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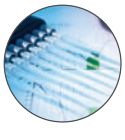

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The Bogus in Big Data

BIG DATA IS BIG—it's the one trend in healthcare that demands to be described in superlatives. To fully grasp the scope, we must venture to the very end of the alphabet for the right word—zettabyte—that quantifies the vast amounts of random data being generated every day through human activity on the Internet. Sometime this year, the world will have made the transition to the era of the zettabyte, with Internet traffic accumulating by a compounded factor of 21 zeros, a volume equivalent to the storage capacity of 250 billion DVDs. To use another comparison, we are producing bytes of computing activity at sufficient scale to give all of the earth's seven billion people access to 200 newspapers per day. And the pace is headlong: some 90% of this data has been generated just within the last two years.

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On July 28, the New York Academy of Sciences held an expert symposium on the implications of the big data revolution on drug development. Underlying the discussion was an awareness of how disruptive the data revolution is to traditional ways of bringing medicines to market. While there is potential for cost efficiencies and risk mitigation in areas ranging from precision medicine in fighting cancer to the innovative repurposing of old drugs, there is a larger issue at stake: how to turn data quantity into data quality. As one speaker put it, "the big data revolution now gives us access to a billion health records, yet all of this data is flawed in some way. That said, is it acceptable to draw on this vast and diverse record pool in developing useful inferences for research? The answer requires we confront our propensity for bias: if we do find something interesting in a survey of 30 million patients, how can it be wrong?"

The consensus was it is not bigness alone that hampers reliance on data to identify efficient health solutions. Instead, it's the complexity within the data that often lead researchers astray. These include factors like reliance on different hard/software infrastructure; enrollee nomenclature gaps like double-counting patients or the inability to track the full patient journey through an episode of care; impact of concomitant medicines use (the co-Rx effect); and risk-adjustment problems, illustrated by the conflict between the impulse toward uniformity in a centralized data base and individual privacy mandates like HIPAA. In essence, marking the transition from big data to a study model designed to perform a specific task—one consistent with a hypothesis that yields true knowledge necessary to drive action—is proving downright messy.

Solving this challenge is critical to achieving the promise of big data. If observation is indeed the starting point of biological discovery, as Charles Darwin famously said, then what must be done to augment the tools that technology now gives us—to move those powers of observation to the next stage? This was the question that *Pharm Exec* joined with Quintiles, several big Pharma companies, and two academic partners to grapple with in our Roundtable cover feature this month.

Our focus was on the review of the internal institutional capabilities of biopharmaceutical companies in leveraging the data surge to improve their value proposition to payers, who often rely on the same data to render judgment on patient access to new drugs. What we discovered is the role the in-house pharmacoepidemiology practice can play in finding better ways to classify and render sensible all the background noise from big data. Derived from two words in classic Greek, epidemiology is the study of people's health and has traditionally focused on evaluating risk factors related to the incidence of disease in a broad population setting. It takes research from the relatively restricted plane of the RCT and elevates it to the population level. Insights from study at the population level allow for the identification of factors to inform treatment decisions at the individual patient level—completing the circle.

This makes the function ideal for capitalizing on big data's potential in building broad observational studies to drive understanding of how medicines actually work, in real-world settings, where patient satisfaction and overall health outcomes count. The group's advice on how and where pharmacoepidemiology can sharpen its impact is useful reading.

Finally, our Roundtable convened just 10 days after the death of the father of the evidence-based medicine (EBM) movement, Dr. David Sackett. It's worth noting that a man associated with aggregated data-based pathways to drive treatment never intended to take the physician and patient out of the picture. In his seminal 1996 *British Medical Journal* article on EBM, Sackett avowed that "external evidence can inform but never replace individual clinical expertise." Now that the anonymized zettabyte is becoming a "numbers don't lie" measure of system performance, his advice remains pertinent: to improve health, the best algorithm is found in the face of every single patient.

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Epidemiology Arising

William Looney, Editor-in-Chief

Experts from industry and academia sit down with *Pharm Exec* to probe the changing role of pharmacoepidemiology and how this below-the-radar surveillance function is adapting to a "show-me-the-outcome" system of healthcare.

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Patient Adherence

The Adherence Journey: Patient Activation

Casey McDonald, Senior Editor

The concept of adherence is no longer. The emphasis is now on "patient activation"—but for this movement to sustain itself, drugmakers will have to become more collaborative in engaging and empowering patients. *Pharm Exec* explores how.

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Manufacturing Strategy

Manufacturing's Quality Compass

By Ian Wilcox and Conrad J. Heilman

Biopharma needs to combine a "culture of quality" with value-added process improvements in manufacturing. This feature outlines the critical steps that can lead to excellence in manufacturing—and deliver bottom-line results.

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Cover Photo: John Halpern

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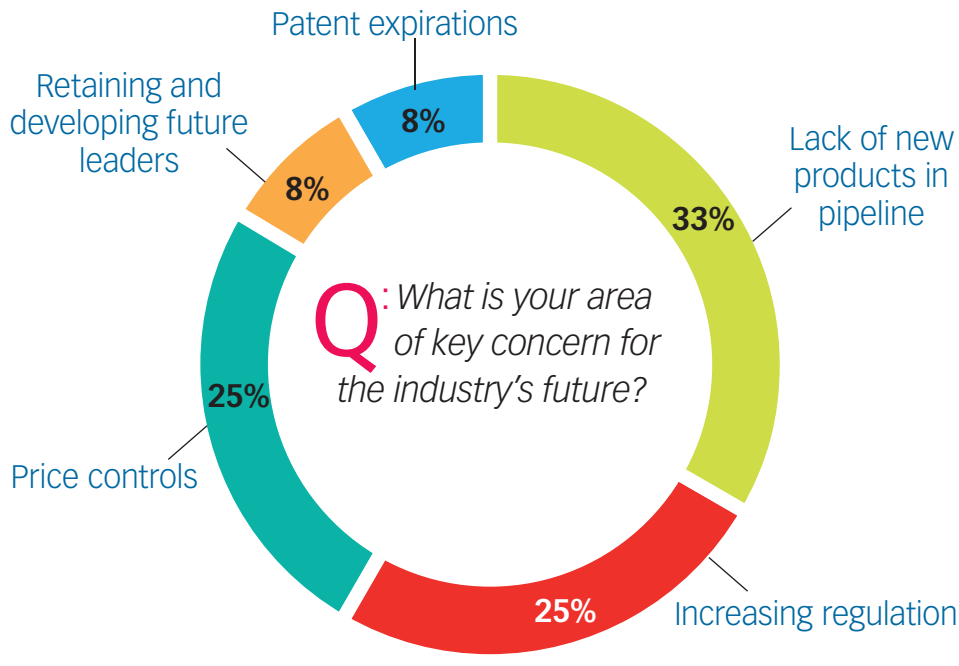

Readers Weigh In on Twitter

■ @Pharmaprocess, @PharmExecutive ...true, whenever you go to a new shop, one becomes apprehensive about counterfeit products.

Bharatula Eswara Rao, @berao1939, 7/22/15
"'Fake Medications, Real Solutions"
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■ US capital markets will continue to lure EU Biotech—US better equipped to understand the sector.

Rhiannon Meaden, @Rhi_Me, 7/14/15
"US Capital Markets Will Continue to Lure European Biotech?"
bit.ly/1M3MvI6

■ Interesting article from @PharmExecutive about speeding up #clinicaltrials. We recommend adding financial visibility.

Clinverse Inc., @ClinverseInc, 6/16/15
"Speeding Up Clinical Trials: What Works and What Doesn't"
bit.ly/1dlGecP

■ Key driver behind healthcare consolidation is desire to leverage volume for better purchase terms.

Amerinet, @AmerinetInc, 6/11/15
"When Care Models Collide"
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Hurdles Ahead for 'Cures' Legislation, PDUFA Renewal

FDA reform may get tangled up in user fee negotiations, budget debate

Getty Images: Nigel Hicks

Despite overwhelming House approval last month of the "21st Century Cures" Act, bipartisan support may fall apart in the coming months as key provisions face opposition in the Senate, negotiations begin on reauthorizing FDA drug user fees, and the presidential campaign shifts the debate to broader health issues. Congressional action on the Cures bill moved forward in July after the Supreme Court decision in favor of the Affordable Care Act, ending the prospect of endless health reform debate. But the House legislation still almost faltered due to opposition from consumer advocates claiming it would bring more unsafe drugs to market, and from fiscal conservatives about boosting mandatory spending. But House Energy & Commerce Committee chairman Fred Upton (R-Mich) orchestrated a 344-77 vote in favor of the measure by providing funds for the National Institutes of Health (NIH), while Democrats led by Rep. Diana DeGette (D-Col) helped sideline the FDA critics.

Upton and his allies also garnered support from hundreds of patient groups, research organizations, medical societies and biopharma companies. They applauded provisions to more fully incorporate patient experiences in considering a drug's benefits and risks, expedite new drug approvals through biomarker qualification, streamline clinical trials, provide leeway for sponsors to utilize data from clinical experience, and added incentives for developing antibiotics and treatments for rare diseases.

The House measure now faces an overhaul in the Senate, where there's talk of developing a very different, narrower bill by September; at a minimum it will drop provisions related to health information systems and Medicare and Medicaid reforms, which fall outside the purview of the Senate Health, Education, Labor & Pensions (HELP) Committee. Some Senate Republicans will strongly oppose the mandatory funding increase for NIH and the sale of strategic petroleum reserves to offset the cost, eroding Democratic support for the measure. If the Senate does enact a bill, it would face difficult conference committee negotiations with the House, and the process could extend well into next year.

In addition, Congress faces its usual impasse over the federal budget for fiscal year 2016. Democrats have blocked an increase in defense spending without similar gains for discretionary government programs, including healthcare and transportation infrastructure. Congress also will be absorbed in the coming months by debate over the Iran nuclear arms pact and major trade agreements.

On to PDUFA

Many of the main elements of the Cures legislation may end up in a broad FDA bill to reauthorize user fees for drugs, generics, medical devices, and biosimilars by summer 2017. FDA launched the PDUFA VI negotiating process with a public meeting July 15; monthly discussions with industry begin this fall, along with regular meetings for FDA to hear the views of patient, consumer, and health professional representatives.

However, there's pressure on all sides to craft a leaner legislative package because the user fee reauthorization process, for the first time, coincides with a presidential election campaign. A new administration and a new Congress in January 2017 means that any user fee agreement and authorizing legislation will have to be ready for lengthy reviews by both outgoing and incoming administration officials.

Speedy negotiations won't be easy, though, as seen in the range of issues raised at last month's PDUFA opening session. The importance of the process to FDA was apparent in appearances by acting commissioner Stephen Ostroff, who likened efforts to accelerate new drug discovery to the remarkable Pluto fly-by; by deputy commissioner Robert Califf; and by

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Center for Drug Evaluation and Research (CDER) director Janet Woodcock. She highlighted the importance of patient input in drug development and review, interest in expanding FDA's Sentinel program to strengthen oversight of postmarketing safety, and further efforts to bolster regulatory science. CDER "continues to struggle" with the recruitment and retention of critical staff, Woodcock observed, reflecting numerous comments that FDA's ability to attract top scientists is key to achieving a more predictable and efficient drug development and approval program.

Patient groups and professional organizations offered a range of initiatives meriting PDUFA support: validation of more biomarkers and patient reported outcomes (PROs), pediatric and neonatal drug development, expanded use of registries, data transparency initiatives, and greater consistency across CDER review divisions on acceptance of expedited review pathways. Several commentators urged further assessment of the 60-day waiting period, established under PDUFA V, to ensure that new drug applications are complete before starting the review clock, and whether it has accelerated or slowed application review times.

A main theme was expanding the use of "real-world" evidence to accelerate drug development. Greg Daniel of the Brookings Institution described how PDUFA VI should shift from a focus on streamlining application review, to strategies for tapping clinical evidence and other data to support agency decisions and to document product safety in the postmarket setting. Allan Coukell of the Pew Charitable Trusts similarly emphasized the value of better access to observational data from health claims data bases, in addition to clinical trials. And Marc Boutin of the National Health Council highlighted the need to clarify that sponsors engaging with patients early in the development of new experimental uses of a therapy does not constitute off-label promotion.

Kay Holcombe of the Biotechnology Industry Organization (BIO) emphasized the goal of further integrating patient perspectives into drug development and regulatory decision-making by shifting from an anecdotal to a data-driven, systematic process built on a structured benefit-risk framework and clear FDA guidance. Sponsors also seek improvements in FDA communication and practices across CDER review divisions: a BIO survey finds that half its members report very beneficial and productive interactions with FDA, but half see "room for improvement."

FDA officials emphasized that the user fee program deals only with agency processes to achieve a more predictable, efficient drug development and review process—and not policy issues that require legislative or regulatory action. Yet, proposals to expand the use of "real-world evidence" and other data sources may fall into the "policy" bucket.

There's pressure on all sides to craft a leaner legislative package because the user fee reauthorization process, for the first time, coincides with a presidential election campaign

And Holcombe raised a clear legislative issue: industry wants Congress to ensure "long-term stability" for PDUFA by clarifying that user fees are not subject to future budget sequestration actions—a development three years ago that delayed implementing then-new PDUFA V initiatives. PE

Access and advertising

Although most drug marketing and prescribing issues fall outside the purview of user fee negotiations, they continue to emerge in FDA reform discussions. At the July PDUFA meeting, Sally Greenberg of the National Consumers League called for FDA review of all DTC ads before public dissemination, particularly for newly approved products. And she raised concerns about patients not knowing when a prescription is for an unapproved use of a drug, urging FDA to consider ways to inform patients about off-label prescribing and alternative treatment options. And expanded access to experimental drugs came up when MIT economics professor Ernst Berndt cited the need for a clearer understanding of what factors may limit patient access to unapproved or marketed drugs, including actions by payers and insurance companies. He proposed coordinated action to seek broad stakeholder agreement on policies affecting patient access, including adaptive licensing available in Europe and reimbursement by payers.

Front & Center

Maximizing Patient Value

Benefits of Patient Education, Engagement and Support Solutions

Pete Megronigle, *Vice President, Integrated Market Access, Quintiles*

Biopharmaceutical manufacturers' focus on new patient acquisition has historically been a mainstay of marketing and sales efforts. However, in the current, rapidly evolving healthcare environment, an initial diagnosis and treatment decision is but a first step in achieving a positive patient and healthcare provider (HCP) experience with a particular product.

Today's focus has shifted to achieving lower costs, better care and driving patient outcomes. Success in the marketplace now requires a more comprehensive and innovative approach inherent in a multi-channel marking and sales strategy. An approach that can pull through the demand of a drug, engage patients throughout the entirety of their treatment journey and educate healthcare providers to the true value of a therapy.

Pete Megronigle, Vice President, Integrated Market Access, NA, Quintiles

An emphasis on patient outcomes shines a spotlight on adherence. The two go hand in hand when assessing treatment efficacy, according to the World Health Organization (WHO), which states: "The population health outcomes predicted by treatment efficacy data cannot be achieved unless adherence rates are used to inform planning and project evaluation."

Too often, however, patient support is sub-optimal, which can result in poor compliance, a challenge across all therapeutic categories. According to Dr. Chowdhury et al. at the Centers For Disease Control and Prevention (CDC), an estimated 20–30% of prescriptions are never filled, and medication is not continued as prescribed in about 50% of cases. Only 51% of Americans treated for hypertension are adherent to their long-term therapy, and some 25–50% of patients discontinue statins within one year of treatment initiation.

What exactly does adherence mean? The WHO definition extends beyond the taking of a prescribed medicine to include (among other determinates) "a cluster of behaviors that are simultaneously affected by multiple factors," which also takes into account the relationship between the patient and the healthcare provider. Be it physician, nurse or other health practitioner, the WHO states that the relationship should be mutually beneficial and more like a partnership that draws on the abilities of each party. In 2003, the WHO's adherence project adopted the following as its official policy definition: "The extent to which a person' s behavior—taking medication, following a diet, or making healthy lifestyle changes—corresponds with agreed-upon recommendations from a healthcare provider." [1]

Overall, between one-third and one-half of patients with long-term conditions fail to adhere to therapy—for reasons relating to the healthcare system, patient, therapy, condition, and socio-economic status—regardless of the severity of the condition. In addition to significant health impacts, non-adherence is linked to direct costs of $100 billion to $289 billion annually.[2]

Intervention: The key to improving adherence

Against this backdrop, innovative healthcare solutions and patient support services are called for. Inherent in multi-channel marketing and sales strategies are Clinical Educators (also known as Clinical Nurse Educators, Nurse Advisors or Health or Medical Educators).

Clinical Educators (CEs) are credentialed healthcare providers (i.e., nurses). Highly trained, CEs have a minimum of 2–3 years of experience in managing patients with a specific chronic disease. CEs are, therefore, qualified to work directly in a practice. Perfectly positioned, CEs serve to increase brand adoption and support sales force objectives. In addition, CEs can improve a HCP's understanding of the clinical aspects of a brand, drive accuracy in diagnosing patients and successfully engage patients and care-partners in improved treatment regimens. In short, CEs have the power to drive brand adoption and adherence, and maximize brand ROI. (Figure 1)

When it comes to patients, CEs employ their considerable skills in disease management to increase patient engagement. CEs provide patients with disease and treatment education, help accelerate program shifts, improve and monitor treatment regimes to enhance adherence, and facilitate ways for patients to connect with other people living with the same condition.

