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COMMERCIAL INSIGHTS FOR THE C-SUITE
VOLUME 39, NUMBER 6



2019 PHARM EXEC 50

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Pharm Exec 50 Hints to Rest of '19

MANY THANKS to EvaluatePharma for compiling the data around this year's *Pharm Exec 50*, which lists the top 50 global biopharmaceutical companies by sales. And thanks to our Managing Editor Michael Christel for putting details and context around the data, including recent or impending mergers, highlights around brands and their speculative futures, and insights around the current situation in R&D and clinical trials. Some of the themes that Christel notes make this month's feature an excellent foundation for the remaining issues in the *Pharmaceutical Executive* content pipeline.

In August, *Pharm Exec* is highlighting Gene and Cell therapy and the associated challenges and hurdles in drug development, reimbursement, and commercialization, and will provide an update on FDA and EMA's progress in constructing specific regulatory guidelines for these products. We will also feature comments from Jeff Marrazzo, CEO of Spark Therapeutics, during his fireside chat with Veeva Systems Co-Founder and President Matt Wallach at their recent commercial summit, which touches on pricing, patients, and the supply chain in the first year of Luxturna's availability.

Where Christel notes on page 13 the supply chain challenges with CAR-T therapies, Marrazzo describes turning the one-time curative gene therapy of Luxturna's supply chain "on its head" to bring the patient to the drug rather than bringing the drug to the patient. Clearly, CAR-T medicines and Luxturna, which targets inherited retinal blindness, are delivered completely differently, but this is where we are in drug delivery in 2019, signaling the winds of change.

Our September issue is devoted to Product Launch, where we will highlight five brands that launched in 2018 and showcase their launch stories, as well as dive into the needs of the payer before and after launch, forecasting net present value on both brands and portfolios, and sales training needs for a brand launch or refresh.

With clear attention on what these sales numbers mean to pharmaceutical companies outlined in the *Pharm Exec 50*, the September issue will be a must read.

October will be a Tech-Tour for the C-suite. As Christel notes, pharmaceutical companies are looking at ways to trim unwieldy processes through the use of technology. Now the number of processes touched by technology are numerous, as are the applications themselves, so the tour will serve to highlight the process, the underlying technology, and the pluses and minuses of each, all with eye on brevity and key takeaways.

Another upcoming issue where June serves as a needed stepping stone is another milestone issue—our Annual Pipeline Report. Not to be outdone by sales numbers, the *Pharm Exec 50* includes R&D spend, the representative investment in a company's future. While Christel dives into the challenges of the R&D landscape, the Pipeline issue, which this year will be our 16th, looks at the therapeutic areas that are ripe with new scientific developments, as well as the ones that were promising, but have lost direction in failed trials.

December is a wrap with Market Access. We don't have a lot of detail here, as it's still in development, but to be sure, there is no discussion around a prescription drug that doesn't include formulary decisions, insurance coverage, pharmacy management, and patient access. Clearly, policy decisions around rebates will

The proposed rule to eliminate manufacturer rebates is under a comment period, with no clear path in sight. Stay tuned.

continue to be a part of this discussion, amid recent directions from the HHS proposed rule that would eliminate pharmaceutical manufacturer rebates to Medicare Part D plan sponsors and Medicaid managed care organizations. The rule is under a comment period, with no clear path in sight; suffice to say that PhRMA is on the pro side of eliminating rebates, while the PBMs are anti. Stay tuned.

Now that 2019 is halfway over, and I just fast forwarded us to the start of a new decade, let's come back to the present. Enjoy your summer and take *Pharmaceutical Executive* with you wherever your hopefully restful plans find you.



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2019 Pharm Exec 50

Michael Christel, Managing Editor

Pharm Exec's 19th annual listing of the top global biopharma players reveals some interesting maneuvering of ranks, as companies focus on diversification, big-brand expansions, and positioning a new wave of products to compete in an advancing but complex future treatment market.

'Vision' Quest: Leading Through Change

By Lauren Seufert

Exploring the critical go-to strategies for biopharma C-suite executives in navigating organizational disruption and the impact of global change and volatility on their employees and business.

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Med Affairs: A New Blueprint

By Robert Groebel

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HTA Evidence Boost

By Barbara Arone

An analysis of 10 years of decision-making by health technology assessment (HTA) agencies shows that the use of external comparators could provide a clearer picture of the economic benefit profile of more "common" drugs—and better inform HTA and payer determinations.

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Frank S. David, Greg Belogolovsky
bit.ly/2Wxxmvq

2018 Emerging Pharma Leaders

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**Pharm Exec's 2019 Industry Forecast**

January issue online
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bit.ly/2WjzQ92

Is There Evidence in Real-World Evidence?

Blog post
Partha S. Anbil
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Profile: HBA's 2019 Woman of the Year

April issue online
Christen Harm
bit.ly/2lkrJsZ

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Pharm Exec Podcasts

Episode 32: Behavioral-driven Health

Pharm Exec's European Editor Julian Upton talks with Johnson & Johnson's Jennifer Turgiss, VP of the company's Behavior Science & Advanced Analytics group, who shares her thoughts on the importance of incorporating behavioral strategies to the health and wellness solutions being developed at J&J.
bit.ly/2Qh7TAU

Episode 31: The Law of the Land

Editor-in-Chief Lisa Henderson speaks with Bill Newell, CEO of Sutro Biopharma, about how his background in corporate law has helped him in his role as a biotech executive and discusses the need for collaboration between big pharma and biotech.
bit.ly/2lJyJf5

Episode 30: Renal Disease R&D

Pharm Exec editors interview Anna Sundgren, renal disease strategy leader, global medicines development at AstraZeneca, about the current cardiovascular, renal, and metabolic (CVRM) disease landscape, challenges in renal drug development, and new therapeutics for chronic kidney disease.
bit.ly/2UUAkKf

Episode 29: Prevention & Interception

Julian Upton talks with Ben Wiegand, head of J&J's World Without Disease Accelerator unit. The two discuss the role of patients, providers, and payers in boosting preventative care.
bit.ly/2UQGtXg

Episode 28: Digital Medicine

Pharm Exec editors speak with Otsuka's Bill Carson and Kabir Nath about digital medicine, mental health therapies, and creating a smooth and collaborative relationship between R&D and commercial.
bit.ly/2YtlmRU

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Pharm Exec talks with Seth Lederman, co-founder, CEO, and chairman of Tonix Pharmaceuticals, about how to navigate creating and developing drugs for conditions such as PTSD and AIDS.
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bit.ly/2tHjCOQ

Reader Feedback

■ I 1,000% agree. It's my duty to call out this common and highly problematic oversight that us pharma marketers routinely overlook. Pharma marketers, take heed. Those that pay little attention to this vital segment of the pharma value food chain, ignore at your own peril.

George Tsiolis
"Are Pharma Marketers Fighting the Last War?"
bit.ly/2UkDq9K

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New Strategies Sought to Pay for Costly Cures

Cell and gene therapies in crosshairs of pricing focus, prompting stepped-up proposals on ways to finance these products

As Congressional leaders and White House policymakers assess a range of measures designed to manage or reduce outlays for prescription drugs, pharma companies and other stakeholders are weighing innovative reimbursement models for new therapies promising to cure or treat serious illnesses. Payers, manufacturers, providers, and patient advocates are collaborating on projects proposing to pay for such medicines over time and that vary related to evidence of treatment effectiveness and safety.

The issue has moved to center stage as more biopharma companies near market approval for new therapies with six- and seven-figure price tags. Sight-loss therapy Luxturna from Spark Therapeutics is priced at \$850,000 in the US; new cellular cancer drugs list for \$400,000 to over \$600,000, and more are on the way. Novartis' new gene therapy treatment, Zolgensma, promises to cure spinal muscular atrophy (SMA), a lethal inherited disease in infants, but at a \$2 million cost for one-time treatment. This is slated to set off a battle for market share with Biogen, which already offers a competitive treatment, Spinraza, at a lower initial cost but requiring repeat injections through the patient's lifetime. Biogen recently negotiated a coverage deal with the UK's NICE (National Institute for Health & Care Excellence) to make Spinraza available

to certain SMA patients at an undisclosed price.

Cost concerns were on the agenda of the recent annual meeting of the American Society of Gene & Cell Therapy (ASGCT) in Washington, D.C., a departure from the usual scientific presentations on test results for promising therapies. So far the small number of patients eligible for treatment with the new therapies limits outlays, but that will change as more new breakthrough treatments come to market. Over the next 10 years, experts estimate that 40-60 cellular and gene therapies will be approved in the US, offering viable treatments for about 50,000 patients. The cost of curing a range of serious genetic disorders, deadly cancers, and rare diseases will exceed \$200 billion, according to the MIT FoCUS (Financing and Reimbursement of Cures in the US) consortium.

These exciting gains are prompting a broad assessment of the promises and challenges for financing curative therapies. The FoCUS group and others are examining "precision financing" concepts, such as annuity-type arrangements that would allow one insurer to hand off a contract to another, and milestone-based contracts designed for state Medicaid programs. Installment payments by insurers and risk-based contracts for costly new therapies were discussed at the ASGACT meeting, along with

concerns that such approaches may require exemptions from Medicaid "best price" reporting requirements.

Value-based payment arrangements for manufacturers and payers have received considerable attention, but raise questions about whether initial positive treatment results prove to be durable, or if promising therapies turn out to have limited benefits—or even harms—over the long run. In such cases, how would financing agreements respond and change? And how would long-term follow-up be covered? Such financing plans require agreement on what constitutes treatment "failure" and "success" and whether one insurer will accept a contract transferred from a competitor. In some cases, costs and benefits may not support treatment for an elderly individual, or for a patient that responds less than expected.

Legislation likely?

These issues have emerged as Congress and the Trump administration struggle to devise legislation able to reduce drug costs more broadly. Analysts seek to maintain rewards for innovation, while expanding patient access to treatment at a cost that society can afford. Many policy makers insist that drug prices are too high to begin with and look to peg US rates to those at other industrial nations, such as the UK, Canada, and Japan.

The administration has ordered pharma marketers to post list prices in DTC drug ads in the name of price transparency, but is reconsidering earlier proposals to limit or alter rebates paid by manufacturers to pharmacy benefit managers



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(PBMs). There's much interest in boosting competition from generics and biosimilars to put pressure on brands, particularly to lower insulin prices, along with growing enthusiasm for more lenient importing of medicines, despite long-standing safety concerns.

An agreement between Democrats and Republicans on some kind of legislation around drug pricing appears more likely this

The cost of curing a range of serious genetic disorders, deadly cancers, and rare diseases will reportedly exceed \$200 billion

year than in the past, as consumers, states, payers, and Washington look to rein in healthcare spending.

Industry and some patient advocates try to make the case

that R&D cutbacks could limit the development of more innovative therapies, but political pressures appear to be boosting the chances for legislative action by 2020. **PE**

FDA Acting on Global Pharma Challenges

Concerns about the quality and safety of the growing volume of medicines imported to the US, pressure to set international policies for genome editing of other scientific developments, and escalating international trade disputes have prompted FDA to examine and update its programs for overseeing global operations and international affairs. The Office of Global Policy and Strategy in the newly named Office of Policy, Legislation & International Affairs (OPLIA) aims to better link consideration of international policy and trade issues with the challenges in ensuring the quality of ever-more imported medical and food products. The change reflects the importance of FDA's global public health mission and its engagement in multiple initiatives to streamline and harmonize international standards and policies for regulated products.

A "clear global policy strategy" has never been more important, says Anna Abram, FDA deputy commissioner and OPLIA director, noting the need for FDA to respond quickly and effectively to international disease outbreaks such as Ebola and to deal with a soaring amount of food and drug imports. More than three-fourths of active pharmaceutical ingredients (APIs) are produced by firms located outside the US, Abram noted at the recent annual meeting of the Food and Drug Law Institute (FDLI) in Washington, D.C., adding that the agency's network of foreign offices provides a valuable overseas "presence" for FDA and are important in supporting foreign inspections, obtaining feedback on international developments, and for explaining FDA actions and policies to foreign constituencies.

Mutual reliance

FDA is involved with a number of partnerships and collaborations with regulatory counterparts designed to "streamline procedures for bringing new products to market" in multiple regions, Abram noted. An important challenge is to inspect the thousands of foreign facilities that export to the US to ensure the quality of imported

pharmaceuticals and other regulated products. As this task has expanded exponentially, FDA seeks to rely more on inspection reports produced by competent regulatory authorities in the European Union and other advanced nations. FDA and EU authorities have negotiated a mutual recognition agreement (MRA) that enables sharing of inspection reports for domestic drug manufacturers as a way to avoid duplicate inspections and to focus resources on more high-risk situations. The MRA is on track to be finalized this year following FDA's recent announcement that it now has assessed and recognizes inspectorates in 24 of 28 EU member states.

Despite this and other collaborations, FDA still needs to monitor a vast number of drug manufacturers in China and India and other third-world nations that produce APIs and generic drugs for the US. Deborah Autor, senior vice president at Mylan Pharmaceuticals, expects that more drugs and medical products will be coming in from overseas, as manufacturers move to more corners of the world where it is less expensive to operate. Regulatory partnerships for conducting inspections and for establishing product standards are "crucial" to advancing drug development and for expanding patient access to needed therapies, Autor observed at the FDLI meeting, so that manufacturers may satisfy registration requirements in multiple markets based on an approval by one regulatory authority.

More harmonization

International standards for drug testing and manufacturing can further this goal by reducing a proliferation in divergent regulatory approaches around the world, as seen in new initiatives at the International Council for Harmonization (ICH), which has expanded to include representatives of nations from all regions of the world. ICH is shifting from establishing specific technical standards to developing more conceptual guidelines for modernizing good clinical practices, drug safety assessment, and quality production.

