dermatology	Organization-wide cultural change driven by CEO. Revised corporate strategy to reflect patient-focus. Corporate goals focus on patient (improving lives, accessing as many as possible)	R&D/Regulatory/Commercial Patient-engagement platform to access disease information and hear testimonials. Frontline innovation team to gather feedback about new products in development. Clinical programs now all include PROs. Work with FDA to include itchiness on psoriasis product labels
Novo Nordisk	Diabetes	Claims patient-focused heritage dating back to 1930s. Routine engagement with patient focus groups, plus other experts including anthropologists. Various cross-disciplinary studies of behavioral, practical, and perception challenges of managing diabetes	R&D/Commercial Claims higher score relative to industry peers in reputational surveys Working with regulators to develop PRO tools to help enhance quality of life. Starting to engage with technology payers to enhance device connectivity and improve disease management
Sanofi	Diabetes	Patient-centricity census across organization run by chief patient officer; learning by example (peer-to-peer); interdisciplinary collaborations across behavioral science/economics, social learning theory	Commercial/On-Market Online research portals to gather patient feedback/involvement. Brand planning teams consider unmet need in community, beyond informing on product use. Few concrete results to report so far
Shire	Rare disease, ADHD	Spreading patient-centric approaches from the rare diseases teams across the rest of Shire	R&D/Commercial Specialist PRO group established within organization. Learning how to consult, interact with and be sensitive to different kinds of patient organizations
UCB	Neurology, immunology	Company–wide organizational restructure, renaming of business units	Commercial/On-Market Patient feedback led to rewording of product storage instructions and new easier-to-open packaging for a rheumatoid arthritis drug

SOURCE: "Pharma's Patient Centricity," Datamonitor Healthcare, February 2016

regulators and payers. FDA has issued guidelines on how to develop and validate PROs, and LEO is working to get itch-relief into the label for its future psoriasis products by developing a series of questionnaires. Kjøller says the company has agreed with FDA on what a study needs to look like for that product characteristic to be included. "We believe there will be a way to get both efficacy and itch into the product label," he asserts.

Many disease areas lack PRO measures, meaning they have to be developed from scratch. **Actelion Pharmaceuticals Ltd.** is working with PLM on a new PRO measure for patients with a certain type of lymphoma, for instance. "All the questions come from the PLM network," explains Bill Fairey, president, Actelion Pharmaceuticals USA, rather than from clinical and medical experts typically employed to develop PROs. The problem with the traditional approach – which Actelion is pursuing for a PRO in pulmonary arterial hypertension – is that patient-reported outcomes aren't necessarily patient-relevant outcomes.

No drugs have been approved on the basis of PRO primary endpoints alone, although PRO claims are included in some drug labels. But "if regulators aren't yet requiring PROs [as part of drug approval submissions] the time is not far off when they will," opines Angela Coulter, director of global initiatives at the Informed Medical Decisions Foundation, Boston, senior research scientist at the Nuffield Department of Population Health at the University of Oxford, UK, and a member of the *British Medical Journal*'s patient advisory panel.

It's a similar story among payers and health technology assessors: PRO data haven't specifically been used in reimbursement decisions, but the US Centers for Medicare Services (CMS) is pushing strongly for a care quality-based reimbursement model by 2018. Meanwhile, the Canadian Agency for Drug and Technologies in Healthcare (Canada's HTA) routinely solicits patients' input at the outset of treatment reviews, as well as after draft guidance is issued.

TRIAL DESIGN AND RECRUITMENT

The patient-centric movement is also changing how trials are run. Simple practicalities such as the number of required clinic visits, waiting times and complexity of documentation can make vast differences to patients' experience – and thus to retention rates, study length and costs. In 2015, AstraZeneca ran a simulated trial of an injected therapy among lupus patients to gather feedback on how to improve protocol design and trial methodology. Among the 26 recommendations: less waiting time, explanations of their data, easier-to-read informed consent documentation, and post-trial notification and follow-up. In short, patients want to be kept informed, and not to have to hang around too long. "They [patients] challenged us, and we were able to reduce waiting times with no compromise to data [quality] or risk" to patients, reports Guy Yeoman, VP, patient-centricity at AstraZeneca.