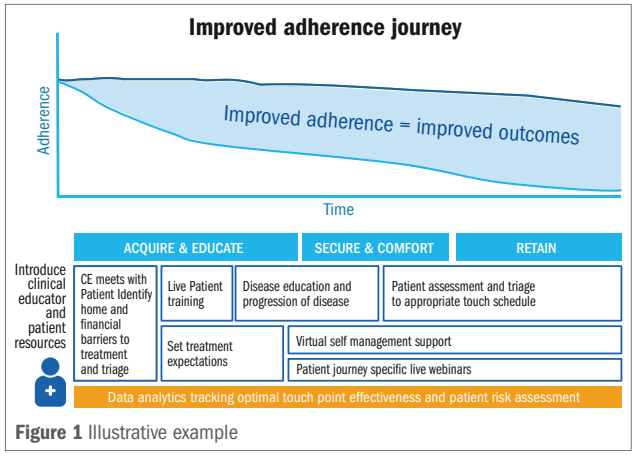

Figure 1 Illustrative example

CE programs represent a powerful differentiator for both physicians and patients. Many therapeutic categories can benefit from the intervention of CEs, including chronic conditions such as diabetes, asthma, multiple sclerosis, oncology and immune disorders, as well as rare diseases and challenging-to-diagnose conditions.

Nurses are highly respected in the US. They have the highest honesty and ethical standards ratings of any professional, according to Gallup. This only adds to a CEs' effectiveness in the eyes of a patient. CEs involvement in a patient's treatment represents changing healthcare provider behaviors. For example, CEs offer a mutually beneficial partnership in our relationship with a patient similar to the one the WHO referred to as being necessary in driving health outcomes.

Impact of Clinical Educator program as a sales strategy

At Quintiles, our CE program functions as part of a multi-channel sales strategy and serves to increase the size of a product's overall market through awareness and advocacy. In particular, Quintiles' CE program serves to maximize sales force effectiveness. Its impact is demonstrated by data showing sales representatives gaining increased access to difficult-to-see HCPs who have opted into the program. CEs also provide access as well as selling opportunities for representatives. Using peer-to-peer knowledge, they help educate HCPs as to the clinical aspect of a therapy with peer-to-peer knowledge of the brands while improving patient care and treatment.

As part of any CE program, Quintiles offers a range of patient support interventions delivered face to face, virtually or telephonically. These can be on a full-time, part-time or Per Diem basis. CE resources added and integrated into a program to improve adherence, further educates patients (with print or online materials), and can remind patients of their treatment regime. Market access solutions to facilitate payment and speed-to-therapy for patients are also available.

To demonstrate the overall impact of their CE program, Quintiles points to a recent case study that made use of Clinical Nurse Educators (CNEs)—to positively improve patient adherence, from less than 50% to more than 90% at 12 months. The program itself was credited to playing an integral part in product growth over the past three years. (Figure 2)

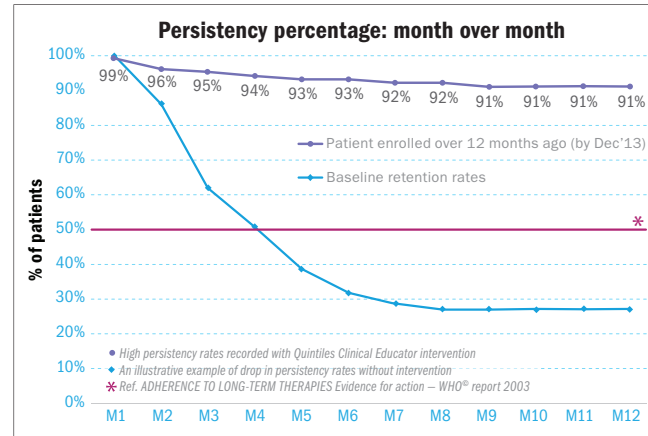

Figure 2 Results from a single case study. Individual program results will vary based upon market conditions and program design.

Conclusion

Developed and deployed correctly, patient engagement programs involving Clinical Nurse Educators support the entire patient journey. Such ongoing support ensures that the patient has the tools and support necessary to obtain maximum benefit from the treatment prescribed. And perhaps just as important, CE's, by way of their patient engagement, their attention and sheer presence can create that positive treatment "atmosphere" the WHO described in its adherence definition. An atmosphere that provides patients, so often isolated by their disease, with a feeling they are not alone, that they have someone in their corner watching out for them.

For further information: To find out about customized solutions to improve patient adherence and outcomes, contact: patientcentric@quintiles.com

1. Sabaté E, editor. , ed. Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization; 2003.
2. Ho, 2009, Circulation; Levine et al. 2013, Annals of Neurology

Greece: More Than the Next Drug Supply At Risk

The volatility of the nation's crisis could pose greater challenges for the industry down the line

There are some evident challenges for pharma in the ongoing Greek crisis. But there are some less evident challenges which may, over time, prove to be more difficult for the industry to cope with.

First, the immediate challenges. And because the crisis is—at least in its origins—economic, the economic challenges are the most obvious. How to make money through normal commerce in a market that has become conspicuously abnormal? For years, drug manufacturers have had difficulty in obtaining payment for their supplies, in the same way as wholesalers and hospitals have had difficulty in obtaining the money to pay manufacturers because of interruptions to their own revenue streams. Estimates of the level of unpaid debts vary, but European manufacturers have spoken of carrying unpaid invoices worth more than north of a billion dollars. And whichever way the broader discussions with international creditors of a resolution to Greece's problems play out over the summer, there is little prospect of things getting better, and every prospect of them getting worse. Those debts are likely to pile up.

The abnormality of the market has other facets. Exchange controls and sharpened economic decline have created new liquidity constraints that impede patients from paying pharmacists, pharmacists from paying wholesalers, and wholesalers paying manufacturers. Wholesalers promised the minister of health to continue to supply the market with the usual quantities as well as with the usual economic terms—but with the obvious risk of cashflow problems. One wholesaler said: "I really do not know (and this is my greatest fear) whether the medicines which I supply to pharmacies will be paid in euro, drachmas, or will never be paid if the economy collapses."

The new strains have come on top of the longstanding disruptions to normal business from parallel trade, where low Greek prices—already among the lowest in Europe—have been a constant temptation to pharmacists and wholesalers to export their supplies to the more generously-priced markets of Germany, the Netherlands, or the UK, rather than sell them locally. The current financial difficulties facing pharmacies is a further inducement for them to make a few euros wherever they can in order to stay afloat. Manufacturers have consequently lost revenues in those more prosperous markets, and—by limiting or even interrupting supplies to Greece to mitigate the problem—have lost revenues there, too.

In principle, parallel trade is entirely legal in the European Union (it is even actively encouraged as a central element of the EU's vaunted single market). But the particularities of Greece had already led to strong pressures to limit it, both from the local authorities fearful of supply shortages and from multinational manufacturers anxious to stem what threatened to become a haemorrhage. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has urged what it calls exceptional measures for what it describes as exceptional circumstances. And in mid-July, the government imposed a formal prohibition on the export of some medicines, warning of "a humanitarian crisis" from siphoning off important drugs for middlemen's profits. The picture is, unsurprisingly, confused—wholesalers claim the problems arise only from manufacturers cutting supplies to thwart parallel trade.

System in shambles

Local reports confirm the dysfunctional nature of much of the health system in Greece. A limited primary care service has for years thrown the principal burden onto hospitals, and the absence of effective triage leads to huge strains, and failings in treatment for patients who really need hospitalization. Hospitals have little tradition of analyzing their expenditure or of accountability, and waste has been endemic. Health insurance coverage is patchy at best, and almost non-existent for the many thrown into unemployment by the downturn, or for the growing number of irregular migrants who reach the country daily. Bribery of doctors remains common—a phenomenon not helped by pay cuts that leave hospital doctors with less than 2,000 euro a month.

REFLECTOR is *Pharmaceutical Executive's* correspondent in Brussels.

The situation has been aggravated by the deal that Greek Prime Minister Alexis Tsipras reluctantly signed up to in mid-July, which prevented immediate meltdown of the Greek banking system, but at a price that included unpopular measures such as liberalization of the pharmacy sector. This precipitated strike action by pharmacies resistant to seeing their monopoly broken by more vigorous competition.

Ripples across Europe

But the real casualties are, as always, needy patients. Mental Health Europe (MHE) issued a statement in July calling on the EU and member state leaders "to halt the humanitarian crisis in Greece," where, it said, "millions are deprived of basic health and mental healthcare" and suicide rates have risen by 35% over the last four years. And the European Organization for Rare Diseases (EURORDIS) has written to the Greek government urging attention to the plight of rare disease patients, who will be particularly hard hit by supply difficulties.

"The European Union has above all a social model to defend and to offer to its citizens. No human being should be left aside in such a time of crisis," said MHE. And this points to the second, less obvious, but arguably more important crisis. The reverse that Tsipras suffered in signing a deal that he was repudiating before the ink had dried has implications that go much wider than Greece's membership in the Eurozone or its financial equilibrium. Irrespective of one's personal political views, the blow dealt to far-left politics in Europe cannot be overlooked, and nor can its resonances.

Only weeks ago, with Tsipras and his radical Syriza party riding high in Greece as they appeared to fight off the massed ranks of the international establishment, the hard left across Europe were riding high with them, in hopes of at last seeing a new pathway carved out to defeat austerity. Podemos in Spain, Die Linke in Germany, the Workers' Party of Belgium (PTB), and other similar new radical anti-austerity movements felt victory was within their grasp. The disillusion that so quickly replaced those hopes has left large sections of society—in Greece and in many other European countries—with a sense of alienation. The risk is that, left unattended, disappointment may turn to disaffection, to increased radicalization, to a widespread anti-European sentiment, and ultimately to a large-scale rejection of the values that Europe is based on (and that, indeed, the pharmaceutical industry relies on).

Europe is not yet in a revolutionary phase—but it would be an imprudent politician (or business executive) that imagined serenity can be automatically guaranteed now that Syriza's dreams have been shattered. Bridges will have to be built by the "winners" to restore confidence in the system to the "losers," and everyone with a stake in the current system will have to be ready to play a role.

The pharma buffer?

Back in Greece, the pharma industry will doubtless continue, for the time being at least, to supply medicines even as the bills mount up. It is conscious that it's not the only creditor in this predicament—and in addition to any sense of solidarity or humanitarian motivation, Greece knows full well that it could hardly bear the damage to its image that would result from cutting off supplies. To this extent, for good motives and perhaps more self-interested reasons, the industry can itself represent something of a bridge across that widening gulf between haves and have-nots, between the establishment and the disestablished, disenfranchised or disenchanted. And that offers, it the chance of being a valuable role model in a wider panorama.

The pharma industry can represent a bridge across that widening gulf between haves and have-nots, between the establishment and the disestablished, disenfranchised, or disenchanted

That, of course, remains tenable as a scenario as long as Greece remains in the euro, and does not resort to massive price-cutting—which would not only increase the risk of parallel imports, but would hit drug prices in all the countries that include Greece in their basket when fixing their own domestic prices. But that is still too far ahead to see. As one senior executive in a major pharma—a Greek national who has managed his group's Greek subsidiary—said, "I've stopped even trying to second-guess the future. It's just too volatile." And not just Greece. PE

Photos: John Halpern

Epidemiology Arising

Experts from industry and academia probe the changing role of the pharmacoepidemiology function as it grapples with the challenges of big data analytics, tightening drug safety requirements, growing post-approval study burdens, and payer expectations around the application of real-world evidence

"Value" is the metric that counts in certifying new products for payer reimbursement. But defining that value is a complex, messy, multipolar task—one that many observers of the process now say should not be left to the cost fixations of academic economists. In this new world of evidence, beyond the narrow parameters of the randomized clinical trial, experience with the actual patterns of disease by flesh and blood patients has brought new attention to the contributions that epidemiology can make to population health, drug development, and market access. On June 4, *Pharm Exec* brought a group of pharmacoepidemiology experts to discuss how this below-the-radar function is adapting to a "show-me-the-outcome" system of healthcare.
— William Looney, Editor-in-Chief

WILLIAM LOONEY, *PHARM EXEC*: ***Product approval in biopharmaceuticals is moving from proof of safety and efficacy to establishing a strong benefit-risk and economic profile—one that appeals to payers and patients as well as regulators. This fundamental shift is transforming the role of the***

FAST FOCUS

» The value of a new drug must now be demonstrated to a wider range of stakeholders—using observational research methods that probe further than the carefully prescribed parameters of a randomized controlled trial.

» Big data is not the cure-all but the context; it is critical that pharmacoepidemiologists don't just analyze what they can measure, but attempt to make sense of the bigger picture in the clinical setting.

» Biopharma needs to conform to the idea that many of its technologies may be cost-effective, but not cost-saving, as the reality is new drugs will usually cost more than existing standard of care. Payers, in turn, need more help to better estimate the disease patterns and potential financial burden from reimbursing a new medicine.

in-house pharmacoepidemiologist at every stage of the drug development and commercialization cycle. Can we identify the key forces driving the change as well as their impact in redefining the mandate of this mission-critical function?

JOHN DOYLE, QUINTILES: We face a major transition in the way healthcare is financed and delivered. For the pharmacoepidemiology function ("epi," for short), this requires a different approach to drug development. Beyond the basic parameters of safety and effectiveness, it is now necessary to demonstrate the value of a new medicine to a wider range of stakeholders, beyond the regulator. But exactly what is this concept of value we are aiming for? The answer requires that we begin with a clear perspective of what proof points stakeholders are seeking for the future state of healthcare. It's all about the patient: the key players, from payers and insurers to drug manufacturers, physicians, retail pharmacists, and the integrated hospital networks, have endorsed patient centricity as the ultimate destination.

The challenge is that adoption of this new patient-driven value metric is not proceeding in a linear fashion—the stakeholders differ in the pace of progress. Not only do we see gaps in the adoption of patient centricity among individual segments of the healthcare business, there are variations in readiness at the geographic level. Overcoming the gaps requires a stronger commitment to service—and, more importantly, information—integration. We also need a common vision of population health linked to the achievement of better value and outcomes. With its capabilities to assess the risks and benefits of a health intervention across a broadly diverse study set, in actual clinical practice, the epi function is one of the key elements of a strategy to make that happen.

There is so much that needs to be investigated with observational research methods that extend further than the carefully prescribed parameters of a randomized clinical trial to the real world. Epi work allows us to see that patients will behave differently when they are asked to participate as active consumers of healthcare (i.e., the "Hawthorne Effect"). Payer reliance on utilization controls like tiered co-pays is becoming more prevalent and reliable observational data can take us much further in assessing the long-term impact of these tools on value and outcomes. Likewise, you have the giant retail pharmacy and drug distributors now leveraging claims data to understand better what motivates the patient—what are their health-seeking behaviors? Can we take information on consumer buying habits at the front of the store in retail pharmacy and apply it to shape actions when the patient has to fill a prescription and navigate through all those co-insurance and co-pay channels?

The conclusion I take from this is pharmaceutical companies must upgrade and accelerate the manner in which they collect, analyze, and apply "big data" to attain a premium position on that summit we call patient centricity. Some stakeholders are already well ahead in this race, including the integrated hospital systems like Kaiser and Geisinger, which are applying big data to develop their own clinical guidelines and formularies to evidence value from the pharmacy benefits they provide to covered populations. Drugmakers are already under scrutiny for the short-term costs of medicines on the health system. The industry has no choice but to step up and validate the benefits, risks, and outcomes from use of its products.

In a patient-centric model of care, the determinant of value is going to be what Harvard Professor Don Berwick codified as the "triple aim." That is, are you (1) solving for population outcomes, (2) enhancing the patient experience on his/her care journey, and (3) doing both while saving money for the system overall? This is the real question that the pharmacoepidemiology function in your companies will have to answer to stay relevant. The future is not about a siloed dialogue around one drug, one physician, and one patient. It is a dialogue driven by clinically relevant information, with the

Roundtable Participants

Stella Blackburn, Vice-President and Global Head, Risk Management, Real World and Late Phase Research, Quintiles
Joshua Cohen, Research Associate, Tufts University Center for the Study of Drug Development (CSDD)
John Doyle, Senior Vice-President and Managing Director, Quintiles
Julie Locklear, Vice-President, Health Economics and Outcomes Research, EMD Serono
Alfred Neugut, Professor of Epidemiology and Myron M. Studner Professor of Cancer Research, Columbia University Medical Center
Rob Reynolds, Vice-President and Global Head, Epidemiology, Pfizer
Paul Stang, Vice-President, Global R&D Epidemiology, Janssen Research and Development
William Looney, Editor-in-Chief, *Pharm Exec* (Moderator)

objective to reconcile that individualized intervention with system-wide efficiency and cost savings goals. We are definitely entering a new era of healthcare catalyzed by real-world research.

"Not only do we see gaps in the adoption of patient centricity among individual segments of the healthcare business, there are variations in readiness at the geographic level."
— JOHN DOYLE, QUINTILES

Data don't tell all

PAUL STANG, JANSSEN: Further progress in health reform depends not just on amassing the data made available through technology advances. The reliability of these data as a basis for informed decision-making is even more important. The problem we see with big data is the *benefits* from a particular intervention are often not revealed in the clinical record. People don't go to their physician just to say how good they are doing; there is no ICD-9 code for "feeling better." Those who work in the epi field must avoid the tendency to analyze only what we can measure. There is a much bigger picture that is obscured because our current data methodologies don't take account of it. Grasping and making sense of that bigger picture has to be part of the epi agenda.