Predicting the Future of European Health Policy

With a new Commission looming, here's who's vying for the top spot in shaping EU strategy, including key questions in pharma

By the time this article appears, part of the destiny of the European Union for much of the next decade will be a little clearer. And that should throw some light on how European health policy will evolve in the coming years, and what sort of place medicines will be able to claim in it. Will the drug industry continue to enjoy support on patents, or suffer cutbacks in incentives? Will research grants continue to promote drug innovation, or will regulation be tightened up with a new emphasis on relative efficacy? Will medicines even retain their place in health policy, or will the focus shift increasingly toward programs of prevention and promotion?

The results of May's European Parliament (EP) elections will provide some guide to the still more influential issue of what the next European Commission is likely to do.

But only some guide. And things are only a little clearer. Because although there is a connection between the outcome of the EP election and the shape of the next European Commission, it doesn't provide a definite answer.

In principle, the new EP, when it takes up office this month, will decide who should be the president of the new Commission, which is due to start work in November. Whoever

gets that job will have a determining role in EU strategy, because it is the Commission that proposes EU legislation, and because the person at the top decides which are the policy areas to concentrate on over the next five years, and who should be in charge of each of them.

Again, in principle, the person the EP nominates is supposed to receive automatic endorsement from the governments of the EU member states. But that is only in principle. When the national prime ministers and presidents get together at a summit meeting, they just might decide on an outsider instead.

Top contenders

What we know so far is who the main candidates are, and what their manifestos say—or don't say—about their attitudes to health and to innovation.

One of the strongest candidates is a center-right German MEP, Manfred Weber, who is broadly industry-friendly and favors joint action at the EU level, particularly against cancer. He has said he wants the EU to work together on “an ambitious approach on medicine research” because “nobody thinks that one single country can win the fight” against the disease.

Weber's main rival, Frans Timmermans, is a Dutch socialist (and currently a vice president

of the Commission). He emphasizes “strong welfare states, social safety nets, and quality public services,” and the “duty to protect people if they fall sick” with “the right to quality healthcare.” But his manifesto displays attitudes to industry that are a little more ambiguous. “Europe's industrial strategy must channel investment into research and innovation,” he says, but “we will not bow to uncontrolled market forces.” In his view, “the concentration of wealth and property in the hands of a privileged few must stop.”

Another senior official from the current Commission is also campaigning, but as a liberal: Margrethe Vestager, a former Danish economy minister, better known in the European health sector over the last five years as the competition supremo who has been pursuing anti-trust actions against drug manufacturers for impeding generic launches. In her view, “Europe is a place where it's great to do business. Everyone is welcome. But you have to play by the European rules.” She firmly endorses the need for equality, but health gets scarcely a mention in her manifesto, except in relation to women's sexual and reproductive rights, and in her calls for “a healthy planet.”

The Greens have fielded two candidates, Ska Keller and Bas Eickhout, both current MEPs, who advocate “a social Europe, making sure that globalization is not just a playground for multinationals,” but say little or nothing about health itself.

On the more extreme left wing of the political spectrum, a Belgian trade unionist, Nico

Cué, and a Slovenian MP, Violeta Tomic, back equal access to health through modernized public services with guaranteed social rights, but their manifesto for the European Left in Europe—which has not been updated since 2004—is overtly hostile to “globalized capitalism” and “big capital and lobbies” that seek to make health “subject to market rules.”

By contrast, the right-wing European Conservatives and Reformists group is represented by a Czech MEP, Jan Zahradil, who opposes compulsory vaccination, and insists on the merits of a common market as a means to promote prosperity but that “must not be used as a pretext for creating additional regulation such as attempts to harmonize taxes, as well as social and healthcare systems.”

Depending on the political arithmetic of the new European Parliament, on the ability of MEPs to reach a clear view among themselves, and on the readiness of EU leaders to accept that view, Weber, or Timmermans, or Vestager might well be putting together a new Commission by midsummer, ready for launch in the autumn.

But there are some dark horses that may still appear. The most conspicuous non-declared candidate is Michel Barnier, who has won wide admiration (except perhaps in the UK) for his role as the European Commission’s Brexit negotiator over the last two years, and more of a technocrat than an ideologue.

Another longer shot might be Josep Borrell, foreign minister of Spain’s socialist government, and a former president of the EP. As always in the EU, the final

decision will be the result of a complex compromise forged among more than two dozen conflicting national views.

Lost in shuffle?

Meanwhile, a coherent EU health policy is conspicuous by its absence, and the prospects for seeing one emerge remain slen-

the the health department now carry out could be redistributed among other more vigorous Commission departments responsible for research, industry, digital, or social affairs. A new Commission boss is entitled to shuffle the Commission cards whichever way he or she chooses.

The limited activities that the health department now carry out could be redistributed among other more vigorous Commission departments responsible for research, industry, digital, or social affairs


der. For the last two months, the EU has not even had a commissioner for health, since the incumbent, Vytenis Andriukaitis, took time off to contest (unsuccessfully) the presidential election in his native Lithuania.

The few health-related initiatives undertaken by the health department are either insignificant—such as gathering health service performance assessments—or blocked by broader political conflicts, which is the fate of the proposal on health technology assessment or the planned review of research incentives.

The very idea of an EU health policy lives under the perpetual shadow of the limits that the treaties impose on EU powers in this area. For two years now, uncertainty has reigned over whether the health department Andriukaitis is responsible for will even continue to exist in the new Commission. That has left its recently-appointed director-general apparently paralyzed, with no scope for new initiatives. The limited activities that

The signs were not promising when the leaders of the EU met for a set-piece discussion of the future of the EU in early May. Health was not even mentioned in the main preparatory document that the current Commission provided for the conference, “Preparing for a more united, stronger, and more democratic Union in an increasingly uncertain world.” There were passing mentions of health in other more detailed policy documents, but they were hard to find among the more substantial passages on defense, sustainable consumption and production, or a multilateral, rules-based global order.

Pivotal stretch

The coming six months, while the leadership of the new European Parliament and the new European Commission are agreed and policies are formulated, will determine many of the options and opportunities for pharmaceutical and life sciences executives through to the late 2020s. 



2019 Pharm Exec 50

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Pharm Exec's annual listing of the top global biopharma players reveals some interesting maneuvering of ranks, as companies focus on diversification, big-brand expansions, and positioning a new wave of products to compete in an advancing but complex future treatment market

By Michael Christel

The top spot in our annual scorecard updating the 50-best drug sales producers in global biopharma—now in its 19th iteration—remained unchanged for the fourth straight year (Pfizer, please step forward). However, the jockeying of positions underneath, interestingly, experienced its fair share of movement compared to recent years. The maneuvering may be indicative of factors such as business diversification; still well-entrenched patent protections; further expanded indications of popular therapies; more targeted portfolio and pipeline pursuits; and the challenges for once-novel drugs—even curative “firsts”—in maintaining market share.

Or perhaps the modest shuffling is a small signal to the bigger changes to come for the biopharma and healthcare enterprises—changes in operational strategy and advances in medical science and technology still too far on the horizon to manifest themselves significantly in big pharma and biotech’s commercial output.

In data again provided in partnership with life sciences market intelligence firm Evaluate Ltd (see the explainer on how the listings were calculated on facing page), Pfizer ranked first in 2018 prescription drug revenue, totaling \$45.3 billion. Notably, sales of breast cancer drug Ibrance, which in April won FDA approval for men with HR+, HER2- metastatic breast cancer, spiked 31.7% last year from 2017 full-year figures. Pfizer’s oncology portfolio, along with Eliquis and the company’s biosimilars, are reportedly expected to drive near-term earnings growth for the pharma giant. Last year, Eliquis overtook warfarin to become the leader in the US oral anticoagulants market.

Roche and Novartis swapped the second and third slots in the latest rankings, with Roche inching past Novartis with an increase of 6.8% in Rx drug sales. Roche also spent more than any company on R&D, investing \$9.8 billion. Herceptin remains Roche’s top-selling medicine, but its patent has expired, and according to a report in *Reuters*,

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the drug's sales dropped 16% in Europe last year, and potential US competition looms this year from biosimilars from Celltrion and Teva, Pfizer, and Mylan. If the deal goes through, Roche will add sales and pipeline assets via its February acquisition of Spark Therapeutics for \$4.8 billion (as of press time, the offer was in its second extension period). In late 2017, Spark won approval for Luxturna, the first-ever targeted gene therapy, which treats inherited retinal blindness. Spark also focuses on gene therapies for hemophilia, lysosomal storage diseases, and neurodegenerative disorders.

Novartis, which posted a 3.8% rise in drug revenue on our list, has received a lot of recent attention around its own gene therapy product, Zolgensma, approved by FDA late last month to treat children under two years of age with spinal muscular atrophy, a potentially deadly disease. Novartis priced the one-time infusion at \$2.1 million, a sticker price that has turned heads, and is illustrative of the new waters gene therapies in general pose for healthcare systems and payers, and government and regulators, in figuring out how to cover and fund these products (see our Washington correspondent's

report on page 8). After first deeming Zolgensma not cost-effective at the \$2.1 million price tag, the Institute for Clinical and Economic Review (ICER) reversed course last month based on review of new data and value-based payment plans. According to published reports, Novartis says it has ample manufacturing capacity to meet Zolgensma launch demands. Production hurdles contributed to a slower roll-out for Novartis's cell therapy Kymriah, the world's first CAR-T drug, which gained its first approval in August 2017. Kymriah targets acute lymphoblastic leukemia (ALL).

		Rx Sales*	R&D spend*	Top-selling Drugs*	
1	Pfizer NEW YORK, NEW YORK [PFIZER.COM]	\$45.302	\$7.962	Prevnar 13	5.802
				Lyrica	4.970
				Ibrance	4.118
2	Roche BASEL, SWITZERLAND [ROCHE.COM]	\$44.552	\$9.803	Herceptin	7.140
				Avastin	7.004
				Rituxan	6.905
3	Novartis BASEL, SWITZERLAND [NOVARTIS.COM]	\$43.481	\$8.154	Gilenya	3.341
				Cosentyx	2.837
				Lucentis	2.046
4	Johnson & Johnson NEW BRUNSWICK, NEW JERSEY [JNJ.COM]	\$38.815	\$8.446	Stelara	5.156
				Remicade	4.890
				Zytiga	3.498
5	Merck & Co. KENILWORTH, NEW JERSEY [MERCK.COM]	\$37.353	\$7.908	Keytruda	7.171
				Januvia	3.686
				Gardasil	3.151
6	Sanofi PARIS, FRANCE [SANOFI.COM]	\$35.121	\$6.227	Lantus	4.211
				Pentacel	2.066
				Fluzone	2.017
7	AbbVie NORTH CHICAGO, ILLINOIS [ABBVIE.COM]	\$32.067	\$5.093	Humira	19.936
				Mavyret	3.438
				Imbruvica	2.968
8	GlaxoSmithKline BRENTFORD, ENGLAND [GSK.COM]	\$30.645	\$4.987	Triumeq	3.535
				Advair	3.234
				Tivicay	2.188
9	Amgen THOUSAND OAKS, CALIFORNIA [AMGEN.COM]	\$22.533	\$3.657	Enbrel	5.014
				Neulasta	4.475
				Prolia	2.291
10	Gilead Sciences FOSTER CITY, CALIFORNIA [GILEAD.COM]	\$21.677	\$3.897	Genvoya	4.624
				Truvada	2.997
				Epclusa	1.966

Source: EvaluatePharma® May 2019, Evaluate Ltd, www.evaluate.com

*numbers USD in billions

How the listings were compiled: 2018 Rx Sales and R&D Spend analyses were provided by life science market intelligence firm Evaluate Ltd via its EvaluatePharma® service, www.evaluate.com. *Pharm Exec* would like to thank EvaluatePharma for assisting in the development of this year's Pharma 50 listing. **PLEASE NOTE:** 2018 figures represent prescription pharmaceutical sales from the named company only, and exclude revenues from royalties, co-promotions, etc., as well as sales from non-prescription pharmaceuticals. Evaluate's Sales and R&D Spend figures represent the fiscal year that ended in 2018. For most American and European companies, that means the year ending December 31, 2018. For many Japanese companies, the fiscal year ending March 31, 2019, was used. Historic averages were used in the conversion of companies' native currency to USD.

With less fanfare than the CAR-T wave received, but perhaps with greater blockbuster potential in the near-term, Novartis won regulatory clearance last month for Piqray, the first drug designed specifically for HR+/HER2- breast cancer patients with a PIK3CA mutation. It's also the first novel drug approved under the FDA's Real-Time Oncology Review pilot program. Mainstay Gilenya generated \$3.3 billion in sales in 2018, but reports state that dermatology drug Cosentyx eclipsed Gilenya in the first quarter of this year to become Novartis's top-selling product.

The company's philosophy has been not to rely on one or two treatments to drive growth,

but to anchor drug assets across six therapeutic areas (in recent reports, Novartis claims to have 25 blockbuster candidates in the clinic). Predictions published by Yahoo and FiercePharma say Novartis will be the world's top drug seller by 2024. Could the Swiss-based giant leapfrog Pfizer and Roche in our Pharma 50 rankings in the next few years to secure the top perch for the first time since 2015?

Other notable shifts in top 10 positioning include:

- » Johnson & Johnson's move up one spot to No. 4, behind drug sales growth of 12.8% compared to the previous year.
- » Merck & Co., though ceding way to J&J, posted a 5.6% gain on the steam of its expanding

flagship Keytruda, the cancer immunotherapy. Sales of the drug rose 88% in 2018, to \$7.2 billion. (Keytruda is projected to reach annual sales of \$10 billion in its fifth year). It won FDA approval in April as a first-line treatment for patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemotherapy. Keytruda was also greenlighted in combination with Pfizer's Inlyta for previously untreated kidney cancer. » AbbVie flipped spots with GlaxoSmithKline—jumping to seventh on the list. The company posted a 15.6% gain in Rx drug revenue behind \$19.9 billion in sales of Humira.