Patients' input into trial design needn't involve simulated trials. Increasingly, it can be collected remotely, via a growing number of highly engaged online patient communities. That feedback can also inform pharma's dialog with FDA. "If FDA stipulates a certain trial design … and we talk to a virtual patient community" that outlines changes to make the study practicable, "we can go back to FDA and discuss what compromise can be reached," explains Yeoman. FDA is openly encouraging, and being influenced by, patient input: guidance for assessing muscular dystrophy treatments, for example, was based on draft guidelines submitted by the patient advocacy group Parent Project Muscular Dystrophy.

Trial recruitment is also being transformed by the tech-enabled patient-focused movement: web-based patient networks, advocacy groups and non-profits like CancerCommons (a network of patients, physicians and scientists) or MyTomorrows (which provides information about clinical trials and early access programs) offer online trial-matching platforms to help patients pinpoint an appropriate trial for their particular condition. Data analysis tools can more effectively link to and scan hospital electronic health records. "Only a very tiny percentage of eligible patients for a given trial actively try to enroll", says Vasant Narasimhan, MD, global head, drug development and chief medical officer at *Novartis AG*, and a significant share drop out, often due to the time commitment required. "There's a huge opportunity to [use technology to help] find the patients, and to make it easier for them to participate in the study," he says. Novartis has partnered with several data analysis firms to more rapidly identify eligible patients via EHRs.

Meanwhile, tools such as **Apple Inc.**'s *ResearchKit* platform, which pools together hundreds of millions of *iPhone* users as potential trial participants, are enabling mass trial recruitment. Researchers at **Stanford University** recently found 11,000 patients signed up for a cardiovascular trial via ResearchKit within 24 hours. Granted, this kind of remote mass recruiting isn't suitable for all therapy areas or for all trials. And there are plenty of challenges to sort out around trial selection bias (iPhone users only) and data contamination. But virtual trials, and studies of the impact of virtual care, will grow. "Telemedicine and other app-based technologies allow us to move beyond trial sites altogether, and use online networks and videoconferencing," says Novartis' Narasimhan. For now, these kinds of trials remain in the pilot phase at Novartis. But a recent study of the impact of virtual house calls (via videoconferencing) among Parkinson's patients, published in *Telemedicine journal and e-health*, revealed high interest in at-home care by patients limited by this chronic condition – and that remote recruitment, enrollment and assessment is feasible.

More targeted, efficiently recruited, technology-enabled trials that are less disruptive to patients' lives and engage them more fully in the process are not only patient-centric but also make economic sense for pharma. They are likely to retain more patients, generate richer data, progress faster and thus be cheaper. As Anne Beal, MD, VP, patient-centricity at **Sanofi**, insists: "Patient-centricity makes business sense."

WHICH PATIENT VOICES, AND WHEN?

The trouble is, as Beal acknowledges, no one in pharma really knows how to do patient-centricity, let alone operationalize it. "We're making it up as we go along," she said in an interview at the end of 2015. There are many challenges: public mistrust of pharma remains considerable; there are also gaps in each side's understanding of the other. Some pharma executives remain unconvinced that patients should be involved in R&D as more than subjects – though these are a minority, as suggested in a survey reported in *BMJ Open* in January 2016.

At a practical level, one big question for

pharma is which patients voices to listen to, how to listen, and at what point in the discovery and development cycle to do so. Not all patients' voices are captured within professional advocacy groups, or within big data trawls. Not all patients are English-speaking, or members of networks such as PatientsLikeMe. Beal and other patient-focused senior executives underscore the importance of listening to as many kinds of patient voices as possible – those within organizations, those that are unaffiliated and those of individuals, including in person. "It's important to still hear stories and understand that not everything can be measured" by a tool, insists Marilyn Metcalf, PhD, senior director of benefit risk evaluation at GlaxoSmithKline.

Metcalf works with patient groups to incorporate more of their thinking into how GSK weighs the benefits and risks of its development candidates. That evaluation isn't just about efficacy and safety, she explains, but "it goes further, beyond clinical measures, to ask 'is the patient actually doing better?' and 'what are the patients talking about?'"