JOSHUA COHEN, TUFTS CSDD: There is not only an asymmetry in information, the systems that allocate prices and costs for medicines are, in my view, irrational. Consider the structure of patient cost-sharing for physician-administered drugs here in the US. Despite many differences in the clinical performance and, hence, the value of these drugs, we see co-insurance rates of 20% or more applied across the board. Also, in Europe, patient cost-sharing is usually calculated at a fixed amount for all drugs, which provides little incentive to utilize high-value products.

STELLA BLACKBURN, QUINTILES: In the UK, patients pay a fixed co-pay for a prescription, regardless of what the drug costs the National Health Service (NHS). Combined with the pressure on physicians to prescribe the cheapest drug available for a condition, and to use generics where possible, this means that, in some cases, the co-pay amount imposed on the patient may actually be higher than the cost of the drug itself. And that assumes the drug is offered through the NHS at all—not all authorized medicines are available in the UK. The National Institute for Health and Care Excellence (NICE) follows criteria for the cost-effective assessment of new medicines that reflects its own distinctive approach to value but may sometimes be at odds with the preferences of society at large. You have heard the stories. NICE approved access to *Viagra* but allegedly would not initially finance an important new drug for macular degeneration until the patient was blind in one eye. Also, *in vitro* fertilization can be provided by the NHS while some oncology drugs are not. It is hard to quantify the logic behind these disparate judgments. It would help if industry had better ways through data to document why this regulatory approach is sometimes too narrow and short-sighted.

Answers beyond cost

LOONEY: ***What are the implications for pharmacoepidemiology of including a drug's cost in determining its value to payers, providers, and patients? How is the incorporation of this economic evidence in access and P&R decisions likely to shape priorities of the in-house epi team?***

DOYLE: It certainly ordains a larger, more visible role. Epi work has been concentrated on identifying populations targeted for disease indications as well as assessing risk vs. benefit on specific therapeutic interventions. If value becomes the focal point of a drug's market potential, and efficacy gives way to the concept of effectiveness, in which cost is a major variable, then the consensus is that pharmacoepidemiology can best serve as an integrator of the various data-driven functions that ultimately drive market access—for example, HEOR, Medical Affairs, or Key Account Management. Development of patient registries and benefit/risk profiling are examples of specific tasks that can be addressed through epi. That is the more strategic role we see going forward.

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Biopharma companies today want to take advantage of innovative marketing strategies to engage busy physicians, but they often struggle to implement a multichannel approach that delivers a consistent brand message across all touch points. One of the biggest obstacles they face is how to link disparate data streams between marketing and sales departments, to ensure all brand messages are accurate, engaging and on-point, regardless of the messenger. This webinar will explore how organizations can overcome these challenges by creating effective cross-department marketing campaigns to support integrated multichannel engagement (IME) strategies. We will explore how companies can build stronger lines of communication between marketing and sales, how they can streamline legacy systems and processes, and how they can harness the power of digital media to deliver a multi-tiered messaging campaign that will effectively engage their target audience.

Key learning objectives

- Based on research among pharmaceutical companies, learn about the industry's opinion and current use of multichannel marketing options
- Learn how to overcome potential internal and external hurdles and how to find the right partner to successfully deploy effective activities
- Get an insight on the results you can expect, which will help you demonstrate ROI to your stakeholders

Who should attend

Decision makers in Sales and Marketing, Digital Marketing, Stakeholder engagement, Product & Brand Managers, Head (VP) of Marketing / Sales, Multichannel marketing, Physician / Patient / Payer communication

Presenters:

Peter Lammers
Vice President Integrated Multichannel Engagement
Quintiles

Liz Murray
Director Integrated Multichannel Engagement
Quintiles

Moderator:
Casey McDonald
Editor
Pharmaceutical Executive

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Pharmaceutical Executive

QUINTILES

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ROB REYNOLDS, PFIZER: One activity for epi is identifying the right patient population for the drug, early in development. The goal is to optimize the benefit and minimize the risk in a targeted subset population, showing to regulators that the compound will work as intended and yield a positive health outcome. The ideal time to do the work is at the Phase IIB stage of a trial, or early in phase three, but not later. Such data can also be useful to the payer because it provides a strong indication that value will be optimized in the actual clinical setting.

ALFRED NEUGUT, COLUMBIA UNIVERSITY MEDICAL CENTER: We are in a grey area today. The familiar certainty of the randomized controlled trial (RCT), where one drug can be shown as statistically superior to another, is yielding to different measures that are harder to quantify. For example, in oncology trials, it is now common for quality of life and cost factors to be assessed in parallel with survival and other standard end points. If you look at where reimbursement is moving—toward bundled payments—then the template for this kind of research will always put the least costly drug at the top of the value chain. Why should anyone pay for the more expensive drug under such circumstances? This is a bit limiting.

STANG: The pharmacoepidemiologist might see things differently than the health economist. Each profession uses and interprets data differently. Epi has a more inclusive, complex view of data and this leads us to a less definitive conclusion than that of the health economist, who is inclined to say that the cheaper drug has greater value simply because it costs less; they have all the relevant cost/charge data available to them in the database. I wonder if payers have any incentive to see the distinction between the two approaches.

False pretenses?

JULIE LOCKLEAR, EMD SERONO: Payers are constantly looking for data to inform formulary decision-making. Comparative effectiveness data is routinely part of payer requests. As a manufacturer, we aim to conduct robust, reliable and relevant studies evaluating comparative effectiveness research (CER), real-world evidence [RWE], and RCTs to help payers in making formulary choices. There seem to be situations where products have demonstrated clear clinical superiority over the current standard of care, and are bolstered by a strong economic value argument, yet still don't get a listing on the formulary. It leads one to conclude that the rationale for payer decisions is contradictory and does not always follow the evidence.

STANG: We haven't mentioned the elephant in the room, which are attitudes toward the industry's evidence and the extent to which it may/may not be biased. Industry does bring in independent third-party groups to help vet its study research and abides by peer-review publishing rules that stipulate disclosure of the sponsoring organization. I think it's time we in the industry started pushing back. If the science is as good as we profess it to be, it ought to be able to stand on its own.

BLACKBURN: Value proposition research carries a tendency to reduce real people to data points—a homogenous blob. It's an assumption industry must work to dispel. We don't go far enough in trying to clarify the factors that will predict a benefit to the individual patient. Epi gives us potential tools to do that; with them, we can realize the promise of personalized medicine by identifying "benefit factors" and using these to predict individual response to a drug. I would add that industry devotes disproportionate attention to singling out risks compared to benefits, when most desperately ill patients are much more interested in the latter. The same holds true for side-effect profiling. One side-effect may not matter to one patient but may be hugely important to another.

NEUGUT: Personalization of drug therapy is the hottest area of epi right now. Optimism is widespread that personalized medicine will render moot some of the objections to the high cost of medicines. We can drill down and identify the best subset of patients who will truly benefit from access to an expensive drug, helping payer manage their cost exposure. At present, for every 100 patients, we treat all of them yet provide a benefit for only 20; all 100 also get the side-effects. Biomarkers and other tools mean we can provide that expensive drug to only those 20, while the funds once spent on the remaining 80 can be applied elsewhere. Pharmacoepidemiology research provides a very valuable service here.

A patient agenda for epi

LOONEY: ***As a group, can we conclude that being "patient centric" depends on three***

research commitments as the basis for accumulating evidence of value? These include: (1) focused attention to the benefits as well as the risks in granting patient populations access to a new drug; (2) assessing side-effects from the perspective that each patient will experience these differently; and (3) developing evidence that will allow clinicians to prescribe the right therapy for the right patient. Anything else?

BLACKBURN: I would add to this a commitment to treat the patient, not the disease.

REYNOLDS: Pfizer is doing more to explore directly with patients what their preferred trade-offs are between risk and benefit. We are proposing studies relatively early in development where we work with patients to better understand what they would value most in a particular medicine—how much risk in terms of side-effects they would tolerate in return for symptom relief or a higher quality of life. This also allows us to make the case to the approval authorities that certain risks are acceptable to the prospective patient population.

However, I'd emphasize that patient centricity, narrowly defined, is unlikely to make a huge difference in moving a drug candidate across the approval line. There are exceptions, of course. *Lotronex* and thalidomide for leprosy are examples where I think the patient view has been hugely important to regulatory approval. In my experience, arguments focused on patient convenience or accessibility that we uncover during development hold less sway with how the FDA and its panels decide. This is why we need to get beyond those so-called patient factors such as convenience or dosage regimens to improve adherence. Rather, we can define patient-centric drug development as bringing medicines to market that matter most to patients, such as those that significantly increase years of life or offer cures, and finding ways to understand patients' tolerance to accept risks for certain types of benefits.

STANG: There is an evolving methodology in epi—which Janssen is now putting to use—that seeks to capture quantitatively how patients evaluate the potential for harm from a particular drug against its benefits. Simply put, it is a statistically weighted utility measure that provides very useful insights on how patients approach the trade-offs in a decision.

In fact, this work has been instrumental in at least one decision to kill a compound at a much earlier stage of development, which is more efficient financially. We presented the methodology graphically in a recent presentation to an FDA advisory committee reviewing Janssen's blood thinner drug *Rivaroxaban*. It was well-received.

Pfizer and Eli Lilly have been conducting study research along similar lines. I expect other pharmaceutical companies to follow suit in applying these methods to weed out non-viable products before they starting draining money and resources. R&D today is all about managing finite resources, and this work puts us on the right path to a cost-effective, clinically relevant product proposition we can make to all stakeholders.

"We are proposing studies relatively early in development, where we work with patients to better understand what they would value most in a particular medicine—how much risk in terms of side-effects they would tolerate."

— ROB REYNOLDS, PFIZER

Regulatory challenges

LOONEY: ***This leads to a larger issue. If we agree that a more robust evidence base concerning patient perspectives on risk vs. benefit can open up the approval process, does this mean it will be accepted uniformly by different regulatory authorities? For example, do the FDA and EMA apply the same measures to secure the same result for the same product?***

BLACKBURN: The evidence suggests they don't. There are numerous discrepancies, simply because the application and evidentiary processes have been

devised separately. A drug approved for sale in both jurisdictions may carry a different indication; the definition of the disease itself can vary. That means the calculation of risk and benefit will go in a different direction as well. Rotavirus is not the health problem in Europe that it is in the US; therefore, there will be different assessments of the benefit and risk of vaccines to prevent disease. The notion that standard approaches are somehow more efficient for industry requires a bit of caution. It might be more helpful to conclude there is no single best way to measure benefit against risk.

STANG: The big issue is whether payers are going to see any of these improved methodologies as an aid to the decision-making process on access and reimbursement—one that they will actually use and apply transparently. Can we make that connection?

DOYLE: There is a common interest among both regulators and payers to see more real- world data through observational studies. Those responsible for drug approval have an interest in how the patient response in a clinical setting tracks their own assessment, while payers certainly would like to apply data from a patient registry to help document a value-driven decision to list a product on formulary. You could say that real-world data is the common denominator between the licensor and the payer.

COHEN: I agree. The first thing a P&T committee does when considering a listing is review the authorization package, including a meta-analysis of the risk-benefit studies submitted to key approval agencies worldwide, as well as other relevant research. One specific thing they are looking for is ways to stratify the eligible treatment population. They want to be able to know, with some objective probability, which category of patient will benefit most from the drug, or which patient will be more likely to suffer an adverse event. This feeds into the process for evaluating cost.

BLACKBURN: The need is certainly there. At the authorization stage, there is strong evidence of a drug's overall efficacy, but little knowledge of its safety profile. Pressure is only going to grow to redress the gap through systematic reliance on real-world studies that can reveal the true balance between risk and benefit.

LOCKLEAR: Safety and risk are particularly important as we know more about the biology that underlies key diseases like cancer. Breast cancer or small cell lung cancer express themselves differently in individual patients; these are not one disease, but many—and rare. This makes the identification of risk through real-world evidence a more daunting task, but the need to do so is equally evident. There is the added value of targeting that subset of patients most likely to tolerate the therapy compared to others. Herein lies a major opportunity for epi work.

REYNOLDS: In the past, pharmacoepidemiology was used infrequently in the oncology development and post-approval space. Epidemiology has always been important in oncology drug development—molecular epidemiology and natural history of disease studies have been key to identifying targets for many years. They will continue to be important as precision medicine approaches advance and genetic data are linked to electronic medical records (EMRs) and other data sources used by pharmacoepidemiologists. But until recently there were very few Phase IV observational study commitments on cancer drugs. Today, with the possibility of additional approvals for new indications, combined with the much larger data sets available, that scenario has changed. There are big opportunities for epi here, extending of course into other rare diseases.

STANG: Data and the methodologies to interpret it are developing in such a way as to allow for a better understanding of the way diseases actually affect patients. Providers and payers are focused on one disease at a time, when in fact the co-morbidity rate in most chronic diseases is high—60 to 70% of patients with a chronic disease have another. This raises many interesting areas for investigation, such as the impact of these co-morbidities on the effectiveness of the treatment being assessed—or could the treatment even be creating the co-morbidity itself? We are starting to see this with diabetes, depression, and other conditions that seem to have an inflammatory etiology.

NEUGUT: Another case for this kind of work is the litigation explosion. Adverse effects from drugs are almost always small and can be contained yet the "1-800-Lawyer" trend is well-established and in my view is out of hand, in proportion to the risk. Real-world evidence can help put the adverse events issue in its proper perspective.

LOONEY: ***There is an obvious lack of alignment on methodologies to develop real-world evidence, but, overall, do we see a genuine commitment from***

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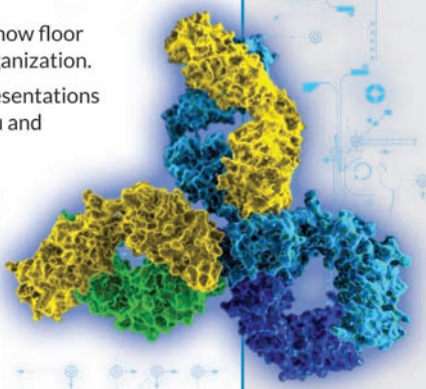

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regulators to pursue a more patient-centered approach in their interactions with the industry?

COHEN: It is true we can see little harmonization among payers, particularly in Europe. A good example is the sharp variance between the evaluation methodologies employed by NICE in the UK and IQWiG in Germany. At the same time, there are signs of small incremental steps by numerous payer representatives toward risk-share contracting with individual companies. This does require acceptance of a clear methodology on benefit, how to allocate costs, and other elements of a pay for performance model: will the company rebate the payer if the drug doesn't pass on performance or, alternatively, will the payer accept a higher price if the drug works? It's a work in progress.

On patient centricity, we can see some effort to insert the patient perspective in outcomes measures, such as EuroQol in Europe and the Patient Centered Outcomes Research Institute (PCORI) here in the US. But the interesting question is how these new institutional structures feed in to actual decisions on access and reimbursement. It's unclear. The big positive is the stakeholders are now listening to each other.

Epi research agenda—trending social?

LOONEY: ***Are there examples of large-scale long-term observation studies underway that in your view have the potential to advance the potential of epi and its new research tools?***

NEUGUT: One big initiative is a multi-target study examining aspirin as a therapeutic agent for multiple cancers. There are several randomized trials in progress in such areas as aspirin, as a post-treatment and preventive for colon cancer. Another is with *Celebrex*. We should see all this work shaping the armamentarium on cancer in the next few years. One project we are completing at Columbia Medical Center is a randomized trial around use of text messaging to boost rates of adherence to medication.

"There is the added value of targeting that subset of patients most likely to tolerate the therapy compared to others. Herein lies a major opportunity for epi work."
— JULIE LOCKLEAR, EMD SERONO

LOONEY: ***How is social media shaping the environment for pharmacoepidemiology research?***

REYNOLDS: The key players—Google, Facebook, Twitter, and IBM—are all seeking ways to harness their vast data streams for pattern recognition and other algorithms that yield insights on patient behavior. This approach has been effective in monitoring flu. Other infectious diseases are likely areas for investigation, particularly in tracing adverse events. I don't believe social media is going to be productive in furnishing insights on individual cases; there is not enough detail, but it may be useful for detecting patterns for further evaluation that you are not picking up using conventional methods. One such example is in the post-launch cycle, when real-world data is still scant, you can tap patient commentary and physician-specific data streams that accumulate on social media.

LOCKLEAR: Another example is PatientsLikeMe, which is a rich source of real-time information for patients with rare diseases. Patients can come together and find that 100 other people have the same gene mutation and can, thus, expedite participation in a relevant clinical trial. This kind of community-building would be impossible without social media.

STANG: In our community health studies, we have been evaluating the work of social network scientists like Nicholas Christakis (an MD and PhD) to attempt to determine how an individual's social network influences his or her health behaviors.

DOYLE: New epi study designs are emerging to tap the opportunities unleashed by big data. One example is a hybrid design that links a retrospective evaluation using claims or EMR databases with information that is collected prospectively at the patient and population level. This as well as other opportunities can be leveraged to help epi

build on the promise of big data and advanced analytics.

STANG: Janssen has adopted a similar model, which we call a readiness cohort. Data is compiled from following patients' behavior, but we also test them as well to uncover data that cannot be captured by conventional means. When the patient crosses a certain threshold on these tests, he or she is invited to join a randomized pool. Now that technology gives us the opportunity to access truly large data sets, this is going to emerge as an important new area for pharmacoepidemiology research. Similarly, we are looking at opportunities to use "randomizing into the database" in the post-marketing phase, where in situations of clinical equipoise, a patient who consents is randomized to a choice which is then followed to track their health status over a period of time—but solely in their own EHR.