		Rx Sales*	R&D spend*	Top-selling Drugs*
11	Bristol-Myers Squibb NEW YORK, NEW YORK [BMS.COM]	\$21.581	\$5.131	Opdivo 6.735 Eliquis 6.438 Sprycel 2.000
12	AstraZeneca LONDON, ENGLAND [ASTRAZENECA.COM]	\$20.671	\$5.266	Symbicort Turbuhaler 2.561 Tagrisso 1.860 Nexium 1.702
13	Eli Lilly INDIANAPOLIS, INDIANA [LILLY.COM]	\$19.580	\$4.993	Trulicity 3.199 Humalog 2.997 Alimta 2.133
14	Bayer LEVERKUSEN, GERMANY [BAYER.COM]	\$18.221	\$3.417	Xarelto 3.689 Eylea 2.581 Mirena 1.350
15	Novo Nordisk BAGSVAERD, DENMARK [NOVONORDISK.COM]	\$17.726	\$2.347	Victoza 3.857 NovoRapid 2.974 Levemir 1.774
16	Takeda OSAKA, JAPAN [TAKEDA.COM]	\$17.427	\$3.012	Entyvio 2.331 Velcade 884 Leuplin 809
17	Celgene SUMMIT, NEW JERSEY [CELGENE.COM]	\$15.238	\$4.084	Revlimid 9.685 Pomalyst 2.040 Otezla 1.608
18	Shire** DUBLIN, IRELAND [SHIRE.COM]	\$14.993	\$1.608	Vyvanse 2.358 Gammagard Liquid 2.290 Advate 2.169
19	Boehringer Ingelheim INGELHEIM, GERMANY [BOEHRINGER-INGELHEIM.COM]	\$14.834	\$3.206	Spiriva 2.849 Pradaxa 1.755 Jardiance 1.726
20	Allergan IRVINE, CALIFORNIA [ALLERGAN.COM]	\$14.700	\$1.575	Botox 3.577 Restasis 1.262 Juvederm Voluma 1.163

Source: EvaluatePharma® May 2019, Evaluate Ltd, www.evaluate.com

*numbers USD in billions

** 2018 figures for Shire are estimated, given its acquisition in early 2019 by Takeda.

Though Humira's EU patent expired last year, AbbVie has reached settlements to fend off US biosimilar competition until January 2023. In preparation, however, the company is attempting to bolster sales for its newer drugs Skyrizi and upadacitinib; for example, it's offering discounts on Humira to secure favorable formulary coverage for Skyrizi, a monoclonal antibody approved in the US and Europe in April for psoriasis (it boasts advantages in less-frequent dosing and had better skin clearance rates during clinical testing than similar drugs on the market).

» Gilead, which despite strong sales from its HIV drugs, fell

one spot to No. 10. The biotech's overall prescription drug revenue dropped 15.5%, due in large part to continued declines in its hepatitis C virus (HCV) drug franchise, where the once-pioneering medicines Harvoni and Sovaldi—which cure patients of HCV after one course of treatment—have lost market share to rival drug launches in recent years.

Rest-of-field observations

Just outside of the top 10, Bristol-Myers Squibb claims the 11th spot in our rankings, with Keytruda PD-1 inhibitor rival, Opdivo, pulling in \$6.7 billion in sales, a 36% increase. The momentum may be squelched

some by BMS's voluntary withdrawal earlier this year of its application for Opdivo in combination with Yervoy as first-line treatment for advanced non-NSCLC patients with tumor mutational burden, and Opdivo's failure in a Phase III brain cancer study, announced last month. Eliquis, which BMS manufacturers in partnership with Pfizer, continued to grow at a more than 30% annual clip.

BMS is poised to climb up the rankings ladder in the coming years after its \$74 billion merger with Celgene, which after months of wrangling, was finally approved by BMS shareholders in April. The deal is expected to close in the third

	Rx Sales*	R&D spend*	Top-selling Drugs*	
21 Teva Pharmaceutical Industries PETACH TIKVA, ISRAEL [TEVAPHARM.COM]	\$13.122	\$1.213	Copaxone Bendeka Methylphenidate Hydrochloride	2.366 642 481
22 Mylan CANONSBURG, PENNSYLVANIA [MYLAN.COM]	\$11.144	\$586	Glatiramer Acetate EpiPen Ethinyl Estradiol; Norelgestromin	450 246 207
23 Astellas Pharma TOKYO, JAPAN [ASTELLAS.COM]	\$11.036	\$1.909	Xtandi Prograf Myrbetriq	3.004 1.431 1.328
24 Biogen CAMBRIDGE, MASSACHUSETTS [BIOGEN.COM]	\$10.887	\$2.587	Tecfidera Avonex Tysabri	4.274 1.915 1.864
25 CSL MELBOURNE, AUSTRALIA [CSL.COM.AU]	\$8.270	\$724	Privigen Hizentra Human albumin	2.294 942 929
26 Daiichi Sankyo TOKYO, JAPAN [DAIICHISANKYO.COM]	\$7.033	\$1.888	Lixiana Nexium Namenda	1.061 706 453
27 Merck KGaA DARMSTADT, GERMANY [MERCKGROUP.COM]	\$7.001	\$1.928	Rebif Eribitux Glucophage	1.699 964 866
28 Otsuka Holdings TOKYO, JAPAN [OTSUKA.COM]	\$5.726	\$1.863	Samsca Ability MAINTENA Rexulti	817 797 629
29 UCB BRUSSELS, BELGIUM [UCB.COM]	\$5.138	\$1.371	Cimzia Vimpat Keppra	1.708 1.272 751
30 Les Laboratoires Servier NEUILLY-SUR-SEINE, FRANCE [SERVIER.COM]	\$5.103	N/A	Diamicon Vastarel Aceon	548 500 416

quarter of this year, adding several new drug candidates from Celgene's pipeline, including potential multiple sclerosis blockbuster ozanimod. BMS will also gain the rights to Revlimid, Celgene's longtime big seller for cancer, and its CAR-T portfolio, which the biotech acquired last year through its \$9 billion takeover of Juno Therapeutics. Revlimid continues to expand into new patient populations, winning FDA approval in late May, paired with Roche's Rituxan, as a chemotherapy-free combination drug for patients with previously treated follicular or marginal zone lymphomas.

In Rx drug sales, Celgene leapt from the 21st spot to 17th

in this year's rankings. According to Evaluate's data, BMS and Celgene increased their R&D spend in 2018 by 6.4% and 35.4%, respectively. Celgene's spike was the highest among companies investing at least \$1 billion in R&D. Another notable R&D output was Regeneron's, who despite ranking 38th in drug sales, spent the 21st most on R&D, investing \$2.2 billion.

New entrants this year in the Pharma 50 include Hong Kong-based Sino Biopharmaceutical at 42nd; Boston's Vertex Pharmaceuticals at 43rd; and French biopharma Ipsen and China-headquartered Jiangsu Hengrui Medicine at 46th and 47th, respectively.

Dealing and diversifying

The BMS-Celgene and Pfizer-Spark deals, along with Eli Lilly's \$8 billion acquisition of Loxo Oncology, may signal the start of a wave of M&A activity in the industry that will last into 2020, analysts say, as companies look to increase diversification into new areas and put more R&D resources into therapeutic niches with strong pricing power, such as rare diseases. According to a report by Evaluate, rare and orphan drugs will make up one-fifth of worldwide prescription sales in 2024, amounting to \$242 billion in spend.

Takeda's acquisition of rare diseases specialist Shire, first announced in March 2018, was

		Rx Sales*	R&D spend*	Top-selling Drugs*	
31	Bausch Health Companies LAVAL, CANADA [BAUSCHHEALTH.COM]	\$4.631	\$413	Xifaxan 550 Ocuvite Wellbutrin XL	1.195 305 263
32	Eisai TOKYO, JAPAN [EISAI.COM]	\$4.531	\$1.309	Humira Lenvima Halaven	549 544 373
33	Abbott Laboratories ABBOTT PARK, ILLINOIS [ABBOTT.COM]	\$4.422	\$184	Drospirenone; Ethinyl Estradiol Ademetionine Choline Alfoscerate	26 22 14
34	Fresenius BAD HOMBURG, GERMANY [FRESENIUS-KABI.COM]	\$4.328	\$631	Heparin Sodium	79
35	Sun Pharmaceutical Industries MUMBAI, INDIA [SUNPHARMA.COM]	\$4.222	\$321	Absorica Atorvastatin Calcium Ciprofloxacin Hydrochloride	155 143 137
36	Grifols BARCELONA, SPAIN [GRIFOLS.COM]	\$4.154	\$284	Gamunex-C Prolastin-C Flebogamma	1.279 795 792
37	Alexion Pharmaceuticals CHESHIRE, CONNECTICUT [ALXN.COM]	\$4.130	\$704	Soliris Strensiq Kanuma	3.563 475 92
38	Regeneron Pharmaceuticals TARRYTOWN, NEW YORK [REGENERON.COM]	\$4.106	\$2.186	Eylea Arcalyst Libtayo	4.077 15 7
39	Chugai Pharmaceutical TOYKO, JAPAN [CHUGAI-PHARM.CO.JP]	\$3.649	\$855	Actemra Edirol Alecensa	345 298 187
40	Sumitomo Dainippon Pharma OSAKA, JAPAN [DS-PHARMA.COM]	\$3.543	\$776	Latuda Brovana Merrem	1.688 307 203

officially closed in early January for \$62.2 billion, making it the largest biotech employer in Massachusetts and thrusting the company into the top 10 of pharma revenue producers. In other mega deals, GSK last year bought out Novartis's stake in their consumer health joint venture for \$13 billion, and merged its consumer business with Pfizer, as part of GSK's plan to split into two separate businesses; and Sanofi completed its acquisition of Bioverative, a US biotech focused on hemophilia and other rare blood disorders, for \$11.6 billion.

On the generics front, Mylan, ranked 22nd in our list with \$11.1 billion in 2018 drugs sales, agreed in May to buy Aspen Pharmacare's portfolio of

prescription and over-the-counter products in Australia and New Zealand for \$130 million; and Mallinckrodt, ranked 48th, announced plans to spin off its generic drug business as a separate unit and rename the remaining specialty branded drugs business to Sonorant Therapeutics Plc. Mylan and Teva are among 20 generics makers named in a lawsuit issued last month by 44 US states for alleged price-fixing.

A likely influencer in this year's Pharma 50 is the continued boom of the specialty pharma market. Recent numbers issued by the Peterson-Kaiser Health System Tracker found that among commonly used specialty drugs, branded drug prices have increased by 57% since 2014. Meanwhile, spending for

prescription drugs overall, perhaps surprisingly, has been relatively flat, at least according to government and private industry sources. MarketWatch reported in March that the cost of Rx drugs over the preceding year had dropped by 1.2%—the biggest 12-month decline since 1972.

World gains, mission

Another driver impacting our numbers are the growth rates of multinational drugmakers in emerging markets. According to published reports, in the first quarter of this year, emerging markets growth averaged 13.3% among a selection of big pharmas, with 29% in China—compared to 8.2% growth in the US. With the pharma industry facing rising demands to improve

		Rx Sales*	R&D spend*	Top-selling Drugs*	
41	Menarini FLORENCE, ITALY [MENARINI.COM]	\$3.313	N/A	Bystolic Enantyum Uloric	342 163 115
42	Sino Biopharmaceutical HONG KONG [SINOBIOPHARM.COM]	\$3.142	\$339	Runzhong Tianqingganmei Calcitriol	506 275 147
43	Vertex Pharmaceuticals BOSTON, MASSACHUSETTS [VRTX.COM]	\$3.038	\$1.292	Orkambi Kalydeco Symdeko	1.262 1.008 769
44	Endo International DUBLIN, IRELAND [ENDO.COM]	\$2.947	\$141	Vasotriect Xiaflex Adrenalin Injection	454 265 143
45	Mitsubishi Tanabe Pharma OSAKA, JAPAN [MT-PHARMA.CO.JP]	\$2.913	\$755	Remicade Simponi Radicava	512 345 308
46	Ipsen PARIS, FRANCE [IPSEN.COM]	\$2.628	\$357	Somatuline Trelstar Dysport	1.000 440 411
47	Jiangsu Hengrui Medicine LIANYUNGANG, JIANGSU PROVINCE, CHINA [WWW.HRS.COM.CN]	\$2.570	\$334	Aitan Docetaxel Oxaliplatin	303 209 104
48	Mallinckrodt DUBLIN, IRELAND [MALLINCKRODT.COM]	\$2.543	\$361	H.P. Acthar Gel INOmax Ofirmev	1.110 543 342
49	STADA Arzneimittel BAD VILBEL, GERMANY [STADA.COM]	\$2.467	\$85	Apokyn Amoxicillin Grippostad	82 55 51
50	Ferring Pharmaceuticals PARSIPPANY, NEW JERSEY [FERRINGUSA.COM]	\$2.461	\$357	N/A	N/A

Source: EvaluatePharma® May 2019, Evaluate Ltd, www.evaluate.com

*USD in billions, lower numbers in millions

global health and preserve their public health missions, a new study by the Access to Medicine Foundation found that drug-makers “are taking seriously the problems people face in low- and middle-income countries when accessing healthcare,” but the progress has been sporadic with often only a few diseases in a small number of countries being targeted. The study, which analyzed 10 years of data, does note that the R&D pipeline has more than doubled since 2014 for a set of 47 high-burden and priority diseases, including HIV/AIDS, malaria, and tuberculosis, and

The pharma industry’s overall global trust rating increased four points to 67, ranking in the lower half of the 15 industries studied

that pharma companies are using pricing, licensing, and donations more frequently than before as tactics to improve access in low- and middle-income countries.