In the four or five years since GSK started undertaking formal, structured benefit-risk evaluations, the process has shifted upstream. It used to begin at around proof-of-concept (the start of Phase II efficacy trials), Metcalf explains. "But as we've built experience, we've gone earlier, to ask [patients] about the unmet need, what patients really want and need." In many therapy areas, better data showing the natural course of a disease may be required, for example, so that decisions can be made about where to try to intervene to change it. Patient groups can help provide such data from their membership base. "Those studies are in a pre-competitive space, and can be made available to any drug company. We are encouraging that kind of collaboration," Metcalf says.

Pre-competitive collaboration is also at the heart of the transatlantic Patient Focused Medicine Development (PFMD) coalition, set up in October 2015 by industry firms GlaxoSmithKline, **Pfizer Inc.**, **Amgen Inc.**, **UCB SA**, AstraZeneca and **Merck & Co. Inc.** and the patient community to make R&D more patient-centric. It's inviting further stakeholders, including payers and regulators, to come together to establish a framework for more harmonized patient engagement across the sector, and to share best practice throughout R&D. It's also going to address cultural and communication barriers, as well as legal and regulatory considerations. Parallel efforts to develop consensus-based frameworks for patient engagement and for effectively capturing patients' voices are underway at the National Health Council, whose members include leading US patient advocacy organizations. The Innovative Medicines Initiative (IMI) is supporting development of a Patient-Inspired Knowledge Hub to assemble best practice and guidelines around how to engage patients in drug development. (*See "IMI Offers €12m For Patient Engagement Project"* — "The Pink Sheet" DAILY, *August 3, 2015*.)

Pharmaceutical firms' contact with patients and the public is highly regulated – a considerable factor preventing more outreach to date. Many worry that talking to patients directly about a development program would be seen as promoting an unapproved product. Certainly, it's wise to have the legal/compliance team involved in the patient-engagement process, but the regulations aren't designed to block all contact. Engaging on a disease-focused basis and/or using consulting agreements can help. Patient groups are also getting more sophisticated and experienced in this regard.

ADHERENT PATIENTS, LONGER DRUG LIFE CYCLES

Emerging technologies are being combined in late-stage trials with approved drugs to help patients achieve better outcomes – and thereby support product differentiation and sales. Adherence is the biggest driver of outcomes in many chronic conditions. Hence **Novartis AG** in January 2016 collaborated with technology group **Qualcomm Inc.** to develop a connected version of its *Breezhaler* inhaler for a variety of chronic obstructive pulmonary disease (COPD) treatments. The inhaler will report usage data, plus data on the duration and quality of inhalation, in theory helping patients remain compliant and manage their condition. Disease management and therapy adherence are also huge challenges in diabetes, a crowded, price-pressured segment where patient-centric tools and technologies offer the best chance of product differentiation. Besides smart, cloud-connected insulin injection pens, "we're working on making arguments to FDA that it's not just about blood glucose levels and hypoglycemic episodes, but also about patient-reported outcomes," says Mads Krogsgaard Thomsen, PhD, EVP and chief scientific officer at **Novo Nordisk AS**.

Regulatory hurdles remain, though: FDA recently dashed **Otsuka Holdings Co. Ltd.** and **Proteus Digital Health Inc.**'s hopes of achieving approval of the first "digital medicine": a drug-device combination of mental illness drug *Abilify* (aripiprazole) and a tiny ingestible sensor that measures medication adherence. The device signals to a wearable patch the time that the medicine reaches the stomach, as well as other metrics like activity patterns. This information can then be viewed by carers and physicians, and used to improve outcomes. For Otsuka, this was about life-cycle management: Abilify lost US patent protection in May 2015. The companies say they'll work with FDA to provide the additional data required for approval.