Leaning in to management

LOONEY: ***Is there a CEO perspective on this topic that bears mentioning?***

STANG: The further up you go on the decision chain in a drug company, the more likely that the pharmacoepidemiology function gets placed in the bucket we call "real-world evidence." I am not sure people in general management see any distinction between the two. It's a perception we need to address, as our perspective in epi is necessarily broader.

LOCKLEAR: The best guarantee of our effectiveness internally is to display the skills and leadership traits that will attract the interest and commitment of senior management. Demonstrating timely value and relevant metrics to support these various epi initiatives will be critical to obtain leadership support.

DOYLE: Every drug company CEO spends a good part of his or her day addressing external concerns on whether its medicines are adding value and generating beneficial health outcomes. There is ambiguity about what is meant by "value," so anyone in the organization that can help the CEO grapple with it, particularly on the basis of sound methodological principles, will help make that job easier. The progression toward "value" came about when the discussion of risk expanded to place an equal priority on benefit. Balancing the two leads naturally to a focus on the patient—back again to the concept of patient centricity. This is an instinctive argument to make to the CEO. It's a natural fit for epi.

What's next

LOONEY: ***Looking ahead to the end of the decade, how will the big data revolution shape the way the epi profession conducts its work?***

NEUGUT: Widespread adoption of the electronic health record (EHR) will provide new ways to drive patient care in a more clinically efficient and effective manner. If a health system wants to discourage use of procedures that evidence shows is marginally effective, the physician simply has to type in the proposed action and he or she will receive a "pop up" notice noting that "action is not recommended by guidelines, would you like to continue?" The physician can order the procedure anyway, but the action will be flagged for follow-up around the outcome: we can, thus, see if the pop up leads to a decline in utilization of that procedure and also how the decision shaped the outcome of the episode, and its cost. It's a great tracking tool for the profession.

REYNOLDS: We will see the growth of additional new programs to capture big data for analytical insights. A strong precedent exists with the FDA Sentinel program, which coordinates safety and risk management activity using large integrated data sets built around a common automated model that can be applied to conduct individual studies. The effect of all this work will be to sharply reduce the time required to run such studies with such large populations; what once took several years can now be completed in as little as three months. As the time frame shortens, we can think about looking into events that may not be captured well in the data bases now in use, and bring in alternative sources of data like social media or clinical/patient registries on individual diseases.

STANG: Patient registries will become more prominent, but the jury is out on how efficient these will be in capturing data that is meaningful. Interest is strong from the medical device side, mainly because there are significant gaps in how the industry evaluates product quality and safety—there are still many unknowns. In pharma, the emphasis is on patient registries for orphan drugs or specialty products that carry very specific indications. They are usually established for a reason and, thus, I expect their use in the drug sector is going to grow.

New methods related to this will emerge as well.

BLACKBURN: Patient registries serve an important function in pharmaceuticals. I would like to see a lot more registries set up to track the patient journey with a medicine. One problem we face in epi is that when patients switch drug therapy, as is often the case, their data goes into a different registry, if the registries are product-based. Sever the connection and the follow-up trail can go cold. That, in turn, makes it harder to render useful conclusions. We have to do better in utilizing disease registries to answer the key research question: Does giving drug A at a particular stage of disease progression lead to a health benefit? For how long? And does the sequence of treatment matter?

Another imperative is to get more creative about hybrid study design, such as introducing direct questioning of patients to obtain information not normally contained in a registry, then using one of the EHR databases to follow this group over time. Quintiles, as part of the PROTECT consortium, just conducted a study examining drug utilization during pregnancy. Patients told us a lot of things that could never be gleaned from the EHR; when we combined both streams and examined the results, we got insights that never would have been revealed by relying on one source alone. That's the advantage of hybrid design.

LOONEY: ***Again, looking forward, how will the cost control and pricing environment shape priorities in pharmacoepidemiology?***

COHEN: The evolution toward a "value-based" pricing system will continue in both the US and in Europe. I emphasize the word evolution, because neither market is really there yet. At its most basic, there is a lack of clarity on what "value" is supposed to represent. This makes it harder to build methodologies and metrics that have staying power and are applicable across different market segments and geographies. What *will* drive the agenda around value is the growing volume of data that exists to be tapped in pursuit of price regulation for biopharmaceuticals. The pressure to justify costs is going to intensify. And despite the sheer volume and accessibility of data, measures taken by payers will often seem arbitrary because of the underlying politics of budget austerity.

"Despite the sheer volume and accessibility of data, measures taken by payers will often seem arbitrary because of the underlying politics of budget austerity."

— JOSHUA COHEN, TUFTS CSDD

The biopharma industry and the payer must be realistic. Given the scale of the demographic transition over the next 20 years, the idea that healthcare costs overall are going to remain stable or shrink is a fantasy. We can bend the cost curve, but we cannot break it. The industry has to accommodate to the idea of many of its technologies being cost-*effective*, but not cost-*saving*, because new drugs will usually cost more than the existing standard of care. Where I think more needs to be done is in preparing payers to help estimate the potential financial burden from reimbursing a new medicine to those who need it. We did not see this prior to the US rollout of the new hepatitis C cures last year, and the payer reaction was harsh. Drug companies must pinpoint the prevalence of the diseases they are treating and be very precise in establishing just how many patients will benefit, and, thus, be eligible, for treatment. This is an area where pharmacoepidemiology has much to contribute.

BLACKBURN: Cost concerns are arbitrated in the real world, not in the traditional world of the randomized clinical trial. Hence, as cost becomes more important, pharmacoepidemiology can only rise in prominence. RCTs are useful, but you need to carry on to the bedside to get the truth about what happens to a patient when he takes a drug. It's precisely why we are now having the debate over different standards of evidence as part of the 21st Century Cures legislation now before the US Congress. PE

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The Adherence Journey: Activating the Patient

Adherence is no longer. The emphasis is now on patient activation, but how significant will this change be? How can drugmakers become more collaborative in engaging and empowering patients? Mobile tech and data ownership will certainly play a key role

By Casey McDonald

A patient has been prescribed a drug, your company's drug. What next? Is there an app for that?

Step back and think about the patient journey to this point. In the course of the joys and trials of day-to-day living, a patient may be afflicted with early symptoms. Be they minor or severe, a patient hopefully receives a diagnosis, often after missed opportunities and wrong turns than can stretch for years.

Then, the patient and their caregivers must navigate a maze of bureaucratic networks, cryptic payment terminology, and call centers. And most must do this with limited understanding of their personal physiological perturbation nor of the molecular remedy that has been deemed their savior. Many patients do successfully traverse this path.

Now the patient has your drug (or a slip of paper giving permission to obtain your drug) in hand. The patient can now partake in the great miracle of modern medicinal chemistry. They can begin to reap the benefits of an efficacious and safe therapy, deemed so by years of clinical data.

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» Non-adherence to taking prescribed medication accounts for about half of the US healthcare system's "avoidable costs."

» With today's more proactive consumer base, a movement is underway to evolve mindsets and strategies from patient "compliance" and "adherence" to a more collaborative approach: patient "activation."

» Pharma needs to tap into the mobile tech explosion to better support and engage patients—with the goal of transforming healthcare delivery.

And yet, many don't.

Whether they never get the drug, they fail to take it, they miss days, they start but stop because they don't think it's working or find a side effect unpleasant, patients fail to adhere at all different stages for countless reasons. Many are just forgetful.

Of course the concept of compliance or adherence is not new. Papers have been written and conferences have been convened for years to get at the heart of why patients don't follow orders, and what providers, payers, and drugmakers should be doing to improve the state of things.

As it stands, the annual cost of non-adherence to the US healthcare system is estimated at as much as $290 billion. According to a 2014 IMS report (looking at 2012 numbers), non-adherence accounts for about half of the US healthcare system's "avoidable costs," dwarfing issues like delayed evidence-based treatment practice, antibiotic misuse, medication errors, and suboptimal generics use.

One clear missive from participants at the BIO International Convention, and at CBI's PAAS, the 14th Annual Patient Adherence and Access Summit, both held in Philadelphia this summer, is that this remains an untapped opportunity. But the current mindset of "Compliance" and "Adherence" won't cut it. "Engaging" and "Activating" patients is the new mode of thinking and will be necessary to unlock the potential value. The difference may seem subtle, but a new mentality will be crucial as apps and mobile techs open the door wide to patients' palms and wrists, hopefully for meaningful interactions that motivates positive behavioral change.

Pharma's not so adherent programming

From the perspective of drugmakers, solutions to adherence can be elusive. Progress has been made assisting patients with obtaining and staying on their meds. But their commitment to the problem can be described through numerous "fits and starts", Robert Nauman, principal at BioPharma Advisors Network told *Pharm Exec* in May.

Major pharma players have hired adherence czars and given the issue attention in two- or three-year spurts, but they've never made the radar of mainstream marketing leaders who invested significantly in big brands, he noted.

"Part of the adherence quandary is that these programs are heavily regulated, and as such, they're not valued as independent programs by the very people they are designed to assist, the patients," Nauman added. Content produced by adherence teams is often under valued by patients, because of concerns communicating side effects and adverse events. As programs near launch, drugmakers fear bridging into medical liability issues. Every few years firms look at their adherence programs and ask whether they should be investing in these efforts at all, according to Nauman. "Investments in these tools/programs require resources and commitment, something only specialty pharmaceutical products seem to be willing to do at this time."

In addition to regulatory constraints, staying steadfast to adherence programs is challenging because it takes work.

"Part of the adherence quandary is that these programs are heavily regulated, and as such, they're not valued as independent programs by the very people they are designed to assist, the patients."

"Who's responsible for adherence?" asked Brian Mullinax, national accounts director, market access, for Flowonix Medical, posing the question to a room full of adherence experts at PAAS in June. "Everyone is responsible and that's the tough part of the equation," he said.

Mullinax presented a case study for an adherence program for Genentech's orphan drug P*ulmozyme* for cystic fibrosis (CF), an effort to return value for a drug in a challenging setting, which had been plagued by poor adherence. The approach, traditional and simple but comprehensive, was an education initiative encompassing all aspects of CF care. The strategy focused on delivering the message to patients seven times during each quarterly clinic visit via tent cards, posters, teaching handouts, reward program, and verbally with each healthcare provider able to identify the

knowledge deficiency and link the adherence message.

The *Pulmozyme* program was a success, thus meeting goals for prescription, adherence, and clinical measures pulling the product out of a failing trend. But the need to examine and assert the communications strategy for a failing product illustrates the inconsistent adherence approach that Nauman had described, as these measures and the dedicated messaging weren't fully in place from the start.

Educating a patient population can be a massive effort with the subpar scientific and medical literacy of the lay public trying to comprehend jargon that can confuse and intimidate patients. Thomas Bauer, corporate director of health literacy and patient engagement for Novant Health, pointed to one of the most basic (and dramatic) events in medical communications, the moment when a patient receives test result which can be "positive" and be bad, while "negative" means good—a language obstacle so fundamental that this writer can think of multiple times it's been used as a comedic device in TV sitcoms (*Seinfeld*).

Though the straightforward, traditional adherence effort produced results for *Pulmozyme*, communicators across all walks of life can attest to a basic frustration—the deficit model. Simply put, scientific and medical professionals assume that imparting knowledge and giving a greater understanding will result in altered behavior. But for whatever reason, knowledge doesn't always result in a transformed patient.

The thinking of adherence programs is flawed because they are product-centric, noted Megha Reddy, manager, patient engagement for GlaxoSmith-Kline. Adherence programs are missing an important aspect of the patient experience, she explained. Knowledge is power and patient education is a big focus, but the patient's ability to manage their condition is still limited. Knowledge is really just a part of the equation. Motivation and skills are needed, too. To this end, GSK has focused on influencing behavioral change using 50 years worth of behavioral science research.

Reddy presented examples where GSK has transformed traditional patient resources into more engaging experiences for patients. The example given at PAAS, rather than informational brochures for smoking cessation, GSK presents patients with interactive, informative, and instructional teaching platforms—more like choose your own adventure guides than static textbooks. These have helped patients actively build the motivation and skills to quit smoking, rather than just passively being told what to do, she explained.


Megha Reddy

So drugmakers, payers, and healthcare providers can, and should go to great lengths to educate patients about their disease and treatment options. Simple is key, and adherence starts at the clinic, noted Mullinax. But simply giving information and instructions from a position of authority without engaging patients can be inadequate and can backfire. This is why those in the field are excited to take thinking on adherence in a new direction, towards patient activation.

Does a change to an "activation" mindset really mean anything? Or is this just the newest buzzword for lunchroom corkboards and outward facing corporate PowerPoint's that will be replaced in five years?

Regardless of what patient support will look like in five or 10 years, right now, the change certainly appears to be on. At PAAS, it certainly seemed like attendees who hadn't already done so, would be going back to the office and running a Find/Replace on all corporate documents to scrub out "compliance" and "adherence" in favor of "activation."

Words to deed

According to Alisa Hughley, of enBloom Media, speaking on a panel at PAAS, patients are demanding the change because they are becoming proactive, rather than being acted upon. The mindset of adherence and compliance makes taking a medication an act of submission, she explained. Patients, especially those with a chronic condition, are already submitting to the idea that they have this condition and have to learn to live with it.

"The notion that a physician can just give instructions and you'll be fine is archaic," added co-panel speaker Katherine Leon of the SCAD (Spontaneous Coronary Artery Dissection) Alliance, calling the traditional adherence mindset almost militaristic. "A safer approach would involve patient and doctor taking the time to fully discuss all medications."

Kimmia Forouzesh, of the Foundation for Sarcoidosis Research, noted that her organization has also preferred a different mindset, one of "empowering"

patients. In sarcoidosis, the treatment plan varies by patient as there is (as of yet) no drug developed to treat the underlying cause of the disease, so patient empowerment is crucial, she noted.

Solidifying the point, Hughley quoted participants of a recent focus group: "I hate, hate, hate the word adherence! It makes patients who can't follow instructions to the letter sound like unruly children." And, "Adherence implies a level of obeying. It doesn't feel like the patients and caregivers are partaking in a collaborative effort."

"Words have power," Hughley added. "It's not about getting a patient to adhere. It's about engaging patients in shared clinical decision-making."

Wellness—the deep stream

More than a change of mentality for drugmakers and caretakers to have towards patients, many see the prospect to meet patients in a collaborative way as a huge opportunity with mobile tech and apps as key mediums for connecting.

On another panel discussion just a week prior to PAAS, the Scientific American Worldview Super Session at the BIO International Convention, moderator David Brancaccio of the *Marketplace Morning Report* and *PBS Now*, asked his esteemed panelist what they see as this generation's "plastics," in reference to the famous advice given to Dustin Hoffman's character, Ben Braddock, in T*he Graduate*.

Lee Hood, President Institute for Systems Biology, deemed "wellness" as the next "plastics," pointing out that currently 99% of spending is on disease and just 1% is put towards wellness, but this will change. Hood noted that a key step will be making the study of wellness more scientific. Tech-enabled, activated patient populations should make health and wellness trials possible for attaining true scientific results. Hood recently co-founded Arivale, a Seattle-based firm based on the very idea of scientific wellness which promises to utilize a 360-degree view of its consumers' DNA, blood and saliva, gut microbiome, and lifestyle.

"It's not about getting a patient to adhere. It's about engaging patients in shared clinical decision-making."

—ALISA HUGHLEY, ENBLOOM MEDIA

Echoing Hood's message, Martin Naley, founder and CEO of Cure Forward, said "patient activation" was his 2015 substitute for "plastics." The notion of patients getting activated by their own data will be a huge opportunity, he said. Whether patients are visualizing their genomes or counting their steps, we will see a more engaged patient population.

If the prognosticators are correct, investment in patient engagement and activation platforms may be a major trend. But apps and mobile technology evolve at rates that leave pharma and biotechs choking on their dust. Could pharma exit the adherence/activation game all together and just outsource it?

"Disruptive innovators in mobile and tech may disintermediate drugmakers from adherence efforts," noted Nauman, prior to the PAAS conference. "Diabetes or blood pressure monitoring apps, using gadgets like the Apple Watch, for example—none of these techs are regulated, and innovation is coming at rates that are infinitely faster than pharma can play at," he said. Patient monitoring is going to be something the technologists take on, and as a result pharma may just forgo big patient support programs. Yet following the conference, Nauman noted: "Even mHealth application developers do not want to wade into the water where some tool can help with diagnosis and medication management to track adherence over time for fear it might be considered a medical device."

Biogen's Fitbit trial

Indicating how pharma and biotech companies might manage to keep their skin in the patient adherence and activation enterprise, Biogen has taken major steps to learn how they might just bring patients, drugs, and technology together.

For a start, the company thought it would give Fitbit a chance in a group of email responsive, tech-enabled multiple sclerosis (MS) patients. Director of new initiatives for Biogen's Innovation Hub, Jane Rhodes explained that the company wanted to try out a commercially available device, employ it to patients, and to simply address whether they would use it and allow Biogen and PatientsLikeMe to access the data.

For something so simple, it was quite complicated to begin with, but Biogen ended up choosing Fitbit because it was commercially available and it has an open application program interface, so it was easy to

extract data. The company constructed an "out of the box" experience, which was followed up with interaction to follow patients if they had questions.

Fitbits famously have shown strong sale sales and good early adoption, with a large number of customers falling off, disinterested in a matter of months. In the medical setting, if it's viewed as valuable and the physicians stress the importance, patients will tend to wear the devices, showing high compliance, Rhodes noted.