It’s these dynamics in global healthcare that bring us to this year’s special Pharma 50 accompanying feature by guest author Lauren Seufert, the founder of emOcean Coaching & Consulting (see page 20). In setting the stage for a piece on biopharma leadership strategies amid change, Seufert points to the organizational disruption taking place on a global scale. Examples she cites are trade wars with the East and the continuing debate around global vs. national focus in many regions. Combined with disruptions from technology advancement and digitalization, new business models governing all parts of the value chain, economic fluctuations around the globe, and evolving social and political

landscapes, Seufert emphasizes the importance of pharma executives in preparing their companies to thrive in this future VUCA world (volatility, uncertainty, complexity, and ambiguity).

Meanwhile, pharma C-suite leaders continue to deal with the larger industry’s reputation and trust challenges. That’s particularly true in the US, where public sentiment regarding the industry actually improved some this year, according to Edelman’s annual trust barometer. Its research reported an increase of six points in the US, bringing pharma’s total up to 44 (a score

of 60 or more is considered “trusted” under the Edelman ratings). The pharma industry’s overall global trust rating increased four points to 67, ranking in the lower half of the 15 industries studied.

R&D reshaped

A shifting climate and operational environment for clinical research could begin to start influencing the Pharma 50 sooner than later. In 2018, the FDA approved 59 new molecular entities, the highest annual number in history (see chart on facing page), with 27% of those precision medicines to treat cancer and its symptoms, according to a report by the IQVIA Institute.

In addition, 46% of the approvals were cleared based on data from trials with fewer than 500 patients and 42% were approved on the basis of only one trial.

These trends illustrate the growing number of new drug approvals sponsored by smaller, clinical-stage developers—many funded by private equity and venture capital. IQVIA found that emerging biopharma companies patented almost two-thirds of new drugs launched in 2018, and they accounted for 72% of the late-stage pipeline, compared with 65% in 2013 and 52% in 2003.

Overall, the late-stage pipeline grew by 11% in 2018, the IQVIA report says, and the total number of clinical trials started last year was up 9% over the prior year and 35% over the past five years. According to the Tufts Center for the Study of Drug Development (CSDD), half of all drugs in the R&D pipeline—and about 80% of all investigational drugs for cancer-related diseases—now rely on biomarker and genetic data to target therapeutic agents. Ken Getz, the director of sponsored research at Tufts CSDD, notes in a new column in *Pharm Exec* sister publication *Applied Clinical Trials* that there are now more than 11,000 active molecules in development—a 5% to 7% year-over-year growth rate across the span of two decades.

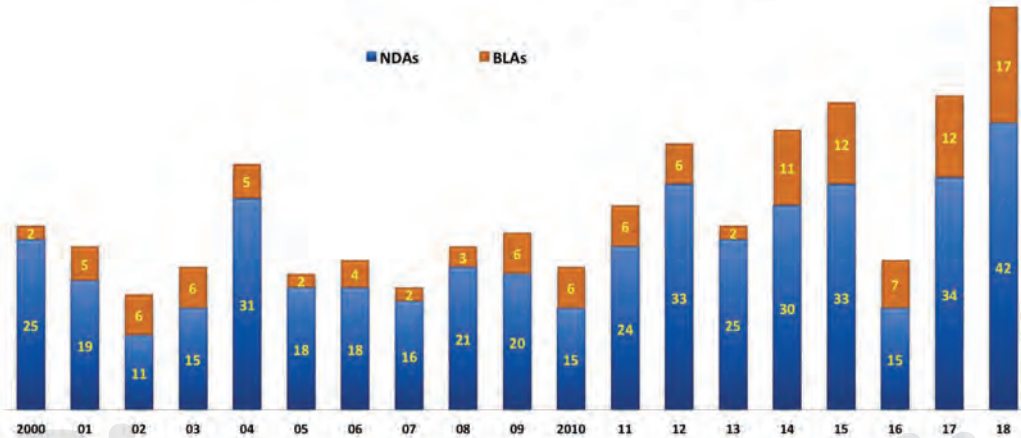
Addressing 2018’s record number of US approvals, Getz notes that 73% were approved under “priority review” status, and that one-third of the new approvals were first-in-class drugs offering new ways of treating certain diseases.

“This is a remarkable achievement, particularly in light of the anemic number of annual approvals that we saw in the 2005 to 2010 period,” Getz states.

But, of course, even amid the reveling over pharma’s innovation

New Drug and Biologic Approvals by Year

Source: FDA



resurgence, drug development remains essentially a high-risk investment. A recent study by Accenture did find that treatments considered more innovative—tied in with things like genomics, biomarkers, companion diagnostics, and new delivery methods—are actually more likely to reach the market, slightly bucking the long-held belief that about nine out of 10 drugs that enter clinical testing fail (in analyzing 60,000 products from 2000 to 2017, Accenture reported a successful clinic-to-market range of 6% to 40%).

While pinpointing exact failure rates may not be an exact science, Getz, nevertheless, reminds us that drug development processes are highly complex and inefficient, and have done little to improve durations. He contends as well that, on average, the typical drug generates a relatively low and declining return on its development investment, given the high capitalized cost of bringing a drug through FDA approval. Getz says that about \$150 billion was spent on global R&D activity in 2018.

“To remain viable, drug developers must transform long-standing R&D operating processes

and practices that are largely insular and sequential, supported by redundant resources and personnel and that underutilize key assets and expertise,” he writes. “The growing prominence of precision medicines and treatments for rare diseases and targeted patient subpopulations—all requiring more complex clinical trial designs and longer durations to identify and recruit patients—intensify the pressure on drug developers to accelerate this transformation.”

Some in big pharma seem to be responding. Last month, Novartis, Otsuka, Pfizer, and Sanofi all formed alliances with Verily, Alphabet’s life sciences unit, in hopes of reshaping clinical trials in disease areas such as cancer, mental health, diabetes, dermatology, and heart disease. The pharmas will develop clinical research programs using technology developed under Verily’s Project Baseline. The Baseline platform is designed to engage larger numbers of patients and clinicians in research and collect more comprehensive, higher quality data. The partners will also explore novel approaches to generating real-world evidence (RWE) using

the platform to organize and activate health information from electronic health records, sensors, and other digital sources.

Pharma’s interest in RWE has grown considerably. Both Pfizer and BMS, for example, recently struck strategic agreements with Concerto HealthAI, which focuses on cancer-specific real-world data (RWD) and advanced artificial intelligence (AI) for RWE generation. The companies will use Concerto’s platform and AI models to identify and develop precision oncology drugs, as well as better understand how medicines are used to help improve patient outcomes.

Overall, the industry has increased its adoption of AI and machine learning on numerous fronts. A recent analysis by Tufts CSDD and DIA found that the clinical operations function makes the highest use of AI, followed by pharmacovigilance/safety/risk management, and information technology. The promise of cloud technology is also building momentum in pharma R&D circles to help process the large volumes of data and multiple and disparate data sources now involved in clinical research. **PE**

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‘Vision’ Quest: Leading Through Change

Exploring the critical go-to strategies for C-suite leaders in navigating organizational disruption in the biopharma industry and beyond

By Lauren Seufert

Those who work in the pharma, biotech, or healthcare industries know that change is constant. In order to stay relevant, companies need to continuously innovate, stay current with upcoming trends, and reinvent themselves in order to best serve their customers. Not only is the world’s population increasing dramatically, access to medicine and healthcare is now thankfully becoming available to regions that may have struggled economically in the past. We are able to get medication to more people faster, and more effectively.

However, there are several other factors having a dramatic impact on the industry and increasing the frequency of change exponentially. Technological advancement and digitalization are disrupting the way companies conduct business, not only in research, but across manufacturing, supply chain, marketing, and sales. Data mining, block chain, and artificial intelligence (AI) are only a few examples of why we cannot continue to do business as we have in the past. Processes will become more efficient, job roles will change, and industries will be impacted dramatically.

In addition to the technological changes that companies face, we are also dealing with economic disruption around the globe. Competition remains fierce and while access to medicine increases, so does access to production and adequate

infrastructure for additional supply. M&A and partnerships continue to dominate discussions of large and small companies across all parts of the value chains. In order to remain competitive, organizations need to stay alert, agile, and ready for new opportunities.

The landscape is also changing socially and politically. We are faced with democratic uncertainty in a large part of Western society. Trade wars with the East remain and we continue to debate global vs. national focus in many regions. Employees have gone from a more traditional “company-minded” focus to working in the rising gig economy. More people work remotely and virtually. There are more virtual freelancers, more service-oriented jobs, and a much more agile workforce. This will dramatically change the way life sciences companies do business in the future.

Leadership in a VUCA world

Top executives are well aware of this VUCA (volatile, uncertain, complex, ambiguous) world and, amid the disruptions, are taking the appropriate steps and actions to prepare their companies for the future. For example, John Upperman, vice president for Procurement, pharma services at Thermo Fisher Scientific, said the following regarding Thermo’s \$7.2 billion acquisition of contract development and manufacturing Organization Patheon in 2017:

“We have gone through major changes in several areas as former Patheon employees. However, I believe we now have

the unique opportunity to share different ideas and experiences, and to develop an improved strategy on how to enhance processes, services, and, most importantly, our customer’s experience, enabling our customers to improve the health of patients around the world. The integration remains challenging; however, in my view it is being very well managed. It has created a much broader path full of opportunities for both our customers and our employees.”

Strategies across many companies and divisions are being reconsidered and rewritten as change continues and organization identities are modified. Companies are becoming increasingly agile, focusing more on automation, improving their internal and external communication tools, and creating an overall better customer experience. With these changes, there is a desire to increase speed and reliability—all while attempting to reduce costs and improve effectiveness in serving their markets.

Change and the impact on employees

Of course, while focusing on strategy and processes are important, it is also crucial to remember the impact on the individuals within an organization when disruption occurs. HR and people strategies are becoming more of a priority across several industries. These strategies not only include hiring, retaining quality talent, and ensuring there is a pipeline of strong candidates to lead the company into

the future; they also focus on the overall employee experience. In pharma, it remains critical for leaders to have this mindset if they want to retain committed talent. “Helping people navigate disruption is one of my favorite parts of my job as a leader,” says Upperman. “In particular, I know it is my responsibility to give my team confidence and peace of mind when we are going through times of change.”

It is important that organizational leaders also ask themselves how this increased frequency of change is affecting employees as not only individuals, but as part of the larger company-wide culture. Change and uncertainty typically have a significant impact on the emotional and mental states of employees.

According to research by Prosci, which specializes in change management practices, more fear leads to distraction, which could lead to a potential decrease in productivity across the organization (see Figure 1). However, companies need productivity to be higher than ever as we navigate the challenging roads ahead. Fortunately, research also shows that if the change is managed properly, productivity may actually increase as a result, and limited attrition will occur. Certain departments may experience the changes differently than others. This is dependent on several factors. However, research shows that effective change leadership always plays a critical role.

Strategic and relational change approaches

As we navigate this challenging space together, it helps to focus on the development of three key areas in what can be defined as

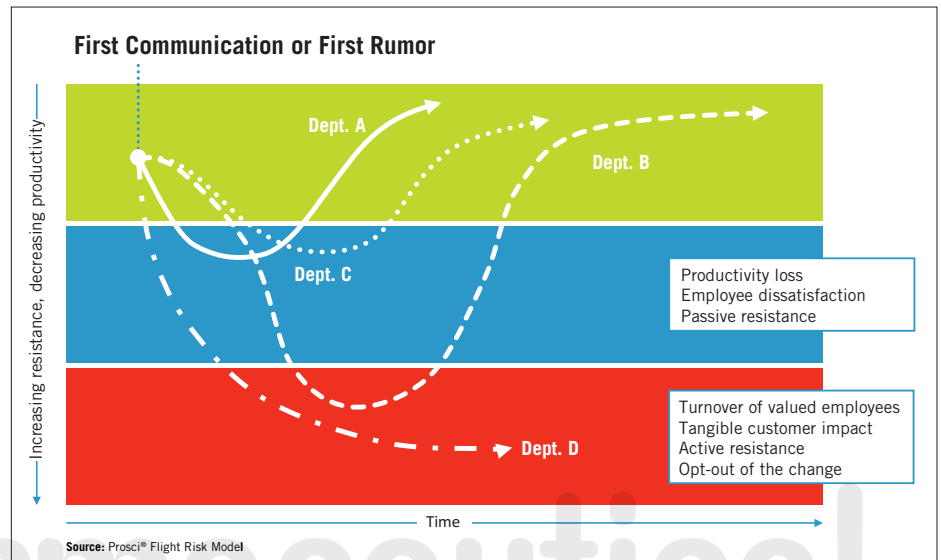


Figure 1

a “transformation triangle”—strategic vision, refined processes, and relational dialogue (see Figure 2 on page 22).

Strategic vision

As it navigates times of change, a company usually first focuses on whether its strategic roadmap still makes sense given the dynamic environment. But it is important to focus on the “vision” aspect of the strategy—where is the company going, and, most importantly, why?

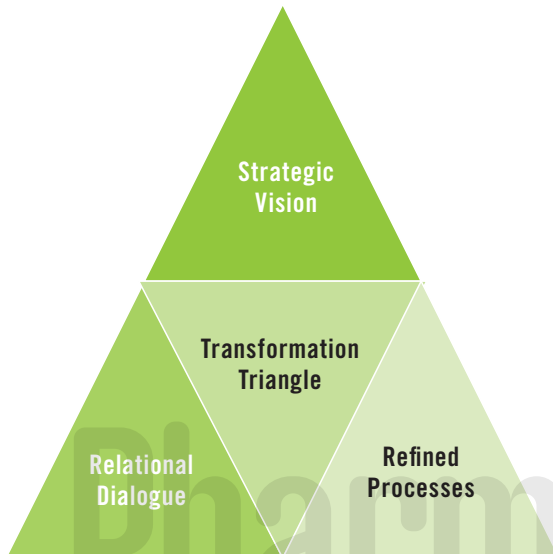
Organizations tend to be drawn to compelling, captivating, and moving stories that capture the minds and hearts of individuals. In many cases, strategies are filled with implementation steps and action plans, moving quickly past “why we are even here in the first place.” This is not just a mission statement or tag line that is somehow surreal or detached from the individual worker. It is about developing a clear purpose for each and every part of the organization. This creates emotional connection, purpose, and a greater sense for why we are coming to work

every day and putting so much energy into the efforts at hand.