PATIENT-CENTRIC TECHNOLOGY DRIVES DISEASE INSIGHTS

Remote monitoring and wearable devices are transforming both the practicalities of running trials, and the level of insights gained from them. Consumer-targeted activity trackers such as *FitBit* wristbands or the *Apple Watch* are finding their way into trials, and there's a growing range of consumer-friendly devices designed specifically for medicine. Milan, Italy and Boston, MA-based start-up **Empatica Inc.**'s wrist-worn seizure sensor for epilepsy patients, or **AliveCor Inc.**'s mobile electrocardiogram-measuring band, which synchronizes with the Apple Watch are just two examples. National Institutes of Health data indicate that there are about 300 trials underway using wearables. "Every trial sponsor we talk to asks whether we have the capability to run trials using wearables," says Mike Capone, chief operating officer at **Medidata Solutions**, whose

cloud-based technology supports more efficient clinical development. "It is starting to become more mainstream, not just at proof-of-concept, but at any Phase, from I through to III."

Besides allowing remote data capture that can reduce the necessary number of hospital or clinic visits, these increasingly sensitive, sophisticated and discreet devices can capture a vast range of variables over long periods in real time, offering a more representative picture of a patient's true state of health and physical ability than a one-off walk-test in a doctor's office, for example. They also allow scientists to better understand the course of particular diseases and specific circumstances or triggers that may lead to, say, epileptic seizure or a "flare" in multiple sclerosis. At the individual level, such data may allow more tailored treatments for specific patients with particular diseases and lifestyle patterns; at the collective level it can help inform the design and focus of future therapies. "There's a tremendous opportunity to leverage technologies … within clinical trials, but even before that, big data analytics and high-powered computing can help identify targets," says Adriana Karaboutis, EVP, technology and business solutions at Biogen.

In 2015, Biogen sponsored a feasibility study among 248 members of the PatientsLikeMe MS community, who wore FitBit activity trackers for three weeks to monitor the number of steps and distance walked in the home environment. More than 80% of patients rated the device as a means to monitor and manage their condition. Since then, Biogen has tied up with **Alphabet**'s life sciences arm, **Verily Life Sciences**, to use sensors and analytics tools to try to figure out how and why MS progresses so differently from one patient to another. The SysteMS study, conducted by neurologists at **Brigham and Women's Hospital**, will deploy up to 2,000 Verily wearable devices to measure movement, activity and vital signs among a cohort of MS patients, as well as gather clinical, imaging and molecular assay data. Analyzing all the datasets to find factors associated with disease severity and progression may help better tailor treatment to each person, allow earlier intervention and ultimately better outcomes for patients.

"Technology is central to developing more personalized therapies that can help patients achieve better outcomes," sums up Rick Rudick, MD, VP, development sciences and head of value-based medicines at Biogen.

Wearable-enabled trials haven't yet formed the basis of a drug approval. But it probably won't be long. And many technologies will likely continue to be used post-approval, to generate the best real-world outcomes. "A majority of [trial] sponsors want to ensure trackers can continue to be used after the drug's on the market," asserts Medidata's Capone. Monitoring and improving outcomes is, increasingly, the key to reimbursement and commercial differentiation. It's also becoming an important component of life-cycle management. (*See sidebar, "Adherent Patients, Longer Drug Life Cycles."*)

PATIENT-CENTRICITY, NOT TECHNOLOGY, IS DISRUPTING R&D

There's a way to go before technology fully disrupts R&D and health care more broadly. Devices and sensors must be tested among a wide range of users and demographics. They must be robust and reliable, as well as secure and tamper-protected – and not too invasive. The data they generate also need to be assessed, interpreted, validated alongside traditional metrics and turned into clinically actionable insights. Equality and access issues need to be resolved to ensure patients who can afford Apple Watches and superfast broadband aren't over-represented or prioritized. Mind-sets within much of the physician and clinician community must shift to embrace new technologies – and their relatively rapid development cycles.

"We're very cognizant of the technical, regulatory and cultural challenges around new technologies," says Biogen's Karaboutis. "But the way we approach it is to put patient-centricity first. It starts and ends with the patients: how to better understand and treat their disease. We work backwards from there to understand what technologies can help, and how to overcome those individual challenges."

This "patient-first" approach – compelled by science and system economics alike – is a bigger disruption to pharma R&D than technology. Pharma needs to be patient-centric to develop valuable, reimbursable new therapies and solutions, and thus to remain commercially viable. Technology is enabling that, but it's not enough. The ultimate test of pharma's patient-centricity, in R&D and throughout, will be whether it helps deliver better outcomes – and whether its decisions and behaviors are seen as patient-centric. There's a way to go.

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