The trial was "fantastically successful" with a high number of responders and active patients all the way to a completed survey. High participation was evident as most patients were interested and able to use the Fitbit. The data will be helpful, because not just walking, but sleep, is very important for MS patients.

Of course, this early work was not rigorous enough to show decisive clinical measures, but Rhodes emphasized that the levels of ambulation collected correlated nicely with self-reported standards indicating the strong potential for further use to provide data points in MS trials.

Besides Fitbit, Biogen's new initiatives director is bringing in other mobile technologies in for its MS mission. Probably the most mature collaboration, the firm is working with the Cleveland Clinic to develop and iPad-based tool designed to be used in the clinic setting to allow patients to conduct their own neurologic testing. "We think it's a huge step forward for a number of reasons," says Rhodes. "Patients only see neurologists a couple times a year and most of the appointment is conversational to try to understand symptom progression, new symptoms and their response to treatments." Biogen and the Cleveland Clinic have take FDA accepted tests for assessing progression quantitatively and put them into an iPad format without impacting the flow of the patient's care.

Speaking to the impact of mobile techs and the impact they will have on patient support and engagement, "My sense is that we've reached a tipping point, and there's going to be an enormous explosion in techs that can gain traction and transform care," says Rhodes. "There's been explosion in consumer space, but it hasn't helped much in healthcare yet. In terms of transforming care in delivery, we've only just scratched the surface."

And Rhodes agreed that biopharma companies will have to partner with technology experts to tackle the mobile patient. "We live in a world of partnerships now. No one can do this alone."

Adherent bites

As a prelude to who some of these disruptors and partners just might be, PAAS attendees listened to rapid fire, elevator-style pitches from several tech startups taking *Shark Tank*-inspired questions, no doubt indicating that adherence-dedicated professionals are on the cusp of tech and TV trends (see sidebar below).

The audience was treated to an array of demos and presentations, including an IT solution for 360 degree patient path monitoring,

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CBI's PAAS *Shark Tank* Awards

After their pitches, conference-goers at CBI's 14th Annual Patient Adherence and Access Summit "invested" with Monopoly-style play money to symbolize their level of confidence in the companies and technologies.

MEMOTEXT: Praised as *Most Global* for bringing speech, mobile, and social technologies together to create mobile (mHealth) and telehealth patient adherence programs. The firm specializes in the design and deployment of dozens of digital patient adherence and behavior change programs globally while advocating for evidence-based approaches to technology-based behavior change.

NVOLVE: Won *Most Innovative* for its system, much more than a pillbox, simple and sleek. The monitoring and intervention system aims to improve medication management services through increased effectiveness and efficiencies. N2 Medical Solutions designed NVOLVE with an intuitive design, personalized interventions, comprehensive tracking, and real-time reporting.

CIRCLELINK: Was awarded *Most Provider-Focused* for its strategy to improve health for the chronically ill via adherence to customized care plans, including medications, using mobile technology. The company helps physicians earn Medicare's reimbursement for chronic care where it counts, in everyday life. CircleLink has been improving care plan adherence for chronically ill patients via mobile at large institutions like Johns Hopkins, Emory, and Yale-New Haven for five years and is rolling out its new, reimbursable product. Beta launched in April; the product is successfully billing Medicare, and the full version will launch in August.

C3i: Took home *Most Comprehensive* for its engagement-focused service targeted to complex therapy regimens that require more than mass marketing and passive adherence tactics to support the patient, caregiver, and HCP. The service incorporates a technology platform, CaseTrack, with multi-channel communications to deliver optimally adherent patients leveraging nurses, HCPs, and other dedicated phone-based professionals.

— Casey McDonald

text message-based adherence programming for a patient-specific, personalized interaction platform, and a mobile phone engagement technology designed for chronic care allowing their physicians to easily earn Medicare's new chronic care reimbursement.

The most intriguing presenter just might have had the simplest and most unassuming technology for aiding patient medication adherence. Andy Bowline, CEO and co-founder of N2 Medical Solutions, presented the iPhone of pill dispensers called nvolve. Designed for the aging patient, nvolve is simply a pillbox device with weight-sensitive sensors providing a dashboard for the physician to monitor and make dosing decisions. It's designed for patients who haven't graduated to assisted living yet and want to maintain independence. The aid, like so many good technologies, can do its job and fade into the background. A device that "fades into the background" may not be in line with the activation theme of the conference, but the questions from the audience certainly indicated the audience's sense that the device's simplicity and functionality would be highly sought after.

Actively forward

One thing was clear, PAAS, the Patient Adherence and Access Summit, might just have to change its name. Though, luckily, changing adherence to activation, the CBI event can maintain its acronym.

But what was also clear from a June of adherence discussions, there is immense excitement and massive opportunity for a changing mindset to work with patients engaging and activating them. The potential for tech and mobile solutions to impact patient care rapidly is real, but the regulatory system, along with keeping an eye on real privacy concerns, will have to keep up.

The stakes are high, clearly as high as $290 billion, and that number can only grow with an aging population and increasing specialty pharma spending. With cures hitting markets, and $1,000 per-day pills impacting payers and care networks, the potential impact of patients being able to remember their pill regimens means the pressure for more patient activation will only increase. PE

Getty Images: Olivier Le Moal

Manufacturing's True North: The Quality Compass

Biopharma needs to combine a "culture of quality" with value-added process improvements in manufacturing. Here are key steps and strategies that can make a difference—and deliver bottom-line results

By Ian Wilcox and Conrad J. Heilman

In pharmaceutical manufacturing, tales of quality failure follow a familiar pattern. A manufacturing site—often offshore—finds itself on the receiving end of regulatory action for violations ranging from missing or manipulated test data and failure to submit field alert reports, to lack of compliance with current good manufacturing practices (cGMP). Duly warned, executives then take steps to improve. Sometimes, this tale ends happily; often it does not. Issues recur, and companies are left to wonder whether their organization is simply fated to have problems maintaining quality.

Biopharma executives who create a culture of quality in their organizations can take control of their own quality story—and thus craft a greater number of stories that have happy endings. What do we mean by a "culture of quality"? A culture of quality is the sum of the good habits possessed by every member of an organization. When these behaviors are in place, work exceeds the standards not only of regulators but also of patients, providers, and payers. In other words, in a culture of quality, every action in the biopharma company, from the most routine to the most novel and inventive, aims to exceed standard practice.

FAST FOCUS

» Manufacturing is now a strategic imperative for biopharma, where doing it right has a measurable impact on the corporate bottom line.

» Innovation in manufacturing is tomorrow's driver of competitive differentiation.

» Successful quality metrics depend heavily on getting the intangibles right, the most important of which is seeding an internal culture of best practice marked by total transparency between employees and management.

Why a culture of quality is critical

There are three major reasons why executives need to build a culture of quality: the cost of quality failure, increased regulatory activity, and the FDA's changing approach to quality oversight.

Cost: Inattention to quality is costly. In the extreme case of a consent decree, penalties have been known to top half a billion dollars. But penalties alone do not provide the full picture. A 2013 McKinsey study of the medical device industry estimated that taken together, routine quality control, "non-routine quality events," and revenue losses from non-routine quality events cost that industry $17 billion to $26 billion annually, a figure that represents 12% to 18% of revenue. But the report also pointed out that improving quality has clear benefits. It cited the example of a medical device company that reduced warranty costs by €21 million per year through reliability engineering. In addition, the company was able to increase its capacity because of because of supplier and manufacturing improvements, and revenue grew by approximately €30 million per year.

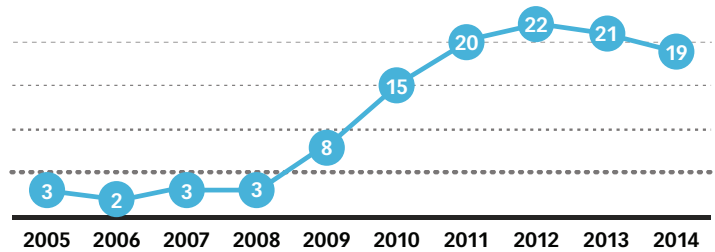
FDA rethink: Over the last 10 years, FDA activity has increased noticeably. The FDA issued more than six times the number of warning letters for manufacturing in 2014 than it issued in 2005 (see chart above). The spike in warning letters doesn't tell the whole story, though. Between 2010 and 2011, field alert reports nearly doubled from approximately 800 to slightly less than1,600. In that same period, OTC recalls rose from 336 to 652, while prescription drug recalls rose from 479 to 605. Drug shortages also climbed, from 178 shortages in 2010 to 251 in 2011. In this same period, shortages of sterile injectables more than doubled, from 74 to 183.

A changing approach to quality: Finally, these numbers are among the factors that have prompted the FDA to revamp its approach to quality oversight and to shift the emphasis of its investigations from the paper trail to product quality. Other factors include "unacceptably high" occurrences of problems attributable to defects in product and process design, an increase over the last decade in the number of post-approval supplements received for review, and a disproportionate amount of attention devoted to low-risk products.

An attempt to place quality review, inspection, and evaluation under one roof, the Office of Pharmaceutical Quality (OPQ) is a step in this direction. On the horizon is an approach to define and measure product-specific quality metrics in order to monitor product performance (including positive and negative trends). Hypothetically, collecting quality metrics will allow regulators and manufacturers to devote more resources to at-risk manufacturing sites while reducing the inspection burden on lower-risk sites.

Warning Letters on Rise

FDA Warning Letters for Pharma Manufacturing (cGMP) Issues 2005–2014



Source: Hay Group; data excludes warning letters related to food and tobacco.

What do these developments add up to? The cost of quality failures, the jump in warning letters (regardless of whether the jump is a result of a downward trend in quality or more vigorous regulatory action), and the establishment of the OPQ are signs that quality needs to become more of a focus in biopharma organizations. From the Board level down, biopharma leaders should ask themselves, "What if we placed manufacturing quality at the center of our competitive strategies? What kind of culture would develop, and what business results would ensue?"

Obstacles to change

It's not much of an overstatement to say that, historically, manufacturing has been a strategic after-

THE JOURNEY TO IMPROVED QUALITY: WHERE DOES YOUR COMPANY STAND?

Organizations typically find themselves at or between four basic stages of quality management:

» At the first level, management is made aware of problems only after they have ballooned into crises.

» While a company is still reactive at the second level, they show a willingness to change. Patchwork corrections are the rule.

» At the third level, companies begin to detect adverse trends proactively or as they emerge. Companies at this level bring major issues to the surface and make lasting manufacturing and systems improvements.

» Companies at the fourth level act preventatively. They create and reinforce a vigilant culture and consistently make meaningful improvements.

Given that process improvements represent such low-hanging fruit, executives should treat manufacturing not as an occasion for risk but as an opportunity to innovate

thought—executional drudgery after the high drama of research and commercialization. However, such benign neglect of manufacturing is misguided. Because quality and reliability matter significantly to patients, they should be central to every company's commitment to health. What's more, a focus on quality also leads to cost savings realized through process improvements. In fact, one company saved $50 million by improving quality across two sites.

To capture cost savings and improve quality—outcomes all biopharma executives wish to achieve—it is critical to make quality central to an organization's culture. Nevertheless, in most companies, significant barriers stand in the way of creating a culture of quality. One such barrier is a misconception that manufacturing is not a major strategic concern. This misguided view holds that quality is extrinsic to the broader mission of the biopharma company and not the shared responsibility of every area of the organization.

Compounding this misconception is a sense that manufacturing is not an asset but a vulnerability. Although an unhelpful way to look at manufacturing, this view is understandable in light of high-profile penalties over the years. During the past decade and a half, the FDA has held numerous pharmaceutical companies accountable for GMP violations, through legal action and by imposing stiff penalties: in one case, a $500 million penalty and a consent decree that required one company to shut down manufacturing for over 50 different products. At the time this was the largest set of penalties the FDA had ever administered.

Lost opportunity to innovate

Surely, failure to properly balance operational performance, cost, and quality leads to regulatory issues, financial cost, and the loss of public confidence. But such failure has another cost: lost opportunity to innovate. While biopharma companies have generated notable scientific innovations over the last two decades, advancements in manufacturing have been comparatively less dramatic. Although lean production techniques have boosted labor productivity and cut variable costs, pharma trails other industries (e.g., food, consumer goods) in modernizing manufacturing processes.

Given that process improvements represent such low-hanging fruit, executives should treat manufacturing not as an occasion for risk but as an opportunity to innovate. By combining a culture of quality with value-added processes and improvements, companies will reduce compliance issues and boost efficiency, reduce risk and increase revenues. With a culture of quality in place, manufacturing will become a source of competitive advantage.

Doing it right: Quality across the organization

To realize this competitive advantage, mindset and culture must evolve so that quality becomes central to how both innovator and generics companies deliver on their value propositions. This evolution requires emphasizing quality not just in manufacturing but in every part of the organization.

An important first step in building such a culture is to understand manufacturing as central to the company's mission. The self-image of a biopharma company includes many elements, and scientific and medical excellence is usually chief among them. Excellence in operations is another, as is excellence in business strategy.

But biopharma leaders should not forget that the goal of these many sophisticated skills is a physical product, one that a patient will swallow or a physician inject. Indeed, the myriad complex cognitive acts necessary to bring a drug to market have a physical, material goal, and if the tangible product is defective, these intellectual efforts, their sophistication notwithstanding, come to naught. Comparisons with art making, where an artist works to realize a mental concept in material form, spring to mind—Failing to include manufacturing as an essential component of the value chain is like Donatello or Rodin ignoring the quality of the bronze in which their sculptures were cast, or a great director filming a brilliant script without considering the skills of the actors.

For biopharma companies, then, the execution needs to be present in the concept from the

Continued on Page 36

Breaking through the complexity:
improving oncology treatment and access in the UK

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Event Overview

In the UK, like on a global level, personalized oncology healthcare approaches have seen a dramatic increase. This would suggest a positive development for patients in the UK, but it also entails some potential huge difficulties for the NHS. Data suggests that half of biopharma are integrating personalized medicine into their product development to help with product differentiation and therefore market access. Local commissioning groups in the UK have to manage the budget impact of oncology products, with the advances in cancer treatment outstripping the available financial resources. Although measures have been introduced to support patient access to advancing cancer treatments in the UK, the current variation in access is undermining public confidence in the NHS.

This webinar sponsored by Quintiles, will bring together experts from key oncology viewpoints, a market access expert from Quintiles and a consultant clinical oncologist to provide valuable insight on this important biopharma debate.

Key learning objectives

- Uncover best practice approaches to improving access to innovative cancer treatments in the NHS
- Explore the current challenges facing NHS oncology clinics
- Discover the approaches that can have an impact on making oncology innovation feasible while ensuring patient access on a local level in the UK.

Who should attend

Decision makers in Market Access, Regulatory Affairs, Real-World / Late Phase research, HEOR, patient-centric / patient engagement programs, payer / provider relations, Brand managers, Marketing Managers/Directors, Pricing & Reimbursement, Medial Affairs, Executive Management, Health Technology Assessment, Pharmacovigilance

Presenters:

Dean Summerfield, DPhil
Senior Vice President,
Commercial and Consulting
Quintiles

Dr Jason Lester
Consultant Clinical Oncologist
Velindre Cancer Centre

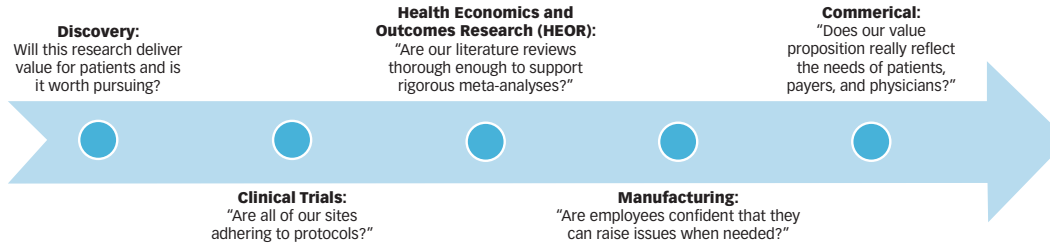
Moderator:
Casey McDonald
Content Manager
Pharmaceutical Executive

Questions: Contact Sara Barschdorf at sbarschdorf@advanstar.com
US: 1 866 267 4479 **EU:** +44 203 564 4649
Web: www.quintiles.com **Email:** marketaccess@quintiles.com

Pharmaceutical Executive

QUINTILES

Quality Questions By Stage



Continued from Page 34

beginning, which in practical terms means this: quality must become the shared responsibility of every part of the organization, a part of every link in the value chain. When a quality mindset inheres in all parts of the company, quality in manufacturing will become second nature.

No matter what department they're in or what their role is, everyone needs to prioritize quality, which must be baked into the organization end-to-end. Although scientists working in discovery or health economists calculating quality adjusted life year (QALY) figures have little direct influence on the quality of manufacturing, per se, their actions, nevertheless, have important indirect effects; actions add up to a culture that supports manufacturing quality. While quality means something different in every part of a company, when enough people make it a priority, it becomes a company norm, a habit reinforced by positive peer pressure.

Which is to say, every area of a biopharma company can contribute to a culture of quality. Questions such as those illustrated in the figure above will help different parts of the organization prioritize quality in the ways that make sense for their various roles and functions.

How leaders set the tone

A culture of quality creates an environment hospitable to excellence in manufacturing, but for such a culture to take shape leaders at the highest levels of the company—from the CEO and board levels down—must first set the tone. In word and deed, they must send the right messages about quality. By raising the organizational profile of manufacturing, for example, they will send unmistakable signals that quality matters. Messages about quality must be clear and consistent.