Only half of the battle of having a strategic vision is creating one. The larger and more challenging part is then getting people’s buy-in and making them aware of why certain changes are needed, and, more importantly, fueling a desire to act. This comes only with a proper coaching and training plan, and also a plan to address any future resistances that may arise.

Many believe that communication is the largest component part of any change process. However, communication goes two ways. This requires a large investment in time, curiosity on the part of leaders, and incorporates the organization’s feedback and input. In particular, in an age where virtual working becomes more common, it becomes even more critical that virtual communication touches the hearts and minds of the people.

In many cases, organizations attempt to do this on their own. However, getting the support of external consultants or facilitators to help steer the process can

Figure 2: A Steady-Eye Formula

Source: emOcean Coaching & Consulting

pay off, allowing the organization to focus on customers and implementation.

Refined processes

These are all of the areas where roles and responsibilities are impacted by change. It can be the rollout of a new tool or a desired change of how people work together either within or across functions and operating divisions. One small rollout can have massive impact across various parts of an organization. When things don't work as they used to, people get frustrated and performance tends to suffer as a result. Therefore, making clear to all company divisions what will be different going forward, how it will affect their activities, and why, are critical parts of any change process.

In most cases, it is not yet clear to upper management how the particular change will impact processes, positions, or job descriptions. For example, the rollout of a new data mining tool will eliminate the need for more traditional roles in a marketing

or sales department. What will be done with those positions or even full departments? As anxiety, particularly around job security or employment, starts to infiltrate an organization, the job of senior leaders is to establish more dialogue with employees, not less.

We tend to avoid the situation until we have clear answers. However, the less vocal or present leadership is during times of uncertainty, the more focus is put on these topics by the organization. This results in rumors and, in most cases, a decrease in performance and the overall well-being of the company.

During times of uncertainty, it is critical that leaders engage employees in the process of defining the future. There may be ideas that employees have as to how they can modify their roles or adapt in order to add the most value. They may request training to support them in developing skills geared toward a specific direction. Investing in the employees that are willing to learn and adapt can create tremendous value for the future. It may also help to avoid potential complacency of the employees, if they feel their value-add is declining.

In addition to the dialogue, it is important for life sciences leaders to focus on and emphasize the areas and processes that are working well. "When things are working, we like to give our employees the freedom and autonomy to continue doing what they have done in the past," says Upperman. "This gives people confidence and the ability to realize there may be some quick wins to celebrate."

Relational dialogue

This is probably the most critical, yet most overlooked part of

the transformation triangle. Communication can be challenging; it becomes even more difficult when you mix in different cultures, value systems, experiences, and beliefs. Organizations are becoming more diverse, but this does not always make dialogue easier.

In order to bridge cultural, racial, gender, and generational gaps, companies need to be open, empathetic, and inclusive. This requires time, patience, and curiosity. Biases, conflicts, and misunderstandings can occur, sometimes leading to teams being hesitant to provide open feedback and enter into dialogue. With added deadlines and the time pressure most organizations are under today, it is no wonder that individuals tend to avoid the elephants in the room.

"We need to remember that the people in our organizations each have their own worries, hopes, dreams, and personal issues," says Upperman. "I try to always apply three things when leading through change: understanding the emotional state of my people, exercising a high level of empathy, and being the calm leader that people can always go to with their fears."

Dialogue is not always easy and sometimes may result in conflicts, especially when topics are challenging, emotions are involved, and stakes are high. However, conflict or negative feedback, if presented in a healthy way, can move teams forward and allow them to elevate to another level of performance.

When working with organizations on relational dialogue, the focus should be on these critical areas:

» **Inclusive listening and curiosity.**

Making sure that the voices of all employees are heard not only creates a culture of taking risks and of people wanting their ideas to be known, it generates a more innovative dialogue, which may ultimately help contribute to a better, thought-through solution.

» **Enabling an open feedback culture.**

People can always grow and learn, and that usually happens with the support of external observation and feedback. However, giving feedback can be a tricky, especially when it's not positive feedback. To that end, there are techniques that have proven to work well and that can be applied within organizations. Ultimately this creates more vulnerability, open communication, higher trust, and tremendous growth. In many cases, conducting a first-group feedback round with a trained facilitator can be useful.

» **Facilitating conflict when stakes are high.**

Typically, when conversations get tough, we sometimes tend to table them for another time. But are we revisiting the topics that really need ultimate discussion and conflict resolution to get issues hashed out? When organizations can address these areas openly without fear of feelings getting hurt or emotions running high, they can make tremendous progress. Emotions are normal. Bringing well-managed emotions more into business environments can lead to greater commitment, and ultimately more sustainable results.

» **Understanding how decisions are made.**

It sounds obvious, but, in many cases, companies are not clear how decisions should

be made. Who is the ultimate decision-maker and for which topics? Do we need a full team buy-in, or is it ultimately the decision of one, with expectation of full commitment? If this decision process is not talked through and understood, organizations have the risk of either moving too slow and not making decisions fast enough, or steam-rolling the organization with decisions that, in the end, will not be implemented. There are ways in which decision processes can be better understood, discussed, and implemented across companies. Committing time early on to this topic, particular with new teams, pays off greatly in the long run.

Leading through change

As a company institutes its own practices around the three pillars of the transformation triangle, several questions emerge that perhaps should be at the top of the leadership agenda. Going through the following checklist can be helpful for an organization.


- » Is the company vision clearly communicated to the broader organization?
- » Is the vision communicated in various ways where all people will feel a connection and clearly understand their ability to contribute to the greater purpose?
- » Are there certain roles changing in the organization, and is there enough investment going into how things will develop for these individuals in the future?
- » Is the organization's values clear to everyone?
- » If so, do they represent what will result in increased

curiosity, innovation, healthy dialogue, and resilience to change among the employees?

- » Is the company investing enough in soft skills across its leadership and broader organization?
- » Is dialogue, in particular where there are differing opinions, healthy and appreciated on all levels?
- » Is there not only a diverse environment of individuals in the organization, but does it have an inclusive environment, where all viewpoints are respected and heard?
- » What behaviors are expected from employees and, even more so, the C-suite that people look up to?
- » Is the organization focusing on not only the awareness and recognition for a need to change, but also creating desire for the employees to do things differently?

Defining success for future organizations

Many top business leaders and executives raise the question: What will differentiate the good from the great companies of the future? In times of change in the life sciences and healthcare industries, it is critical that we put organizations and their people at the forefront.

While strategies, processes, and business models may differ, one thing that most companies share in common is the relational elements of their employees. As investments in technology, new production, and supply chain infrastructure continue, it is the asset of human capital and the larger organization's commitment to it that will likely determine future success within corporations large and small. 



Pharma Medical Affairs: A Blueprint for Future

Changing customer preferences and a growing need for specialized knowledge are challenging the traditional scope of the medical affairs function. Here are six ways pharma MA departments can drive more collaborative relationships with caregivers

By Robert Groebel

As medicine grows more complex and targeted, healthcare professionals (HCPs) and care teams increasingly rely on medical affairs organizations as a trusted source of information to educate them on the latest therapies. In oncology, for instance, complicated treatments target not only a type and sub-type of tumor but also a specific tumor pathway or biomarker, making it important to establish a close partnership between caregivers and drug providers.

Life sciences companies also depend on medical science liaisons (MSLs) for their scientific engagement with leading physicians to generate, interpret, and communicate feedback throughout the product lifecycle.¹ “MSLs are highly trained scientifically and medically so they can have deep, multi-faceted peer-to-peer discussions with expert

physicians and bring those insights back to the organization,” says Eric Toron, director of global medical affairs operations at Merck & Co. “From R&D to commercial, these insights can shape medical strategy, spark a new clinical trial, or inspire a change in drug delivery.”

The rising importance of MSLs in the industry is reflected in their 12% industrywide growth from 2014 to 2016 and 31% growth in specialty areas such as oncology.² In many cases, MSLs are a physician’s top resource for information on game-changing interventions and play an integral role in improving patient outcomes. “MSLs are considered highly trusted peers. For many rare diseases, MSLs have even greater, more current information than the physician simply because physicians are not seeing patients with

these symptoms often or at all,” says Jennifer Vernazza, director, medical operations and strategy at Sanofi Genzyme. “In these cases, especially, doctors turn to MSLs first for help with a medical inquiry.”

As the industry shifts toward more complex, precision drugs and new generations of HCPs seek deeper collaborations, medical affairs teams must embrace a broader and more data-driven approach. Here are six ways these teams can build a stronger blueprint for collaboration in today’s changing environment.

1. Engage deeper with scientific experts

Only one-third of top physicians or scientific experts are satisfied with their MSL experience.³ One way MSLs can improve engagement is by developing a richer understanding of the individual interests of scientific experts. In the past, companies drove engagement through general data distribution, events, advisory boards, and clinical trials. However, 81% of physicians prefer specific information and are more likely to engage when provided relevant communications through preferred channels.⁴

“MSLs must provide more than just knowledge,” says Vernazza. “The most successful MSLs are excellent storytellers who can present scientific evidence in a way that tells a story about a new product centered on the patient while also nurturing the physician relationship at the same time.”

MSLs who understand physicians’ scientific interests, patients, and therapeutic focus can tailor their interactions. It’s also important to offer clinical evidence that demonstrates the value of new therapies in comparison with existing treatment options. A successful engagement is often based on an MSL’s familiarity with an HCP’s latest research and the ability to align study opportunities to clinical interests. Companies that deliver more useful information will succeed in building more meaningful relationships.

To achieve this goal, medical affairs departments must hire and retain MSLs with a more strategic mindset that takes into consideration corporate objectives and patient needs, while providing scientific value to top doctors. Some organizations are implementing new MSL training programs that focus on how to conduct richer peer-to-peer exchanges with HCPs. Improved training strategies and coaching will help MSLs develop a better understanding of their responsibilities and increase

their performance, all while establishing more credibility in the medical community.

2. Tailor patient-centric data

The overwhelming growth of clinical data require life sciences companies to better align patient-reported information gathered from across different stages of the patient’s journey. A greater understanding of the patient experience throughout treatment, combined with clinical data, allows life sciences companies to better tailor their engagement with HCPs and other stakeholders, including payers. Through the delivery of more meaningful information, including disease knowledge, emerging data, and outcomes, MSLs provide doctors with a greater understanding of new interventions in order to make well-informed therapeutic decisions.

“The insights that MSLs bring back in to the company are critical because they are real-world and happening in real time.”

MSLs can support a life sciences company’s development processes by bringing real-world evidence back from key experts about how different therapies are being accepted by patients. This is particularly important with rare disease therapies that are being fast-tracked through regulatory approval and, therefore, spend less time in controlled clinical settings where data is collected. The ultimate goal is to improve the speed at which

FAST FOCUS

- » The way physicians consume medical information is evolving, with many embracing the convenience of digital channels that provide content on demand. Reportedly, by 2025, only 13% of oncologists will be baby boomers who prefer face-to-face engagement with medical science liaisons (MSLs).
- » There is a growing recognition of the need to hire and retain MSLs who have a more strategic mindset—focused on balancing corporate objectives and patient needs, while providing scientific value to top doctors.
- » Some pharma companies have instituted new MSL training programs and coaching strategies to foster deeper peer-to-peer exchanges with doctors. Some are also emphasizing increased real-time response; for example, creating libraries of information that are tagged to help MSLs quickly answer questions, and an online portal staffed by medical information reps and MSLs.

Growing Knowledge Interchange

Past	Present	Future
<ul style="list-style-type: none"> • HCP was the key stakeholder • Traditional communications channels • Competition: other branded agents 	<ul style="list-style-type: none"> • Payer/budget holder influence is increasing • Multichannel approach to communication • More complex science 	<ul style="list-style-type: none"> • Broader spectrum of healthcare decision-makers • Patient as influencer • Health economics outcomes research and real-world evidence increasing complexity of choice

Figure 1. MSLs will develop relationships with a broader range of stakeholders through varied channels.

Source: Veeva Systems

emerging data and evidence translates to clinical practice.

“The insights that MSLs bring back in to the company are critical because they are real-world and happening in real time,” says Vernazza. “The goal is to share these insights with other parts of the organization like R&D, market access, and commercial, but much of it is done manually. This process is starting to evolve, and becoming more automated and more structured with the help of new technologies.”

3. Provide real-time response

Rather than distributing new drug information to doctors through engagements that may or may not be relevant to their current patients, medical affairs teams must become more responsive to specialty therapeutics-related inquiries from leading physicians. Considering MSLs as trusted sources of information on complex drugs, doctors contact them directly instead of waiting for the next introduction of information. “MSLs have their top doctors’ personal cell phone numbers and receive calls all times of the day and even into the evenings,” explains Vernazza.

Medical affairs are starting to build new competencies to expand therapeutic area and health-economic knowledge and address inquiries with timely responses that align with specific stakeholders. For example, some companies have created libraries

of information that are tagged to help MSLs quickly answer questions. One pharmaceutical company is building reactive decks based on frequently asked questions that MSLs can access to present more focused presentations or provide better answers to questions.⁵

Another pharma organization recently created an online portal staffed by medical information reps and MSLs to immediately answer physician inquiries. By leveraging inquiries captured across engagement channels, organizations can create more meaningful content for future engagements.

4. Adopt better communications technology

By 2025, only 13% of oncologists will be baby boomers who prefer face-to-face engagement, while the remaining 87% will consist of younger generations that prefer multichannel and remote engagement.⁶ Even today, many doctors prefer mobile and interactive platforms.

To better collaborate with newer generations of physicians in their preferred communication modes, MSLs must become more adept with an expanded set of technology solutions. Technology also makes it possible to reach geographically disperse care teams that are difficult to meet face-to-face. Online meetings, webinars, chats, and events enable the distribution of timely information to

global locations. These additional options give organizations an edge as they compete for the attention of HCPs.

Technology also helps with proper timing of engagement. For example, companies could leverage de-identified claims data to deploy MSLs in real time. Claims data shows that a diagnostic test has been ordered, signaling a potential rare disease patient in the doctors’ office—an MSL could engage at that time and add even greater value and relevance to the physician relationship.

5. Broaden collaboration among different stakeholders

Precision medicine requires engagement with more than just key physicians, driving MSLs to capture insights from a broader array of stakeholders (see Figure 1). For example, MSLs can provide information to payers on the economic impact of diseases and the progress of their therapies to address them. They share information with patients and patient advocacy groups. Many MSLs work with oncology nurses to learn greater details about the patient’s experience with a drug or chemotherapy. Developing relationships with all critical stakeholders expands therapeutic knowledge and insight-oriented discussions throughout the changing scientific landscape.

Some organizations are establishing a new, specialized role in medical affairs called Medical

WE MAKE IT EASIER FOR YOU TO CHANGE LIVES

For patients, the best technology belongs in the background. We make it a little bit easier for people to participate in a trial, and for sites and study teams to run one. That way, patients provide the life-changing insights your research deserves - and simply move on with their day.

[PATIENT DATA] [PATIENT EXPERIENCE]

[CLINICAL SUPPLIES] [ENDPOINT QUALITY]



Outcome Liaisons (MOLs). Medically trained like MSLs, MOLs bring scientific expertise to conversations with the payer market—including formulary committees and managed care organizations. “This strategy is especially valuable in therapeutic areas where there is less medical knowledge about certain indications,” says Vernazza. “With many rare diseases having just a few thousand patients, formulary committees need to be educated on the disease as well as the therapeutic intervention and competitive differentiators.”

“The industry must adopt solutions that directly address the unique needs of medical affairs teams, incorporating more advanced insight-driven data analytics and new digital channels.”

6. Consider the impact of artificial intelligence

A recent industry survey shows nearly half (44%) of life sciences professionals use or experiment with artificial intelligence (AI) technology and 94% expect to increase use within two years.⁷ With the exponential growth of scientific data, organizations leverage AI to more rapidly and accurately analyze large volumes of data to understand trends, identify new insights, and make recommendations for next-best actions. AI also automates the optimal use of data and can draw new understanding from previously siloed information to improve decision-making and generate more actionable insights.

For medical affairs, AI presents an avenue to learn about leading physicians and other

stakeholders in a more granular way by revealing actions, evidence, and insights in real time. For instance, AI can serve as a virtual mentor in guiding MSL engagements by making suggestions on the next best message or channel and right evidence for MSLs to use for specific individual specialists.

Further, AI will provide more structured insights—something often lacking in medical affairs organizations—to improve strategy. With AI, medical affairs have the opportunity to create a critical competitive advantage

today while developing a structure for future efforts in an ever-complex healthcare landscape.

“New AI technologies will automatically deliver actionable insights to MSLs,” says Vernazza. “It will also be able to quickly combine those insights with other data and external data, bringing it all together so we can take a more holistic look at the needs of the patient and the needs of the doctor and serve both better. It’s the next evolution and it has the potential to be revolutionary.”

High expectations

As the life sciences industry recognizes the need for new competencies, technology solutions, and data sources to support better patient outcomes, MSLs will play a more critical role. Like-

wise, physicians will continue to increase demands on medical affairs teams for more real-time and detailed information in their preferred communication channels. To effectively meet the industry’s growing expectations, medical affairs must evolve current business processes to support future models for success.

“These changes are only going to accelerate,” says Toron. “The industry must adopt solutions that directly address the unique needs of medical affairs teams, incorporating more advanced insight-driven data analytics, new digital channels, and automated information sharing.” **PE**

To learn more about the challenges and opportunities facing medical affairs leaders, read the “Medical Affairs 2025” report (<https://bit.ly/2HR7zox>), written in conjunction with leading life sciences companies.

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The Argument for External Comparator Adoption

Its use, new data shows, could boost the economic benefit profile of more “common” drugs—and better inform payer decisions

The practice of using external comparators for regulatory approval and health technology assessment (HTA) agency decision-making has long been the norm in the rare disease drug space. However, there is increasing evidence that comparators are also becoming more important in regulatory and payer decision-making in other circumstances.

Expanding definition of external comparators

External comparators, also sometimes referred to as “synthetic control data,” are used to provide context to a single-arm study where it would be impractical or unethical to design the study with a placebo or active comparator arm. External comparator data is any data generated from patients external to the parameters of the parent trial that can be compared to the outcomes of a clinical trial. The comparison could be conducted as an unanchored, indirect comparison requiring patient-level data or a real-world benchmark where no adjustments or simulation is made at the patient level. The type of data used will depend on what data is available, as well as the intended audience:

- » Real-world data (RWD) can be used to provide context on outcomes without direct comparison with trial data. It can include data from existing sources (e.g., registries, electronic medical

records, chart reviews, claims). It can also include new RWD collected prospectively outside of the trial setting.

- » Placebo or other treated group randomized controlled trial data from other clinical trials.
- » Datasets created from review of published literature.

Some of the change in how external comparators are applied is being driven by the increasing use of genomics and personalized medicine in drug approval pathways. In many of these circumstances, we are essentially creating new “rare” diseases out of more common conditions by creating biomarker or genomic subsets. We are seeing this most frequently in the oncology space, although the expectation is that this will become the norm in other therapeutic areas as well. This subsetting of patients creates the same pressures faced by rare disease research, where the only practical study design for ethical and practical reasons may be a single-arm study.

The conditions are right for external comparator adoption for other reasons as well. In addition to richer and more longitudinal RWD becoming increasingly available, we know regulators and payers are looking for application of RWD to answer research questions.

There have been increasing signals from regulatory bodies that this data is helpful in their

decision-making, although no formal policy statements have been released. Similarly, HTA bodies have not established formal policies or direction on their use of external comparators in their decision-making. However, recent analysis of historic HTA decision-making shows a correlation between the increasing use of external comparator data and positive decisions.

HTA impact: Historical perspective

A 2019 review of HTA decision-making in the past 10 years using IQVIA’s HTA Accelerator provided insights into payer decision-making—and supports the idea that external comparators are useful to HTA bodies when making reimbursement determinations for a particular medicine. Data scientists extracted and aggregated information and datasets from HTA reports of more than 100 agencies in 32 countries across all therapeutic areas.

A recent review of the available data, led by Dr. Dony Patel of IQVIA, identified 165 single-arm clinical trial submissions to HTA bodies between 1996 and 2018. The first instance of external comparators submitted with these single-arm studies was identified in 2011, and a year-on-year increase was observed, largely focused in oncology.

The analysis identified 44% (72/165) of single-arm submissions made with some form of an external comparator to give context to clinical and/or economic benefit of the product under consideration. Of those who submitted with this comparators data, we observed a 67% (48/72) positive recommendation,



BARBARA ARONE is Vice President, Business Operations Center for Advanced Evidence Generation at IQVIA

as compared to 55% (37/67) in studies where the data was presented without this contextual information.

This indicates the importance of showing clinical/economic context and benefit to aid in decision-making. However, it is important to recognize that the nature of HTA decision-making is based on many different inputs and factors, and a review of HTA decisions demonstrates that the quality of the external data provided, along with the applicability of the analytical method, were important considerations.

Forward-looking application, challenges

There is currently no formal guidance for the use of external comparators to contextualize data for single-arm trials in regulatory and HTA submissions. And the process of selecting the right comparator is challenging because it can be confounded by changing standards of care regionally and over time. For example, a data source may be available but may ultimately be determined to be of insufficient relevance for the product and therapeutic area at hand.

Review of past HTA decisions regarding the indication can be helpful when selecting external comparators; however, the most critical input will come from the HTA stakeholders themselves, preferably as part of an early engagement process. If it is determined that an external comparator will be helpful to decision-makers, the next steps are selecting the right comparator for the target market and determining how to source the data. Here, final decisions must consider the correct methodology

for comparing this data to that of the clinical trial.

Understanding HTA familiarity and comfort level with these approaches will help with these decisions, and the industry's knowledge will grow as more submissions resulting from these decisions reach the conclusion of

the regulatory process. Continued analysis and understanding are needed while waiting for formal guidance.

Future direction from HTA and regulatory bodies

In the absence of current guidance on external comparators, there is acknowledgement that new trial designs will produce new types of evidence, which will eventually become part of the HTA value dossiers. In a series of interviews of UK-based HTA experts documented in "The Future of Precision Medicine," an article by James Love-Koh et al. published in the December 2018 issue of *PharmacoEconomics*, it was noted that the increased sub-setting of patients and the subsequent increasing complexity in treatment pathways will likely raise the need for additional sources of evidence for HTA consideration.

While the environment for the development of that data is maturing, there is a lack of impetus on the part of most bodies for establishing the appropriate use of this data. There is some

hope that newer legislation and regulations, as well as increasing standardization and usage of RWD in the coming years, will help fill the data usage gaps.


In these interviews, there was also open acknowledgment that observational data (registry, cohort studies, electronic health

The increased sub-setting of patients and the subsequent increasing complexity in treatment pathways will likely raise the need for additional sources of evidence for HTA consideration

records) will increase in usage and utility in the next 10 years and be used more consistently in HTA decision-making.

The use of this data requires that the correct statistical and technical acumen be applied to control for the unique challenges of data and information collected for other purposes, including controlling for selection bias and confounding.

Industry focus: Build on the positive

We fully expect that HTA bodies will release direction on external comparators in the future. Until that time, biopharmaceutical manufacturers can use the increasing examples of positive decisions associated with external comparators as their guide. Selection of the appropriate data source and methods for analysis will be critical to maximizing the value of external comparator data to support access and pricing discussions with HTA bodies. Continued review and observation of HTA decision-making will add to our understanding of this quickly evolving space. 

Site Payments: Drilling in on Forecast, Budget Issues

Repurposing existing technology to alleviate traditional ‘pain points’ in ensuring clinical investigator payments transparency

Site payments comprise approximately half of each clinical trial budget. That makes them an obvious target for managing study risks, costs, and timelines. It also means life sciences financial managers need reliable payment forecasting for setting development priorities and helping to ensure their business’ success. Given the complexities of clinical trials, however, accurate updating of actual (incurred to date or inception-to-date) and forecasted site payments for real-time reporting remains one of the largest challenges in medical product development.

A complex business

Many factors confound payments transparency. Clinical trials evolve continuously, and each adjustment to the protocol, work order, or vendor mix requires new budgeting and forecasting. The larger and more complicated the study, the greater the variance in contracts, transparency requirements, procedure fees, currencies, and more exists across sites and countries. Patient enrollment, enrollment timing, site performance, and

activity costs vary by site, often quite markedly. Much of the input that determines payment status, such as *ad hoc* invoices from the sites or approvals from the project team, depends on human schedules and discipline. As suggested by the “challenge boxes” in this article, an infinite range of activities beyond the financial manager’s expectations or control can affect payment projections and cash flow.

Even though thousands of data points are generated in clinical studies, investigator payment forecasting currently relies on highly simplified inputs. That is, financial and project managers—whether with the biopharmaceutical sponsor or contract research organization (CRO)—primarily work with budgeted, in process, and actual payment amounts.

Adding to the challenge is that sponsors, CROs, and other payments vendors manage payments and forecasts via manual systems. Whether using spreadsheets or online fill-in-the-blank software, these are time and labor intensive processes, highly prone to errors, and inflexible.

Delayed, incorrect, or confusing payments can alienate study investigators and site staff and increase the risk of missed timelines and budgets. Unhappy investigators also are less likely to participate in future studies or, possibly, to recommend the launched product to patients or peers.

Manual tracking also makes payment forecasting time consuming and, thus, costly. Syneos Health estimates that manual forecasting takes four to 20 hours per study depending on the forecast granularity and the study complexity (e.g., number

Challenge – Unexpected External Event

Britain passes referendum to exit the European Union, undermining exchange rate projections for current and planned clinical studies with sites in the UK.

of countries, sites, and patients; number and variance of *ad hoc* costs; screen failure rates; therapeutic area; etc.).

Despite the challenges, the stakes could not be higher, especially for small pharmaceutical or biotechnology companies with limited resources. Unexpected fluctuations in costs or costly mistakes in payments can severely hamper such companies’ cash flow. Perhaps more devastating are delays in information that may enable the financial manager or project management team to resolve study risks ahead of delays or cost overruns.

The need for a more timely and precise site payment solution is driving development efforts among sponsors, CROs, and niche software providers. Their collective goal is a solution that will automate the payments

Challenge – Incorrect Assumptions

Original study plan inadvertently omitted two study procedures, and the mistake was not corrected in the project budget or original payment forecast.

SHAUN WILLIAMS is Executive Director, Investigator Management Solutions, Syneos Health

process to manage complexities such as currency exchange, transparency reporting (e.g., the US-mandated Sunshine Act), financial reporting across borders, contracting party issues, and value-added taxes. Automating as much of the process as possible will reduce manual effort and minimize human errors.