Down the organizational chart, among managers, change entails a willingness to train employees to address quality issues, and then to entrust them with the responsibility to do so. In a culture of quality, employees exert control and influence at key process points. It's up to managers to open clear lines of communication and create an atmosphere of trust so that employees feel secure and confident in reporting issues. Certainly, employees will make a few mistakes along the way, but in the end, quality will become habitual throughout the organization. Finally, managers need to set expectations for quality. They need to communicate that quality is a priority, encourage the habits that lead to quality, and hold employees accountable for quality when evaluating them.

One example: data integrity is essential. If leadership sincerely places the proper emphasis on quality, entrusts employees to focus on quality, and celebrates actions to assure quality, the outcome will reduce breaches in compliance that will eventually be discovered and have negative regulatory and compliance consequences.

Entrusting employees with responsibility for quality sounds great in theory. But many readers might wonder where to find employees with the skills to handle it. Finding the right talent is undoubtedly a challenge. However, leaders can overcome this hurdle by investing in the talent they already have. Creating a culture of quality means treating employees as key assets and investing in their futures. It means giving them the technical skills and training to maintain high standards and to understand how the whole manufacturing process works end-to-end.

Imparting this sense of the whole requires communication from management, which may take the form of newsletters featuring articles about different areas of the business, lunch-and-learns, and one-on-one conversations. In addition, research published in the Harvard Business Review suggests that

positive peer pressure is important in rallying employees around a quality culture. For example, managers might organize friendly competitions to see which groups can deliver the most consistently high-quality results.

Leadership styles for quality

In the end, leaders must treat employees as assets whose knowledge, experience, and judgment are critical to the business. Executives should become aware of the styles of leadership they use (if they aren't already) and, as needed, add more tools to their toolkit. This is because using the right leadership styles is vital in creating a trusting, engaging climate that encourages bringing issues to the fore and taking action when necessary.

The best styles to ensure quality are those that make employees feel that their managers have their best interests at heart. Designated "resonant" by Daniel Goleman in his book *Primal Leadership,* these styles elicit the positive emotions that bring out the best in people. What Goleman calls the "dissonant" styles, by contrast, rely on negative emotions like fear and anxiety. In brief, the four resonant styles are 1) **visionary** (showing everyone what the big picture is), 2) **affiliative** (building genuine relationships), 3) **coaching** (helping people become better), and 4) **democratic** (listening to make sure the team's best ideas come to the surface).

Note that certain leadership styles—the affiliative and visionary—are more effective than others in setting the stage for quality. Why? The affiliative style creates harmony and good relations among team members, helping employees feel engaged and, when they need to act on their own, authorized. A visionary style establishes a clear quality standard or goal, communicates it persuasively to the team, and moves the team toward it.

> Down the organizational chart, among managers, change entails a willingness to train employees to address quality issues, and then to entrust them with the responsibility to do so

The dissonant styles, **pacesetting** (relentlessly demanding excellence) and **commanding** (insisting on immediate compliance), have their place in certain situations—in crises, for example. But when overused, these styles have a negative effect on climate. This is important because quality problems—which by their nature tend to require leaders to use the pacesetting and commanding styles—may result in climates that generate further quality problems. When urgent action is needed after a warning letter, for example, the pacesetting and commanding styles are appropriate. But, these styles hurt the climate and often lead to employee disengagement, decreased quality, and more regulatory action. The cycle starts anew. The commanding style in particular leads to another problem—it creates a climate of fear where employees worry about retribution. In such a climate, they are reluctant to challenge the status quo or flag issues. In this way, the commanding style backfires by driving quality issues underground.

Aligning goals is key

Given the increasing pressure on biopharma companies' margins, some executives might feel that the focus on quality we advocate is a luxury rather than a necessity. Naturally, we recognize that life science companies are businesses and have financial performance goals. But we firmly believe these goals are consistent with the need to have a culture of and focus on quality. The goal is to produce safe and effective medicines with each and every batch made. What's more, our experience suggests that most companies have not taken full advantage of operational improvements that will improve quality and bring cost savings.

Nevertheless, leaders might also wonder how they can devote resources to building a culture of quality when so many other areas of the business demand attention. The industry has faced tremendous financial pressure over the last few years, and as the very business model of the biopharma company adapts to new realities, calls abound for innovation and transformation in every area of the business.

In such a climate, how are executives to know where to focus their efforts? On discovery and R&D? The sales force? health economics and outcomes research (HEOR)? Big data capabilities? The answer, of course, is all of the above.

In spite of all of this complexity, we want to make the case that manufacturing provides yet another area where savvy leaders can innovate. Any company that builds—and sustains—a genuine culture of quality across all areas of the business will be delivering innovation at its most practical. PE

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Biosimilar Litigation: Lessons So Far

The case of *Amgen v. Sandoz* signals that preliminary injunctions will play a major role in future patent disputes

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Congress enacted the Biological Price Competition and Innovation Act (BPCIA) in March 2010, as part of the Affordable Care Act, creating an abbreviated FDA-approval pathway for biological products demonstrated to be "biosimilar" or "interchangeable" with a licensed biologic. The BPCIA sets forth detailed procedures for exchanging patent information between an applicant who files an abbreviated biologics license application (aBLA) under the BPCIA (referred to as a "subsection (k) applicant") and the reference product sponsor (RPS). The statute also provides for a "notice of commercial marketing," whereby the subsection (k) applicant "shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)."

The BPCIA expressly provides that the RPS may seek a preliminary injunction to prevent the applicant from making or selling its product until the court resolves patent validity, enforceability, and infringement, after it receives the notice of commercial marketing. Preliminary injunctions are likely to be important for biologics, particularly those approaching or beyond the statutory 12 years of marketing exclusivity provided to the RPS, because, unlike in small molecule abbreviated new drug application (ANDA) litigation, there is no automatic 30-month stay triggered by filing suit that prevents the FDA from approving the generic product.

With FDA's approval of the first biosimilar product—Sandoz's *Zarxio*, a biosimilar to Amgen's *Neupogen* (filgrastim)—earlier this year, litigants are raising challenges to and the courts are starting to interpret the BPCIA's provisions. For example, the U.S. Court of Appeals for the Federal Circuit recently ruled that the BPCIA's patent-exchange process is optional and that an applicant cannot provide an effective notice of commercial marketing until after it receives approval for its BLA.

As litigation in this area continues to develop, preliminary injunctions will play a meaningful role. In *Amgen v. Sandoz*, for example, the district court denied Amgen's motion for a preliminary injunction, which Amgen filed only a month before Sandoz's anticipated commercial launch of *Zarxio*. Some insight can be gleaned from the arguments and district court's decision in *Amgen v. Sandoz*, as well as past Federal Circuit preliminary-injunction decisions affecting the industry.

Amgen v. Sandoz: The Preliminary injunction

On July 24, 2014, the FDA accepted Sandoz's aBLA filed under the BPCIA pathway to market a biosimilar copy of Amgen's *Neupogen*. The BPCIA contemplates that a subsection (k) applicant will provide a copy of its BLA to the RPS, in this case Amgen, not later than 20 days after the applicant receives notification that the FDA accepted its application. This marks the beginning of the BPCIA's patent-exchange procedures. After correspondence between the parties, however, Sandoz informed Amgen that it was declining to engage in the BPCIA's patent-exchange process and would not disclose its aBLA. Sandoz, however, did provide Amgen with its 180 day notice of commercial marketing, despite the fact that its *Zarxio* product had not yet been approved by the FDA.

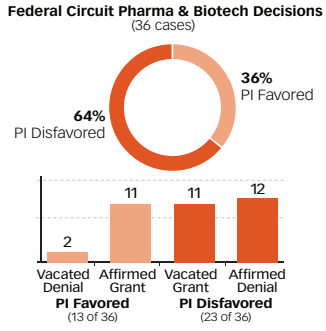
Amgen filed suit on Oct. 24, 2014, alleging unfair competition and conversion under California state law and patent infringement. Amgen's state-law claims turned on the parties' differing interpretations of the BPCIA, namely whether Sandoz's refusal to engage in the patent-exchange process and its provision of notice of commercial marketing before it received FDA approval violated the BPCIA. Less than three months into the case, Amgen moved for the court to issue a judgment on its state-law claims. A month later, after the FDA held a public hearing regarding *Zarxio* and stated its intent to approve Sandoz's product, Amgen filed a motion for a preliminary injunction seeking to stop *Zarxio* from entering the market at least until the court ruled on the parties' motions for judgment.

In deciding whether to grant a preliminary injunction, courts consider four factors: (1) the moving party's likelihood of success on the merits of its case; (2) whether irreparable harm to the moving party will ensue absent the injunction; (3) whether the balance of equities favors the injunction; and (4) the public interest.

In supporting its motion for a preliminary junction, Amgen contended that loss of the BPCIA patent-exchange procedure itself caused it irreparable harm. Amgen identified four further sources of harm from Sandoz's "premature competition." First, Amgen argued that Sandoz's sales will draw sales from Amgen's products, directly impacting Amgen's R&D opportunities, including potential layoffs of scientists for lack of research funding. Second, Amgen identified irreparable harm to three of its emerging products because its sales and marketing workforce would be diverted from launching new products to mitigating share loss for *Neupogen*, as a result of *Zarxio*'s market entry. Third, Amgen pinpointed price erosion as an irreparable harm. Finally, Amgen alleged that its relationship with customers and goodwill would be irreparably harmed if Sandoz launched *Zarxio* and later withdrew it, assuming Amgen prevails in its lawsuit.

Turning to the balance of equities, Amgen argued that the potential harm to Amgen if it prevailed (i.e., loss of its rights under the BPCIA) far outweighed any harm to Sandoz if Amgen did not prevail (i.e., a slight delay in launching *Zarxio*). For the last factor, Amgen argued that the public interest disfavored Sandoz's disregard of a statute "enacted to govern commercial behavior in an area as important to the national economy as healthcare."

In response, Sandoz argued that any harm is "self-inflicted" because Amgen initially refused Sandoz's terms for disclosing its aBLA and waited months to file an infringement suit and many months more before seeking a preliminary injunction. Sandoz further argued that even if it violated



the BPCIA, that does not automatically create irreparable harm. And Sandoz refuted Amgen's alleged harm from loss of research and development, threat to goodwill, and price erosion as speculative.

Because Amgen based irreparable harm on Sandoz's alleged violation of the BPCIA and the district court agreed with Sandoz that no violation of the BPCIA occurred, the district court found that Amgen could not show a likelihood of success. The court further found that the company did not establish irreparable harm in the absence of an injunction, finding Amgen's proffered harms "at best highly speculative." The court, therefore, denied Amgen's request for preliminary injunctive relief, and, for the same reasons it also denied Amgen's request for an injunction pending an appeal to the Federal Circuit.

On appeal, not only did Amgen seek reversal of the district court's decision denying its request for a preliminary injunction, Amgen also filed an emergency motion for an injunction pending appeal at the Federal Circuit. The Federal Circuit granted Amgen's emergency motion on May 5, just days prior to Sandoz's anticipated launch of *Zarxio*. The Federal Circuit issued its opinion in *Amgen v Sandoz* on July 22, wherein the court held that: (1) disclosure of an aBLA was not mandatory; and (2) to be effective, a subsection (k) applicant must wait until after FDA approval to provide its 180-day notice of commercialization.

Case precedent

While the Federal Circuit did not weigh in on the merits of Amgen's motion for a preliminary injunction, some insight can be gleaned from its treatment of preliminary injunctions in pharma and biotechnology cases generally. As shown in the chart, an informal survey reveals that the Federal Circuit disfavored the grant of a preliminary injunction in roughly 60% of biopharma cases involving preliminary injunctions. And although the Federal Circuit affirms grants, vacates grants, and affirms denials in almost equal measure, it rarely vacates a district court's decision to deny preliminary injunctive relief.

These cases most often turn on likelihood of success, particularly where the accused infringer cannot establish that its therapy is clinically beneficial as compared to the patentee's drug. If a patentee cannot demonstrate a likelihood of success on the merits of its case, a court likely will deny its request for preliminary injunctive relief. The same holds true for irreparable harm. However, even if likelihood of success and irreparable harm are shown, a court may deny injunctive relief if there is a critical public interest at stake.

It will be left to future cases to elucidate how courts will receive requests for preliminary injunctive relief in biosimilars litigation. But as the circumstances of *Amgen v. Sandoz* show, especially in cases where the biosimilar's commercial launch might occur well before the completion of the underlying patent litigation, preliminary injunctions will play a significant role. PE

New Payment Models: It's Time to Move

Commercial success for pharma brands now demands proactive strategies and interventions

Fundamental changes in the US access and reimbursement landscape are accelerating for the vast majority of public and commercial stakeholders. Often characterized as accountable care organizations (ACOs) or medical homes, these changes are indicative of the larger trend of payers using a variety of payment models to drive an overall behavior change among healthcare professionals and patients. Whether it's the traditional fee-for-service system which serves as the basis for some new payment models or a new bundled/episodic payment model, pharmaceutical manufacturers need to have a clear line of sight into how each model may impact their specific product portfolios in order to ensure commercial success. As such, the era of simple surveillance is over.

Two-pronged mission

Though data on new payment delivery models are mixed, payers are betting on these new approaches to improve quality and corral costs. The goal of simultaneously improving patient outcomes while also reducing costs is seen as a realistic achievement. Ultimately, pharmaceutical manufacturers need to understand how to navigate the behavior changes brought by various payment models (see table below) by anticipating implications and adjusting commercialization strategies accordingly.

The inflection point for pharmaceutical manufacturers occurred once drug benefits were included as part of the new payment models in a way they hadn't been before. Recall that the first wave of Centers for Medicare & Medicaid Services (CMS)-sponsored ACOs excluded drug treatment from the overall program design. Now we are seeing examples such as those from Houston, TX, which saved the municipality an estimated $42 million in healthcare costs over the past three years through the use of ACOs and narrow networks. By pushing to keep city employees to a small ACO and switching to 87% generic drugs, Houston simultaneously promoted wellness overall and reigned in costs.

Cancer pilot study

A recent pilot program conducted by United Healthcare and published in the *Journal of Oncology Practice* illustrates where the industry is headed through the lens of an oncology bundled payment model. The study, conducted over three years, rewarded physicians for focusing on best treatment practices and health outcomes while simultaneously removing the financial incentives associated with drug acquisition. Data illustrated an overall savings, despite an increase in drug utilization and costs, without compromising quality and outcomes. These successes will add wind to the sails of other initiatives such as WellPoint's Cancer Quality Care and Cigna's Collaborative Care which aim to use incentives to engage healthcare profession-

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Pharmacy Engagement and Prescription Drug Management in ACOs

	Private (N=140)	Medicare (N=111)
At least one accountable care contract including pharmacy spending in calculation of total cost	76.8%	1.8%
Near complete ability to e-prescribe and confirm fill	53.4%	37.3%
Near complete ability to maintain a list of diagnoses and medications in EHR	59.8%	51.0%
Near complete ability to intergrate inpatient and outpatient data in EHR, including medication data from ACO providers	41.9%	37.9%
Near complete ability to provide patients with electronic chart or discharge information	58.6%	49.5%

J Manag Care Spec Pharm. 2015 Apr, 21(4): 338-344

The "Private" column refers to ACOs whose contracts include commercial as well as Medicare and Medicaid. The "Medicare" column refers to ACOs whose contracts include Medicare and Medicaid, but do not include private payers.

als and help drive improved health, affordability, and patient experience.

The implementation of these pilots illustrates that even specialty disease categories such as oncology, which once were deemed strictly off limits to new models, are now clearly in play. These new models will be additive to traditional models such as fee-for-service, further illustrating the need to deeply understand unique program design when developing differentiated commercialization strategies. Consider that the fee-for-service model is in fact the ideal design for immunizations. Physicians are rightly incentivized to immunize more patients because it a) creates an overall healthier population and enhances quality care outcomes and b) aligns to financial goals. The challenge for manufacturers will be to not only surveil the multiple models that exist (see figure at right), but rather to recognize and act upon how these models will ultimately impact the performance and success of their assets.

Payment models will continue to evolve as payers gather more data and continue to work to improve outcomes while reducing costs. Manufacturers can't wait for change to slow before reacting and planning as market changes can and do impact patient access to branded treatments and overall utilization patterns. For example, the Affordable Care Act's Health Insurance Exchange plan models' bronze, silver, and gold levels all carry with them different formulary structures. Astute manufacturers will not only know where their products fall on formularies for each level of plan, they must (or will) build financial models to ensure appropriate funding for patient assistance and co-pay programs to account for coverage dynamics. The most progressive executives then leverage this data to develop tools and training for field representatives so they can confidently address heathcare professional (HCP) inquiries and build credibility with increasingly sophisticated provider audiences.

Manufacturer musts

It's a safe bet that payment models will continue to evolve, reimbursement will continue to be a challenge, and medication will continue to play a role in improved outcomes and cost savings. There are clear steps to take to ensure products are positioned to add value regardless of the payment models to ensure patient access, adherence, and quality care outcomes for patients. Manufacturers should therefore:

- Dedicate a strategic imperative within each brand's business plan to ensure the impact of each of these models on brand performance is well understood and senior management is educated appropriately.
- Invest in the development of educational, promotional, and training resources that provide details on the specific implications of each model.
- Continue to monitor both public and private payers and calibrate activities along the implementation timelines for newer models that are able to deliver concrete results.