A better system

Using technology that is already available, the ideal forecasting solution would harness the full power of each study's data. The tool would draw critical information from all of the study's or portfolio's data systems—at the CRO and, where possible, from the sponsor. This “big data” or “data lake” would be agnostic to data sources and repurpose information already ingested and integrated as a common data model/dataset.

As noted, accurate payment forecasts depend on input from the full project team and clinical trial landscape, rather than just the invoices in the processing queue. A tool that enables financial managers to adapt quickly to all factors affecting site payments could significantly reduce study costs, timelines, surprises, and “re-work.” Such factors include change orders, protocol amendments, delays or surges in enrollment, partial data entry, manual invoices, and more.

A forecasting tool that processes granular site-level detail and uses the actual negotiated clinical trial agreement (CTA) rates for each site could enable financial managers to dial in on exact costs. This contrasts with the use of blended country rates in manually computed forecasts. Beyond delivering highly accurate budgets, this development could enable financial managers to shift funds to initiate or expand other studies in the sponsor's pipeline.

Challenge – Ad Hoc Surprises

A study patient has an unanticipated need resulting in a hospital stay and costs significantly beyond the study budget.

Similarly, with the addition of an *ad hoc* cost management functionality, forecasters could capture the limits or maximum amounts that sites can invoice for *ad hoc* costs. Managing these costs would facilitate more predictive modeling, especially for worst-case scenarios.

Streamlining use of the data lake for current payments and forecasting would enhance accuracy

Challenge – Fee Variances

Different sites in the same country charge vastly different rates for the same procedure – a nuance not fully accounted for in an averaged procedure cost.

in revising budgets and forecasts as the study evolves. It also could shorten forecasting time from up to 20 hours in highly complex studies for manual forecasts to minutes with the forecasting tool.

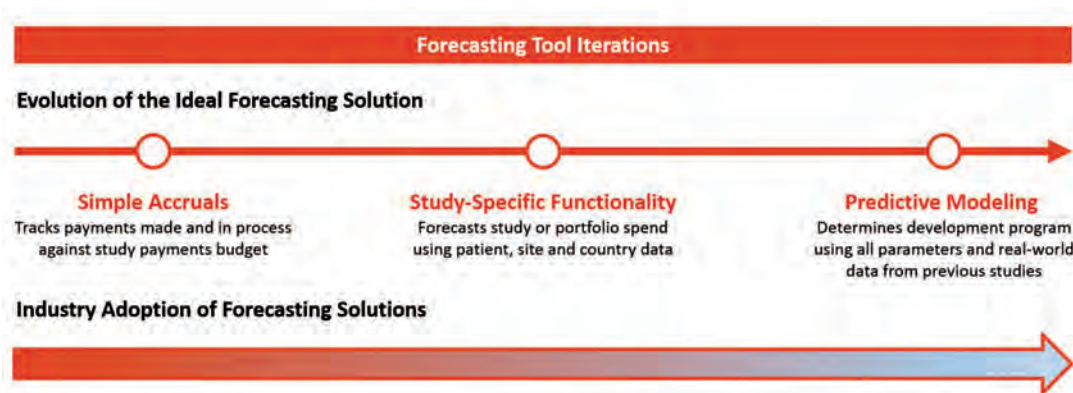
Even though thousands of data points are generated in clinical studies, investigator payment forecasting currently relies on highly simplified inputs

Beyond keeping the payments forecasts current with changing study parameters, an ideal forecasting tool would enable sponsors or CROs to identify potential financial and operational gaps in study performance. Further, it would combine enterprise-wide data for modeling future estimates. Stated another way, this forecasting solution would be a vehicle for continuous improvement from study concept through closeout.

The next horizon

This article has focused on payments forecasting for current or planned drug development studies. But what does the future hold for this capability? A more advanced forecasting tool opens several new horizons. It could be expanded for full-spend forecasting for each study or program. It might be used post-study to analyze site cost and performance data, for example, to inform future site selection, site mix, and contracting decisions. Using that information, sponsors could maximize enrollment at the lowest-cost sites.

By incorporating artificial intelligence (AI) technology, payments forecasting would evolve to power predictive modeling. That is, pharma and biotech executives would be able to harness vast historical study phase and therapeutic area data to quickly compare and contrast a broad range of potential development pathways. By quantifying the actual and opportunity costs of each possible



combination of studies toward product approval in competing regions, financial officers will help drive enterprise success through the ideal forecasting solution.

Today's change drivers

As mentioned, the acute need for better forecasting is spurring innovation from stakeholders across the life sciences industry, including CROs. Companies in this space are well positioned to design and deliver the payments forecasting solution that fully supports sponsors' business goals. They can bring process and clinical development expertise not offered by specialty software developers. At the same time, CROs are acutely accountable for delivering high quality clinical study data on time and on budget. They are able to leverage project team, study, and industry data, and portfolio governance for more comprehensive forecasting and project insights.

CROs also offer the tools and motivation to develop the most pragmatic and consistent payment-forecasting solution.

It is important for drug developers to look to CROs that prioritize investigator payments within their full-service and functional service provider (FSP) operations. For example, is the CRO's investigator payments team a standalone business unit? Does it have dedicated staff specializing in site payments, transparency reporting, and payment forecasting? Will each study have a designated

investigator payments specialist as part of the CRO's project team, and will that individual interact with the sponsor from project award through study duration?

By quantifying the actual and opportunity costs of each possible combination of studies toward product approval in competing regions, financial officers will help drive enterprise success

Another critical filter is whether the CRO's site payments function supports the organization's mission. A CRO that focuses on and is known for its site relationships will make site payments a critical component of its operations. Such a CRO will have a better chance at delivering the solution sponsors need, because it shares the same pain points and its success is dependent on accurate and timely forecasting, too.

Making it happen

Investigator payments and payment forecasting have long been a pain point for biopharma companies, sites, and CROs. The industry has the technology and tools to deliver payments and payments forecasting accurately and on time. Once put in place, the ideal forecasting tool will enable financial executives to manage strong performance in the near term—and to deploy powerful and effective predictive modeling capabilities going forward. ^{PE}

Challenge – Protocol Amendments

A protocol amendment is implemented after site contracts are negotiated, substantially increasing the site payments budgets and the need for close communications with the sites.

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A Critical Juncture for Antibiotic R&D

In a 2016 analysis of the deepening health threat posed by antimicrobial resistance (AMR), economist Jim O'Neill predicted that by the year 2050, the number of deaths resulting from AMR will overtake those caused by cancer. Recommendations from O'Neill on combatting the crisis aligned with governmental bodies, medical societies, health charities, and public health organizations. They include awareness campaigns about the inappropriate use of antibiotics; incentives encouraging development of truly innovative antibiotics and new diagnostics; a focus on antibiotic stewardship across health settings; and a sharp reduction in the use of antibiotics in agriculture.

While AMR is a priority issue on the political agenda and in healthcare policy, there is a lack of tangible momentum in the development of new antibiotics. If you define a new class of antibiotics as one that hits a new target, there has not been a new class developed for nearly two decades. Instead, we have seen analogues of existing classes that generally offer only incremental improvements over existing drugs.

As AMR began to become a major issue, hospital antibiotic stewardship programs took a critical look at what drugs should be used, how quickly, and for which patients. Stewardship committees began to debate whether new antibiotics were worth the cost. Payers favored generics, and because the antibiotics were analogues developed in non-inferiority trials, drug companies often

didn't have the data to make an argument of sufficient differentiation in support of higher pricing for new therapies.

While blame for the malaise that has dogged antibiotic development can't be attributed to a single source, the entire healthcare ecosystem now has a responsibility to pull together to deliver progress. The key to the revival of this sector and finding solutions to AMR lies in innovation: scientific, medical, marketing, financial, and regulatory.

In order to reintroduce innovation to antibiotic development to address the AMR crisis, "push" and "pull" initiatives have been instituted. Push incentives include public research funding; pull incentives are commercial enticements that better guarantee a return on the substantial investment required to bring a drug to market. We are seeing some success with push incentives that provide funding for antibiotic discovery and development, but less progress with pull incentives that will help bring new ones to market.

The economics of bringing new compounds to market remain very challenging for investors, so many have shunned the space in favor of more profitable areas of drug development. The same is true for the pharmaceutical industry—today, only two big companies are still actively involved in antibiotic development. However, there are a number of smaller firms working to develop completely new-mechanism, targeted antibiotics. If we can develop the agent so that it can demonstrate superior clinical outcomes for the patient, we can also

drive down costs for governments and healthcare systems.

Prescribers may be unintentionally shutting down pathways to innovations that will help usher in new drugs and lower costs. Doctors may have fallen into the habit of prescribing antibiotics that may be inappropriate, and hospitals move slowly in reviewing treatment guidelines—typically every five years, which is far too long for novel drugs to be introduced into the hospital system.

The healthcare system also needs to consider the long-term health economics of antibiotic prescription. Paying more for a new-mechanism antibiotic upfront makes sense if it can improve patient cure rates and lead to a reduction in the burden on healthcare systems and the associated expense further down the line.

Scientific advances are making the discovery of targeted antibiotics possible. For instance, genetic modification and next-generation sequencing of bacteria have accelerated drug discovery. This progress, coupled with the rise of rapid diagnostics to identify the bacterial cause of an infection, mean that highly targeted, new-mechanism drugs could be available to kill specific bacteria, providing new front-line therapies for patients. Existing broad-spectrum agents can then be reserved for difficult cases. This could also result in a reduction in AMR.

We're now at a critical juncture. Push and pull incentives are required and the industry needs to demonstrate how innovation in antibiotic development will lead to patient benefit and economic reward. We have a unique opportunity to revive the engine room of antibiotic development to bring wider medical and societal benefits—let's not miss it. **PE**



DAVID ROBLIN is Chief Medical Officer and President of Research and Development at Summit Therapeutics

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When Emmanuel Macron's 'La République En Marche (LaREM)' movement defied the odds to capture the presidency and national assembly back in May 2017, it readily became apparent that the pro-business administration would be supporting innovative pharma and attempting to reinvigorate the country's competitiveness and global reputation for pioneering breakthrough medical science. "We consider life sciences both as a dynamo of technological advancement and host of some of the great emerging high value-added industries of the future ... It is precisely for this reason that we have elevated the sector as one of the centerpieces of our new national industrial strategy," affirms Minister of Economy and Finance, Bruno Le Maire.

Many industry actors appear suitably charmed. "After several years in which French pharmaceutical production and R&D had frankly been losing pace relative to many of our peer markets, I and my members salute the renewed spirit of reform that drives and infuses the incumbent government," declares Jean-Luc

Bélingard, president of the French Federation of the Health Industry (FEFIS) and former CEO of French IVD icon bioMérieux.

Such sentiment is hardly unfounded. France's USD 65 billion life sciences market is now squarely back on the radar of the international investor community with multinationals like GSK, Novartis, Merck and Aspen all proceeding with big-ticket investments and EY calculating that overall FDI has increased 31 percent within the space of only a year. In May 2019, France even entered the top five of US management and consulting firm A.T. Kearney's annual Foreign Direct Investment Confidence Index, beating China in the rankings by two places. At the same time, the local innovation ecosystem seems to be flourishing once again with the association, France Biotech, identifying some "386 drug candidates in clinical development last year, over 720 in-country biotechs and average R&D investments per firm coming in at an admirable EUR 9 million (USD 10.1 million)."

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What is subsequently becoming clearer, however, is that even more profound changes are afoot and that the Macron life science vision actually entails a wholesale reconfiguration of the fundamentals of healthcare provision. This means radical upheaval for the entire value chain, encompassing medtech, generics and even contract manufacturing. “If some people imagined that we were simply going to be tinkering about the edges and contenting ourselves with just a handful of memorable soundbites or cosmetic modifications, then they are in for quite a surprise... we mean genuine, root and branch reform,” confirms Minister of Health and Solidarity Agnès Buzyn.

PLUCKY CHAMPIONS

If any further evidence was needed for the newfound feel-good factor sweeping French innovative pharma, one only needs to consider the rising fortunes of the country’s iconic mid-cap biopharma standard bearers that form part of G5 Santé, a club of companies altogether contributing some EUR 4.5 billion (USD 5 billion) worth of turnover to the home market and more than 46,000 jobs. Many of these medium-sized, national champions – such as Servier, Pierre Fabre and Ipsen – have been ratcheting up a gear and launching bold new strategies to assert themselves internationally.

Servier currently finds itself in the midst of a strategic reorientation. By focusing on oncology, notably through the acquisition of Shire’s oncology arm last year, the company hopes to propel itself to further success in some of the world’s most prolific pharma markets. Group president, Olivier Laureau, notes that, “growing our oncology franchise constitutes the focal thrust in a strategy that we outlined four years ago. We are confident and hopeful that our future oncology revenues will ultimately be on par with those from cardiovascular – which still represents over 50 percent of our sales.”

He continues, “the acquisition of Shire products enabled us to enter the US market, a key milestone in our ambition to spread our global presence. With these integrations we now can lay claim to commercial operations in 149 countries around the world and are planning to quickly add Japan to that list as well.”

Servier’s status as a privately-owned entity means that it faces financial limitations compared to its publicly-traded competitors so Laureau is shrewdly banking upon specialization as the keystone of any future success. “Within each of our therapeutic areas, we have chosen to become extremely specialized on either a therapeutic mechanism or on particular pathologies so as to eke out better use of our finite resources,” he explains.

To continue this growth push, Laureau highlights the importance of finding a new asset. “The next critical step is to identify another molecule, whether in oncology or



Bruno Le Maire, Minister of Economy and Finance; Agnès Buzyn, Minister of Health & Solidarity; Frederique Vidal, Minister of Higher Education, Research & Innovation

immuno-oncology. This could be a US or global license and we are looking for a product either in late stage or already on the market. It can be an item for small targeted populations and we are very open on how we bring in the product; either via acquisition, licensing, or partnership,” he conjectures.