In doing so, pharmaceutical manufacturers can successfully pivot towards proactive engagement in healthcare's new reimbursement reality and sidestep the pitfalls which are sure to ensnarl the passive watchers. The commercial success of your products is what hangs in the balance. PE

ACO Characteristics and Engagement with Outpatient Pharmacy

Some numbers have been rounded.
J Manag Care Spec Pharm. 2015 Apr, 21(4): 338-344

Pharma manufacturers need to understand how to navigate the ensuing behavior changes brought by various payment models by anticipating implications and adjusting commercialization strategies accordingly

PEOPLE VISITING THE CHANGING DIABETES® MOBILE CLINIC Algeria

Investing in Algeria

to close the gap in access to diabetes care

Diabetes is expected to increase by 80% in Africa* over the next 20 years. The number of people with diabetes is expected to reach 52 million by 2035. This trend is also seen in Algeria where diabetes is expected to grow from 1.65 million in 2014 to 2.9 million in 2035.[1,2]

The region is experiencing a rapid change in disease patterns from infectious diseases to non-communicable diseases.[3] As urbanisation increases and populations grow older, type 2 diabetes will pose an ever greater threat and burden to healthcare systems.[4]

As the global leader in diabetes care, providing approximately half of the world's insulin,[5] Novo Nordisk has a responsibility to improve access to diabetes care.

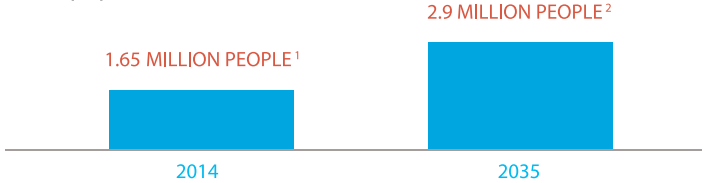
Our key contribution is to discover and develop innovative biological medicines and make them accessible to people with diabetes all over the world. However, we at Novo Nordisk are well aware that our products only do part of the job: it takes more than medicine to change diabetes.

Changing Diabetes® is our response to the growing diabetes challenge. As a global leader in diabetes care, we believe that it is possible to tackle diabetes and improve the lives of millions of people worldwide.

THE DIABETES CHALLENGE IN ALGERIA

1.65 MILLION
ADULTS HAVE DIABETES,
which equals 6.54% of the adult population [1]

BY 2035 THIS FIGURE COULD RISE TO
2.9 MILLION [2]



1 OUT OF 2
ADULTS WITH TYPE 2 DIABETES
do not know they have it [1]

14,000
PEOPLE DIED OF DIABETES-RELATED CAUSES IN 2014 [1]

* Africa is defined as Novo Nordisk Business Area Africa, and covers the entire African continent, excluding Egypt.

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HEALTHCARE & LIFE SCIENCES REVIEW

ALGERIA

Debating The Country's Future

With oil revenues tumbling, a hydrocarbon industry experiencing jitters and a fast diminishing public exchequer, one might have expected Algeria's budding healthcare sector to be feeling the pinch. On the contrary, despite ever-rising healthcare costs (public spending on imported drugs increased by 9.96 percent in 2014) optimism remains high. What's more, the government is adamant there will be no adjustment to an ambitious reform package that has already propelled Algeria to second-largest pharmaceutical market in Africa. Underneath the surface, however, a handful of longstanding concerns loom ominously. Local manufacturing has not yet attained the desired effects, chronic ailments such as diabetes and cardiovascular disease are hitting hard and the financial viability of the country's much-prized public healthcare system is being cast into doubt.

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For exclusive interviews and more info, plus log onto www.pharmaboardroom.com or write to contact@focusreports.net

From left: Abdelmalek Boudiaf, Minister of Health, Hospital Reform & Population; Hamou Hafed, director general of pharmacy and medical devices, ministry of health, hospital reform and population; Djaouad Brahim Bourkaib, director general of social security, Ministry of Labour, Employement & Social Security; Kåre Schultz, former president and COO of Novo Nordisk, and now global CEO of Lundbeck

"Although the unemployment rate has been steadily declining and a greater portion of the population are contributing to our social security system, pharmaceutical expenditure is increasing at a faster rate than our revenue growth can match," warns Djaouad Brahim Bourkaib, director general of social security at the Ministry of Labor. "Just to speak of one of the chronic diseases afflicting Algeria, incidence of diabetes has risen to point where it has now reached epidemic-like proportions. We are talking about a mega-scale problem affecting millions of people and a rapidly expanding patient group," warns Kåre Schultz, former president and COO of Novo Nordisk, now global CEO of Lundbeck.

This is precisely why investor sentiment both inside and outside the country will be much buoyed by the announcement that there is to be no let up and that a bold agenda is to be rolled out in 2015 with a view to consolidating gains made to date and accelerating further progress.

FASTER, DEEPER STRUCTURAL REFORM

"2015 will be the year when our health system will be revived," brazenly declares a smiling Abdelmalek Boudiaf, Algeria's minister for health, hospital reform and population. In a move resoundingly welcomed across the industry, the ministry has reaffirmed its commitment to cultivating a powerful and internationally competitive pharmaceutical sector while simultaneously redrawing the rules of healthcare provision. A raft of new measures will include aggressive promotion of local manufacturing, national plans for cancer and cardiovascular disease, the embracement of new treatment pathways, a ramping-up of infrastructure and even a (still to be fully defined and somewhat controversial) price-slashing on certain medicines.

Most reassuring of all was the unveiling of a generous annual spending plan that received much praise. "The budget allocation for the supply of medicines in 2015 will be even more than last year: close to DZD 100 billion (USD 1.01 billion), against DZD 85 billion (USD 860 million) in 2014," affirms the ministry's director general of pharmacy and medical devices, Hamou Hafed.

MEDICAL EXPENSES: SPIRALING OUT OF CONTROL?

Expenditure on imports of pharmaceuticals rose by 10.44 percent in 2014, costing the state some USD 2.6 billion against USD 2.34 billion the year before. Against that price escalation, overall volume dipped slightly, declining from 34,142 tons in 2013 to 33,593 tons in 2014 according to official figures released by the National Informatics and Statistics Bureau. This means that although import-substitution policies may be starting to make some headway in terms of quantity, they are seemingly yet to relieve the financial strain on an already overburdened healthcare system that is universal and free-at-the-point-of-delivery.

A closer breakdown of those numbers sheds further light on the main crunch points. Human medicines constitute the bulk of the spending, representing 93.17 percent of total imports of pharmaceutical products. Specific niches display a worrying upward trend. Imported antibiotics, for example, registered a value of USD 68.3 million in 2014, against USD 56.8 million in 2013, a cost increase of over 16 percent.

Short-term circumstantial factors may account for part of the rise. Hikma's general manager Raed Ashhab, for instance, is confident antibiotic imports will be significantly lower next year. "We're talking about seasonal products in a pretty volatile market where there have been some strong brands imported over the past year, but we've now invested in an automated local production line that should supply enough to satiate Algerian demand." Meanwhile *Union Pharmaceutique Constantinoise* (UPC)'s president Salah Arabet makes a similar case for the hormones segment. " In 2015, we'll be opening the doors on a brand new hormone production facility, the first-of-a-kind domestically and that directly reduces national import dependency," he declares.

Government policy to promote generics over branded products should also ultimately help to control costs. So too should biosimilars, when expiry dates on patent protection for expensive blockbusters start to enter into force, but all of this will take time to embed. In the words of Diphaco's general manager, Seddik Amry, "regulation on biosimilars in Algeria is still in its infancy: currently registration of these products fall under the jurisdiction of exactly the same law as for other drugs, just with a few extra footnotes and memos in the margin. Much greater clarification and definition will be needed if they're to take off." "It's true that we sometimes find ourselves standing in a bit of a legal swamp with one regulation erasing another, and a paucity of guidelines which impedes investors, including local ones, from investing in areas that ideally they'd like to… regulatory reform doesn't always match the speed of maturity of the market," concurs Generale Pharmaceutique Services (GPS)'s general manager, Brahim Bakhti.

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Meanwhile many opinion leaders suspect the existing system itself may be unsustainable over the long run and that Algerian healthcare provision requires a radical rethink. "We need to review our overarching health policy and determine whether it is feasible to continue with universal coverage that is free for all and we need to critically analyze the workings of the social security system," advocates Senator Louisa Chachoua, president of the Commission for Health in Algeria's upper house, the Council of the Nation.

From left: Raed Ashhab, general manager, Hikma ; Salah Arabet, president, UPC; Seddik Amry, general manager, Hikma, Diphaco; Brahim Bakhti, CEO, GPS

LOCAL MANUFACTURING: CURE OR STICKING PLASTER?

Domestic production has tripled over the past five years and is today worth USD 1 billion. Latest figures demonstrate that 48 drug importers have now established local production facilities and operate 75 manufacturing units. Plans for new projects continue unabated with 101 registered in the space of four years. There can be no doubt, therefore, that market actors have been heeding the government's call to boost national production capacity.

Despite these impressive achievements, however, a proliferation of in-country facilities doesn't seem to be reducing the import bill with the speed and efficacy that the authorities had originally hoped for. Official targets demand that local products satisfy 70 percent of Algerian drug requirements by 2017. With less than two years to go, demand fulfillment languishes between 35 and 40 percent. What explains this discrepancy?

Spotting Winners

Experts speak out about market niches on the rise

Ahmed Hamdache, CEO, LAAP

Laboratoire Algerien d'Approvisionnement Pharmaceutique (LAAP), the first local entity to introduce complementary medicine, wellness and vitamin supplements to the Algerian market is now witnessing demand flourishing. "We were literally the 'guinea-pigs' testing this out, but couldn't have imagined how well our products would eventually be received…today Algeria has evolved into one of the most developed markets in terms of food supplement consumption among Arab countries," proudly proclaims the company's founder and CEO, Ahmed Hamdache.

He puts the popularity of herbal-based, natural therapies down to the increasing sophistication of Algerian patients keen to exercise consumer preference, an issue that has not gone unnoticed by other pharmaceutical marketers. "Today the trend is to resort to a scientific style of communication that appeals to reason rather than to gut instinct, because the market has ripened and we find ourselves addressing a population that is exceptionally well informed," confirms Choukri Sedik, manager of Unilab.

What's even more impressive the market's decisive preference for supplements in spite of the high prices assigned. "We price between 50 to 100 percent more expensive than chemical molecules and this is essentially all down to onerous customs tariffs," bemoans Hamdache. "A pharmaceutical drug only costs 5 percent of duties on its value, but supplements are classified by the prevailing nomenclature as foodstuffs analogous to cake or biscuits. This means we pay ten times more duties than pharmaceuticals when our base price is practically the same," he reveals. To circumvent this, however, he will soon be manufacturing his products locally in which case only a 7 percent valued added tax will apply.

From left: Senator Louisa Chachoua, President of the Commission for Health in Algeria's upper house, the Council of the Nation; Toufik Belhadj, CEO, HUPP

"Domestic production is lacking structure and organization and that's why it's only limping along. Today we have 20 different local factories producing variants of the same product and that doesn't provide any benefit to anyone; it just serves to exacerbate cut-throat competition," affirms HUPP's CEO, Toufik Belhadj.

Some call for the government to do more to assist what can still be considered an infant industry. "The government would do well to deregulate pricing in favor of domestic production of complex forms, which require hefty investments. This should be complemented with a lowering of exemptions on imported goods," urges UPC's Salah Arabet. "When Renault committed to constructing their cars in Algeria they were handed a 3 year concession of virtually guaranteed sales, why not apply that sort of respite to local pharma production to allow it to put down roots and develop a solid foothold?" wonders GPS' Brahim Bakhti.

Discussing Algeria's Future

On the face of it, the Algerian healthcare sector today looks great: a market valuation of USD 3 billion, double-digit sector growth, a population of 38 million and a unique brand of public sector healthcare characterized by state reimbursement and guaranteed patient coverage, all covered by a state budget that is propped up by the country's oil and gas revenues. But now, the time has come for Algeria to discuss its future: the country must find a way to access more innovative treatments, accommodate existing local players in an ever-expanding market, and push government priorities, which currently include a massive expansion of Algeria's domestic production capabilities. PharmaBoardroom recently conducted a round table event with the key opinion leaders of Algeria's healthcare sector, and below is a transcript of the conversation that took place about Algeria's future.

Round Table in Djenane El Mithak in Algiers

1. Algeria's Healthcare Reform: finding the right model

Frederic Boucheseiche, moderator & COO, Focus Reports: There are differences – based on development level or population for instance – between the health systems of various European countries. In some systems, the industry is happy, in others, the state is happy, and in others still, the patient is happy. Can you provide us with an example of a system that works, in your opinion?

Richard Torbett, Chief Economist, EFPIA (The European Federation of Pharmaceutical Industries and Associations): It's a very difficult question. I might answer Denmark because I think it's a good example. The industry gets

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good prices for its products. Broadly speaking, there's good access to treatment. The off-patent market is very efficient, very open. Patients can easily access medicine. However, the growth rate of spending on pharmaceutical products is between two and three percent annually, whereas elsewhere this average is higher.

Habib Bennaceur, North & West Africa regional manager, AstraZeneca: In Algeria we often talk about improving our healthcare system, and when we do we compare ourselves to France, Germany, and other countries, and use them as a barometer for the penetration of innovative products. But we know very well that today in France, for example, the high level of medical service doesn't come from scientific innovation, but from the size of the population and therefore the prices that can be negotiated between CEPS, who set prices, and CNAM, which provides repayment.

What standards should we use in order to find a satisfactory benchmark? Should it be based on innovation, or rather on prices and budgets? There's a huge gap between the moment when a product is released on the market in the United States and in Europe. This is due to registration delays, but also to phasing. We, as multinational companies, have to deal with phasing in terms of file submissions: we tend to start with the countries where clinical research has been conducted, so by the time our products reach Algeria, for example, we don't have a huge window before the generic equivalents arrive.

Richard Torbett: No single system is perfect: there are advantages and drawbacks in every single one.

Richard Torbett, Chief Economist, EFPIA.

I totally agree with what you said about France. For me, discussions between the industry and those that set prices should be a constant dialog. This is especially true as we begin to introduce new types of products such as personalized medicines – the only way to assess the value of such products is to invest in data for the whole treatment lifecycle, an idea that has already been accepted in the world's best healthcare systems. These products would never work in a reimbursement system where all the medicines in a therapeutic category are assigned the same prices.

Djaouad Bourkaib, director general of social security, Ministry of Labor, Employment and Social Security: We are not likely to hurry to include personalized medicines to the list of refundable medicines, because what we spend on medicines is already huge compared to the health budget and it's not sustainable.

Highlights: Algeria's 2015 Healthcare Agenda

- Incentives for local production and generic forms.
- Roll-out and implementation of a new National Health Law.
- National Plans for Cancer, Cardiovascular Disease and Intensive Care.
- Health Ministry's budget allocation awarded 8 percent increase.
- Re-launch of a National Agency for Organ Transplants.
- Promotion of home-based healthcare with pilot projects in Oran and Algiers.
- Writing-off of the entire debts of some 622 public hospitals nationwide.

We have to use our remaining resources to improve the other parts of the healthcare system. We have a price grid that is totally outdated. That is why we try to have a list that answers the medical needs of the population but without including anything we have doubts about.

On the other hand, when there's a need that is not covered, we have no other choice. When there is no convincing treatment for an illness, we accept uncertainty. At that point we may think the way you think because there is an uncovered need and because we have no choice. We are in a very particular situation in Algeria: social security has to improve the way it uses its resources, always keeping in mind what people need.

Badra Benkedadra, advisor to Algeria minister of health, population and hospital reform: As a regulator, what we are interested in, amongst other things, is the value of each medicine, and finding an efficient evaluation system. Mr. Toumi, Europe is evolving towards a European Health Technology Assessment (HTA) agency, which will be able to set up evaluations that all countries can share –including those outside of the system like Algeria. What do you think would be the best option for Algeria? Following the French or the British?

Mondher Toumi, professor in public health, University of Aix Marseille, School of Medicine: I think it's better to work on an Algerian way, as each country has its own environment, history, and culture.

Algeria's issue is that its population is decentralized, so access to medicine varies depending on whether you're in a large city or a more remote area. We work with an extremely small budget, but also with extremely reliable but very expensive products knocking at the door. So the true question is how to arbitrate. In order to do so, you need a very well designed public healthcare system.

2. Algeria's Local Manufacturing Laws: what they mean for local and international companies

Frederic Boucheseiche: The government has the ambition to reach 70 percent local production by 2017, from the current rate of 38 percent. How can they achieve this? Are there specific mechanisms at the fiscal level? What is being done to attract investments in the sector?

Hamou Hafed, director general of pharmacy and medical devices, Ministry of Health, Hospital Reform and Population: The pharmaceutical environment in Algeria is changing right now. Measures have to be taken related to approaching the industry, and talking with the pharmaceutical industries. This is the way we can reach our goals.

Hamou Hafed, director general of pharmacy and medical devices, Ministry of Health, Hospital Reform and Population

One very important feature of Algeria's national production strategy is that every time a product has three manufacturers operating locally, imports of that product are banned. Since this was introduced, local production has begun to soar. I believe this will allow us to reach our 70 percent goal.

List of Participants

- Hamou Hafed, director general of pharmacy and medical devices, Ministry of Health, Hospital Reform and Population
- Djaouad Bourkaib, director general of social security, Ministry of Labor, Employment and Social Security
- Badra Benkedadra, advisor to Algeria Minister of health, population and hospital reform
- Habib Bennaceur, North & West Africa regional manager, AstraZeneca
- Peter Ulvskjold, country manager, Novo Nordisk Algeria
- Rafik Morsly, president, ANPP (National Association of Pharmacy Producers)
- Mondher Toumi, professor in public health, University of Aix Marseille, School of Medicine
- Richard Torbett, chief economist, EFPIA (The European Federation of Pharmaceutical Industries and Associations)
- Salah Eddine Sahraoui, CEO, Clinica Group
- Arnaud de Rincquesen, partner, Deloitte Algeria
- Frederic Boucheseiche, moderator & COO, Focus Reports

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Habib Bennaceur: AstraZeneca showed that it wanted to invest in emerging markets, including Algeria. Today, local manufacturing investments in China have been completed, and nearly completed in Russia, leaving Algeria as the last market where AstraZeneca will open a new manufacturing unit.

What makes Algeria different from its neighbors is the equality in accessing healthcare with an egalitarian repayment system that has limitations and constraints but that also shows lots of advantages – actually, more advantages than constraints.

In Algeria, we are partnering with Saidal. We are collaborating to transfer knowledge and technologies for now. But for us, and because this is a significant investment in terms of time and money, we think this partnership has to reach another level and unfold as a more concrete collaboration for local manufacturing.

Peter Ulvskjold: Novo Nordisk has been in Algeria for more than 20 years. With our production sites, we can now produce for the whole market. We can also export: within the next three months we'll be ready to export to neighboring countries, which we are very excited about because we can start fulfilling the promise we made to the minister of health about becoming a hub for Africa. And this is our plan not just for our production site in Tizi Ouzou but also in our collaboration with Saidal, working together to produce insulin.

Our strategy is to create a production site that mimics what we're doing internationally, allowing us a very high level of engagement in Africa. We believe that in the long-term, we can develop a very strong presence for production and export, together with the local government.

Rafik Morsly, president, ANPP (National Association of Pharmacy Producers): It's important to keep in mind that when we talk about the Algerian pharma industry, we are mostly talking about local manufacturers and family businesses. There are very few listed companies. The Health Ministry helps these companies but banks do not: surely one of our priorities should be to address this, and help speed up our performance. But all stakeholders need to take a seat at the table first.

Salah Eddine Sahraoui, CEO, Clinica Group: The priority should be to encourage manufacturing, not to enforce it. I think the Health Ministry today is working along these lines. The incentives are in place to encourage companies to come and manufacture here.

Mondher Toumi: The authorities are indeed helping to structure the terms of investments and the providing the right incentives, in a very legitimate manner. On a more long-term basis though, some strategies are more efficient than others, and I believe that Algeria's manufacturing strategy is shortsighted: we are already starting to see that the profile of products being brought to Algeria are changing dramatically, including

NOVO NORDISK IN ALGERIA

Novo Nordisk has been present in Algeria since 1936, which saw the introduction of Novo Nordisk products in Algeria. Since then, the company has continuously strengthened its presence on the country. Currently, the company's footprint in Algeria includes local production, clinical trials, and various projects and partnerships focusing on improving access to diabetes care.

As early as 2006, Novo Nordisk established a production facility in Algeria to produce metformin for the Algerian market, and we have ambitions to export locally produced drugs to other parts of Africa in the near future. In 2012, Novo Nordisk signed a partnership agreement with Groupe SAIDAL to produce Novo Nordisk insulin locally in Algeria.[7] In 2015, the portfolio of products produced in Algeria was expanded. The facility will be upgraded to produce oral antidiabetic NovoNorm® from 2016, in line with Algerian government policy aiming to develop a national production.

In addition, we conduct clinical trials in Algeria, with 7 observational and 10 interventional trials, including 9 product development plan since 2008.[8] Clinical trials are a crucial part of the development process for human medicines. However, we believe that clinical trials can also lead to improvements in patient care, enhancement of capabilities, driving of scientific progress and a positive impact on the surrounding economy.[9]

Today, the company employs 420 people and reaches nearly 1 million patients in Algeria.

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NOVO NORDISK WORLDWIDE [5]

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MILESTONES ALMOST 50 YEARS OF EXPERIENCE IN ALGERIA

1936 Products introduced to Algeria

1994 Affiliate established in Algeria

2006 Production facility established in Algeria

2008 First celebration of World Diabetes Day in Algeria in partnership with the Ministry of Health

Launch of the « Changing Diabetes® » campaign in Algeria

2009 Launch of «Diabetes & Children» campaign

2010 Launch of «Diabetes & Ramadan» campaign

2011 Launch of the Algerian Changing Diabetes® Mobile Clinic in partnership with the Ministry of Health

Launch of «Diabetes & Women» campaign

2012 Partnership with Groupe SAIDAL to produce insulin locally in Algeria

Partnership convention with the Ministry of Health to launch the Algerian Changing Diabetes® Barometer

2013 Launch of the Algerian Changing Diabetes® Barometer in partnership with the Ministry of Health

2015 Decision to expand the product portfolio at the production facility in Algeria

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From left: Slim Belkessam, communication director, Ministry of Health, Population & Hospital Reform; Mohamed L'Hadj, director of the health department and hospital reform; Frederic Boucheseiche, moderator & COO, Focus Reports; Mondher Toumi, professor in public health, University of Aix Marseille, School of Medicine

cell therapy and biotech. The amount companies invest in manufacturing today is miniscule compared to the investment that goes into R&D: what investing in manufacturing really means is that we will end up with production facilities that don't manufacture cutting edge drugs, all locked in tight competition with one another and with other countries.

The only way to earn return on investments today is to invest in research. Algeria won't be able to do this on its own. It can only work out if there are real partnerships with real researchers. The more research you can work on and develop, the more value you add. And before you set up a cluster, you need to have a talent pool to recruit from. And this leads us to a second point: the need to develop a strong academic environment.

Hamou Hafed: An additional incentive for manufacturing locally is that the prices of products manufactured domestically receive a 27 percent mark up. We think we can make our offer more attractive than other countries. Security of supply is an important aspect in this for us: we want a list of essential medicines to be manufactured domestically. All the latest developments in R&D are covered by Algerian social security, so as far as we see it, it's up to the industry to fill this need and think regionally, whilst knowing that you will be able to manufacture and sell your medicines in Algeria.

3. Solving Algeria's HR Equation

Arnaud de Rincquesen: People are willing to come to Algeria. It's an interesting market. What matters once again is to have a job market. The biggest issue for a company settling in Algeria is to find people with specialized skills and a good academic level. Handling dry or injectable production sites requires training. Training has a cost – there are technicians to train and schools and universities have to offer such majors.

Frederic Boucheseiche: Mr. Sahraoui, can the industry play a part in this through clinical research? Can clinical research be decentralized to other Algerian cities?

Salah Eddine Sahraoui, CEO, Clinica Group: Our job market for clinical research is hospitals. Every day, we are working with more and more doctors for global studies (phase II and III). It's a real scientific added value for us. It's also a real added value for Algerian doctors, for our healthcare system as a whole, for the success of new therapies. It brings Algeria to a whole new level –a global level. Medicines have to be manufactured the same way in Algeria at they are in the United States or in France. The same is true of clinical trials: they have to be conducted locally but with the same global standards and clinical practices.

There's a real added value for us there, as there's a clear political will. Clinical research is part of the Health Ministry's strategic priorities. We feel great support every day. We have been working on clinical trials here since 2007, during which time we have seen growth in this area of 300 percent, which is fantastic.

Habib Bennaceur: When it comes to localization I feel that it's a bit of a "chicken and an egg" situation, because when you look at investment, you also have to take into account human resources. You have to keep in mind that when you build a manufacturing site it's not only about walls and machines. You also have to be able to afford human resources – even if they have to come from abroad at first so that expatriates can train your staff. And then you can have a 100 percent Algerian management.

Salah Eddine Sahraoui: When we first started the company here in Algeria, in the field of clinical trials, we were the only two people in Algeria that had any kind of background in this area, and the concept was relatively unknown in the country back in 2007 of a CRO.

One of the first questions we had to ask ourselves was how to train and recruit people to come and work with us. Should we train them first and then recruit them? Or should we recruit first then train our new staff? How should we start?

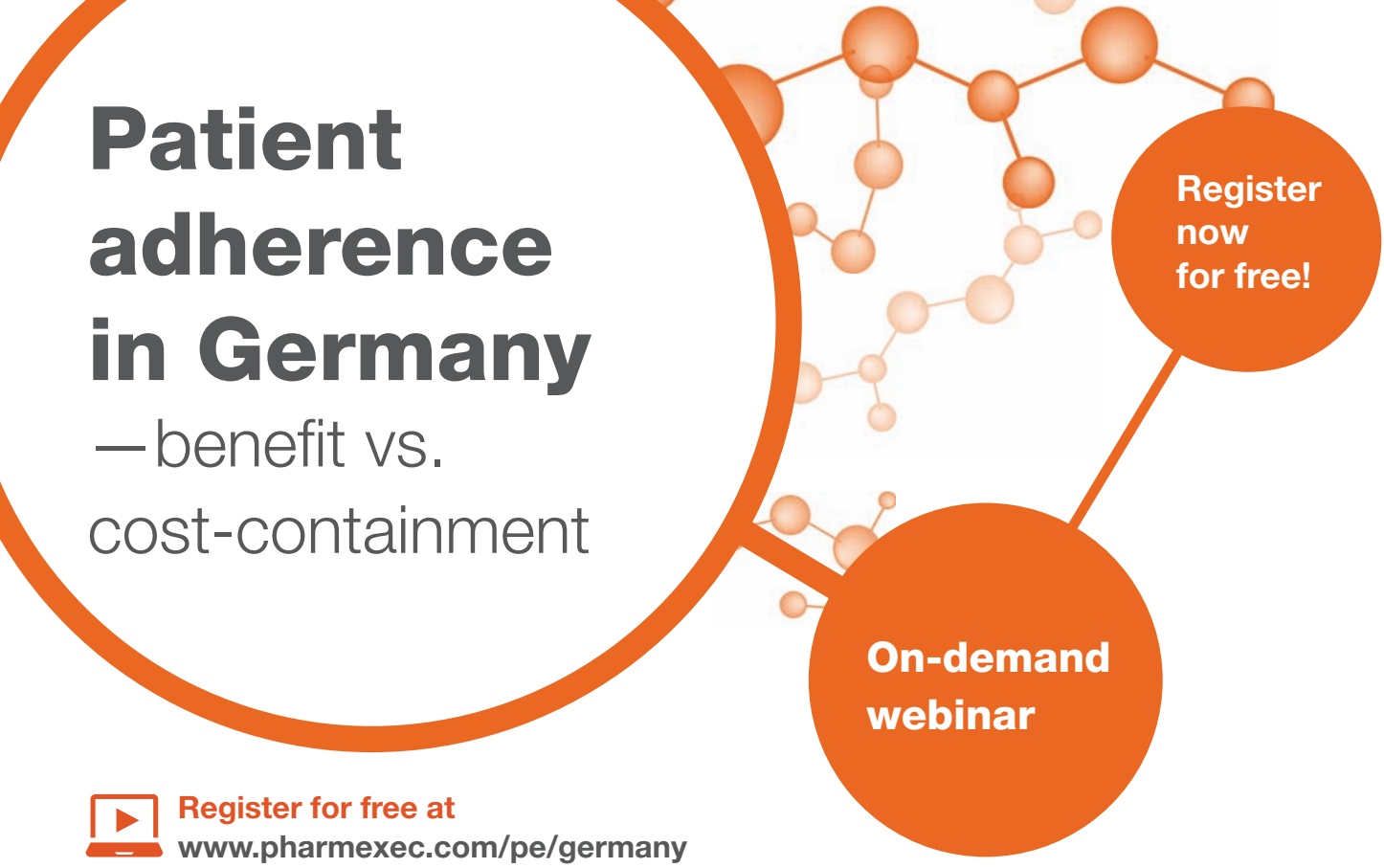
It was at this time that the economic crisis started in Europe, solving a lot of our problems, because Europe started to look a little less attractive to the three million Algerians living and working in France, some of whom decided to come back. And some of these had worked in the field of clinical research.

Today, we are 135 people in the company, all Algerians. After creating our initial network, we worked with the faculty of pharmacy and agreed to recruit the top three in each graduating class in the field of clinical research, and to train them in France and elsewhere in the world.

That's why we shouldn't wait for the people to be there first: we as an industry need to create the need.

Patient adherence in Germany

—benefit vs. cost-containment



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Event Overview

In a healthcare economy that is under pressure to provide cost savings, biopharma must demonstrate a long-term commitment to supporting health systems through effective adherence support programs. This Quintiles sponsored webcast will cover key topics including what it takes to implement successful patient adherence programs in Germany and elaborate on the specifics of engaging in patient support programs in the German market. The legal and regulatory challenges facing biopharma wanting to tackle the German market will also be touched on. The webcast will also cover the benefit of adherence programs from the payer perspective, with an overview of the German sick-fund landscape and cost allocation challenges.

This webinar sponsored by Quintiles, will bring together a German patient support expert from Quintiles and a representative from the IGES Institute for research and consulting in healthcare from Germany to provide valuable insight on this topical biopharma debate.

Key learning objectives

- Uncover best practice approaches to patient adherence programs in the German healthcare market
- Explore the regulatory perspective on how to provide beneficial patient adherence programs in Germany
- Discover what makes a successful patient adherence program based on observation and experience of implementing programs in Germany

Who should attend

Decision makers in Market Access, Regulatory Affairs, Real-World / Late Phase research, HEOR, patient-centric / patient engagement programs, payer / provider relations, Brand managers, Marketing Managers/Directors, Pricing & Reimbursement, Medial Affairs, Executive Management, Health Technology Assessment, Pharmacovigilance

Presenters:

Joanne Thiele
Market Access Project Manager

Hans Holger Bleß
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Moderator:
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Alzheimer's Update: What to Make of Latest Buzz

Alzheimer's disease (AD) researchers have seen more than their share of hopefulness and disillusionment over the years. Recent apparent gains targeting one of the disease's two molecular bull's-eyes may have reinvigorated drug development, or it may have set developers and investors up for letdown once more. To follow the news coming out of July's Alzheimer's Association International Conference in Washington, one had to be prepared for both glass half-full and half-empty interpretations.

Consider headlines targeting the uninitiated public for Eli Lilly's solanezumab, which read as showing "promising results" and displaying the potential to "slow decline." The news for solanezumab may in fact be positive, considering the anti-amyloid antibody had been largely discounted after prior Phase III failures. But saved by *post hoc* analysis, the drug is seeing new life in a subset of milder patients who may show benefit when treated early enough.

Most of the optimism in AD comes from company press releases, and regurgitation and aggregation of said releases. The articles offer positive news to click on followed up with minimal insight, and perhaps some words from doctors who are either involved in the trial, or just in the field and as hopeful as their patients. Their call for caution to await larger, late-stage trials is frequently buried in the last few paragraphs.

Media targeting the more experienced biopharma-minded and investing professionals displayed more measured optimism, and ranged to "slight disappointment." The investment community, having been repeatedly bitten by the AD dog, showed little enthusiasm for solanezumab's potential with Lilly's stock down over 3% during the week of the conference.

Results for Biogen the same week were far less rosy. After pumping up its anti-amyloid agent, aducanumab, with positive data in March, July's presentation at the research conference failed to impress. At week's end, the AD flop did little to stave off a stock tumble that saw Biogen's stock lose 22% after its mid-year earnings call in which the company announced it had missed on revenue estimates and cut its 2015 earnings outlook.

Bruce Booth of Life Sci VC and Twitter fame, offered some perspective on the scale of Biogen's losses, from +$380/share to around $300/share, more value ($20 billion+) than all of venture capital funding into biotech over the past four years combined. Surely the drop had multiple factors, namely Biogen's unimpressive sales growth for its multiple sclerosis drug, *Tecfidera*, but the AD disappointment didn't help.

Of course, the AD field has learned not to make too much of preliminary conclusions. Both products are still enmeshed in Phase III trials that have more important data readouts to come, and both companies remain optimistic, eyeing the massive potential markets that an AD treatment could bring.

Things could be worse. At least the beta amyloid-targeting therapies have Phase III trials of which to speak. Researchers have made far less progress against tangles, AD's stepchild mechanism of action.

But chasing down secondary targets may be doubtful, as funding remains inadequate. In order to see real progress in AD, researchers at the July conference said there needs to be $2 billion a year in funding; the 2014 NIH spend was a paltry $560 million, tweeted MSNBC's Meg Tirrell. The Obama administration's proposed budget for NIH spending on AD in 2016 is $638 million, which still would have to get Congress' approval, according to a report in the *LA Times*.

Also worse off, according to the AD conference? Women. According to research at the conference, women decline twice as fast as men and their brains contain higher levels of amyloid.

But there were a few bright spots concerning AD research. The field is definitely making strides with better diagnostics, hinting at a future spit-in-a-cup diagnostic option for earlier screening of the disease. What value diagnoses hold sans treatments, besides frightening the patient, remains a question. There are bright spots for symptom alleviation. Avanir Pharmaceuticals' *Nuedexta* showed positive data alleviating pseudobulbar agitation secondary to AD, a symptom that can make AD patients extremely difficult for families to manage, according to a *NBC News* report.

Finally, the AD headlines from July's conference that likely received the largest collective sigh: as in all walks of life, we're probably better off with less TV and more exercise. In response to the potential prescription for more exercise, *The Onion* said, "There must be some other way." PE

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