Ipsen, in the meantime, has been undergoing its own transfiguration that commenced with the Beaufour family’s unprecedented announcement that they were opting for their first ever non-French global CEO in a desire to launch the company on a bold new growth path fit for the next generation of medical science. This entails accelerating the de-

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Flagship Tenets of 'Ma Santé 2022'

- Reinforcing the Supply of Care: Health insurance credits to increase by 2.5 percent and a budget of EUR 3.4 billion (USD 3.8 billion) ring fenced for implementation of the overall plan.
- Reconfiguring the Territorial Organization of Care: Deployment of 1,000 Territorial Professional Health Communities (CPTS) and the rebranding of 500 to 600 clinics as 'Hôpitaux de Proximité' (local hospitals) dedicated to general medicine, geriatrics, rehabilitation and follow-up care. Repopulation of 'medical deserts.'
- Restructuring the Functions of the Practitioner: The creation of a single status as a hospital practitioner and introduction of 4,000 'medical assistant' positions with a view towards discharging physicians from many administrative and generalist tasks.
- Revised Financing Models: Dismantlement of funding silos and introduction of fixed-price financing that covers the entire care continuum and valorizes care pathways and the overall patient experience.
- Digital Transformation of the Health System: Reimbursement of telemedicine by the 'Assurance Maladie,' dematerialization of prescriptions and medical data sharing across the entire health apparatus.

development of a specialty care pipeline through a focus on mid-stage assets and innovative deal structures, and pivoting the geographic footprint more towards 'power markets' like the US and China.

"At the very outset, we were very clear in our minds that we needed to unleash a profound and ambitious overhaul right at the heart of the company that would equip Ipsen to face the future with zeal and confidence," recounts American born global CEO, David Meek.

One of the most eye-catching elements of Ipsen's R&D restructuring thus far has been Meek's absolute insistence on the concept of 'open innovation' whereby the firm is "completely agnostic as to where the innovation comes from."

Pierre Fabre's blueprint may be a little different, but again centers upon ambitious internationalization. "We will reach EUR three billion (USD 3.36 billion) in revenues by 2024 with 70 percent of the total generated outside France, compared to 63 percent today... Even though we are based in a small city in France [Castres], we are adamant that our future growth clearly lies abroad, affirms global CEO, Eric Ducournau.

Audacious partnerships are very much the order of the day. "In the pharmaceutical division, we have struck a landmark deal with US biotech Array BioPharma for the development and commercialization of a combination therapy against melanoma and colorectal in Europe and other



Olivier Laureau, group president, Servier; Eric Ducournau, CEO, Pierre Fabre; David Meek, CEO, Ipsen

countries, excluding Japan, Canada and the US... Unlike the largest pharmaceutical companies, Pierre Fabre had honestly been slow to shift to an innovation-driven model. In order to close the gap, we have established milestone partnerships with exciting biopharma companies such as Array and Puma BioPharma," he confirms.

So too is the company reasserting its innovation credentials. "Generally speaking, our focus is on enhanced medicalization," says Ducournau. "Our expertise is reflected in the fact we stand proud as the only cosmetics company able to regularly publish clinical results for all our products in the most prestigious medical publications in the field... Strong R&D capabilities are a prerequisite to medicalize our product portfolio. This is the reason why we invest considerably more in R&D than our competitors with roughly five percent of revenues from our dermo-cosmetics business line being invested in R&D."

MA SANTÉ 2022: REDRAWING THE LANDSCAPE

It is potentially in the healthcare arena, however, where the full brunt of reform fever will end up being most felt. This could, in turn, translate into unprecedented change for the medtech industry. In November last year, Health Minister Agnès Buzyn finally raised the curtain on the government's 'Ma Santé 2022' reform package, which strives to "catapult France into a brave new era of enlightened and rationalized public healthcare provision."

"At the top of the agenda is an attempt to move away from the reimbursement scheme of the past and develop a strategy for financing which is more adapted to the patient journey in the sense that reimbursement will be structured as a single envelope rather than individualized packets for each piece of care," explains Marc-Alexander Burmeister president of B. Braun. "This will have the effect of dramatically remodeling our customer structure from how we know it today. It will be a real game changer... Actually I'm not aware of any plan as radical as this anywhere else in Europe," he marvels.

Bertrand L'Huilier, president of Smith & Nephew perceives this situation to be the logical culmination of a



The ATU: An Accelerator to Innovation Absorption

France's much-loved early access mechanism, the Autorisation Temporaire d'Utilisation (ATU) is often credited with enabling patients with unmet needs to receive latest generation innovative therapies. Signs that policymakers are seriously contemplating extending the ATU to second and third indications will thus be music to the ears of both originator drug developers and patients alike.

"The existence of the ATU is undeniably a key strength of the French system that is envied by many of my counterparts in other jurisdictions. Patients clearly benefit immensely from fast-track access and it is one of the fundamental reasons why the market is so attractive to a young, ambitious firm like Jazz Pharmaceuticals focused on converting biopharmaceutical discoveries into novel medicines. In fact, the entirety of our novel hematology-oncology therapies are benefiting from the procedure," discloses Franck Cousserans, general



Franck Cousserans, general manager, France & Belgium, Jazz Pharmaceuticals; Brigitte Calles, general manager, Ferring



manager for France, the Benelux and Iberia.

"French patients are certainly advantaged by the ATU, but it is not always the case that the mechanism is as swift as you might imagine: there are instances of medicines being registered through the ATU system that spend over 500 days in negotiation," remarks Ferring's general manager, Brigitte Calles.

Luckily, however, there exists specialist service providers equipped to assist drugmakers with navigating the process. Intsel Chimos is a case in point. "We have the capability to manage the entire process: we offer an A to Z solution for our clients, which is particularly important in a market like France, which is perceived to be very difficult to enter. In fact, of the approximately 250 products per year in France benefiting from ATU status, we handle some 25 to 30 percent," proudly recounts company CEO, Finn Søndergaard.



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Marc-Alexander Burmeister, president, B. Braun; Bertrand L'Huilier, president, Smith & Nephew; Stéphane Regnault, president, Vygon.

trend that has been fast gathering pace. “Two years ago the position of many players in the medical device industry was that the purchasing decisions would always lie in the physicians’ hands. However, recent events have demonstrated this not to be true. While, in the past, we adopted the classic sales model of the medtech industry – which can best be described as ‘try it and if you like it, buy it’ – we anticipate this as gradually becoming obsolete. Instead it is increasingly essential to take into account a healthcare provider’s overall KPIs and to approach the sale more in B2B mode,” he opines.

The new rules of the game will not just bring threats but fresh opportunities as well. “Right now it’s almost impossible to measure the cost of treatment for one patient of one disease across the entire value chain, which renders the switch over from volume to value-based pricing notoriously tricky. One of the overarching goals of Ma Santé 2022 is interestingly to establish a process from which this figure can be extracted and this will open doors to those medtech players and tech integrators with the capabilities to really improve healthcare management,” adduces Stéphane Regnault, president of the second largest domestic medtech player, Vygon.

The reforms will likely unlock new avenues for risk sharing as well. “There is a conscious acknowledgment to try and contain the estimated 30 percent of treatment actions in hospitals that are considered useless or redundant. Already there have been some preliminary trials to analyze the impact of transferring risk to healthcare providers. The logic is to flip over from fee-for-service to pay-for-performance,” exclaims Claude Le Pen, healthcare economist at IQVIA.

MEDTECH: BRACED FOR A SHAKEDOWN?

Some industry insiders are suggesting that the medical device sector might have difficulty adjusting to the new paradigm. “The announcements made by the French authorities about a comprehensive shift towards focusing on patient pathways, a more universal reimbursement scheme, and increased caretaker integration are all very positive steps, but this is all occurring in conjunction with swingeing cuts

FRENCH MEDTECH INDUSTRY SNAPSHOT



Turnover total
EUR 28 BILLION



Turnover from exports
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to the social security budget,” decries Philippe Chêne, president of Winncare. “We detect a blatant lack of coherence in France between short-term and long-term approaches to the overall health strategy: the current goals of decentralizing health provision, developing ambulatory surgery and rationalizing care pathways are all at odds with attempts to squeeze the margins of the very medtech players that are striving to facilitate fresh approaches like home care and patient autonomy,” he warns.

Eric Le Roy, director general of the national syndicate of the medical technology industry (SNITEM) wholeheartedly concurs. “Budgetary pressures risk thinning out the medtech SMEs and consequently harming the sector’s offering,” he counsels. “We want to draw attention to the underlying unfairness of the fact that an industry responsible for less than one percent of expenditure is now being called upon to contribute to ten percent of economic cuts,” he asserts.



Eric Le Roy, director general, SNITEM;
Philippe Chêne, president, Winncare



“Our fear is that the drastic price slashing that hitherto afflicted the pharmaceutical industry is now about to hit medtech as well,” regrets Chêne. “Drug developers were generally able to balance the damage and reduce their risk exposure by leveraging their strong international presence. In medical devices, however, over 90 percent of the French sector comprises SMEs with predominantly local footprints. As a consequence for us, France today is not about growing, but rather managing profitability. Winncare possesses 200 employees in France and a majority of the group’s manufacturing base is in-country. The real question we are thus facing is not so much should we stay in France, but can we stay?” he wonders.

“Margins are thin: France already stands out as having some of the lowest prices for medical equipment in Europe and yet we see our clients, the hospitals, asking for ever-more integrated and sophisticated solutions in optimizing their organization. There is a contradiction between rising demand and depreciating reward. The big conundrum for

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The Advent of 'Deep Learning'



François Vorms,
managing
director, **Canon
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Canon Medical Systems has been blazing new trails by successfully equipping Dijon's University Hospital with a first-of-a-kind-in-Europe, Aquilion ONE™ / GENESIS Computed Tomography scanner that incorporates artificial intelligence capabilities. "We are immensely proud to have managed to become the first player to introduce to the French market an AI solution which utilizes deep learning rather than just machine learning," explains managing director

François Vorms. Machine learning uses algorithms to parse data, learn from that data, and make informed decisions based on what it has learned. Deep learning, by contrast, structures algorithms in layers to create an "artificial neural network" that can learn and make intelligent decisions on its own. "The value addition that this delivers is that the hospital will now be able to perform a single diagnostic test to swiftly identify the cause of a stroke, whether that be neurological or cardiological, rather than taking longer and exposing patients to more radiation by doing so separately," he enthuses.



Nicolas Chandellier,
general manager, **BD**

medical device developers is how to best navigate this prevailing environment of managed care, economically motivated customers, consolidation among health care providers, and declining reimbursement rates," concludes François Vorms, managing director of Canon Medical Systems.

While it might boil down to survival of the fittest, there can be no doubt that some of the larger med-tech players have been preparing well for this moment and are ready to seize the initiative. "We are in our second phase of restructuring to transition from a product-orientated to a solutions-based offering. Essentially we anticipated that the care ecosystem is changing, and recognized that hospitals are requiring holistic partnerships more than ever.... Canon Medical Systems has thus crafted a portfolio of products which can address the needs of each particular hospital based on its profile – whether small, large, or specialty," says Vorms.

Another entity that has been preparing itself well for the public health landscape of tomorrow is Becton Dickinson (BD). "Today's patients are much more involved in the health continuum than they used to be, and it must be acknowledged by the industry. The Ma Santé 2022 health reforms seek to connect up patients with healthcare professionals within certain geographic areas with a view to harnessing efficiency and medical devices will clearly be a key driver in building this connectivity. We are therefore positioning BD as the link between the healthcare workers and their patients: the catheters, the needles, and many of our products will serve as the interface," shrewdly posits the company's managing director, Nicolas Chandellier.

THE GENERICS PARADOX: HIGH SUBSTITUTION, LOW PENETRATION

France's generics market has long remained something of an anomaly within Western Europe – characterized by a below-par penetration rate, meager prices and a regulatory framework that admits comparatively fewer categories of drugs to generic competition – but it too is feeling the winds of change.

"Right now, generics constitute a mere 37 percent of pharmaceuticals sold in France while the rest of Europe averages somewhere between 50 and 60 percent and peer markets like Germany and the UK attain rates in excess of 80 percent penetration by volume," points out Catherine Bourrienne-Bautista, head of the Generics Association, GEMME.

For many, the primary cause of these distortions is the regulatory regime currently in force. "Once a drug hits the patent cliff, it does not automatically become genericized per se, but rather a product without a patent... To

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Natural Medicine: Staking a Claim

Compared to neighboring markets like Italy where the natural health product segment is valued at EUR 3.8 (USD 4.3) billion, France curiously pales in comparison coming in at a mere EUR 1.8 (USD 2.05) billion. “French patients are simply not accustomed to paying for their health out-of-pocket and since natural health products are not eligible for reimbursement under Social Security, the behavioral mindset of self-responsible prevention tends to be rather undeveloped in France,” explains Jacques Chevallet of Arkopharma, a European leader in herbal medicines and dietary supplements.

He does, however, spot an unprecedented opportunity to turn around this situation in the light of the sweeping healthcare reform program being rolled out. “Until now, French governments haven’t really had a proper vision of what public health provision of the future should look like, but the Ma Santé 2022 program changes all of that. I very



Jacques Chevallet,
CEO & chairman,
Arkopharma

much view Arkopharma’s responsibility as making the case for why natural health products should be included in this vision of tomorrow,” affirms Chevallet.

“It is my firm belief that natural products have a critical role to play in any serious concept of preventative and integrative care. Natural, herbal-based products carry the advantage of displaying very few side effects and that is precisely why they should be deployed more often in the early phases of disease and as complementary therapies.” The other challenge, he

admits, is to counter any doubts in minds of consumers about the effectiveness of natural products. “Arkopharma conducts clinical studies to prove the efficacy of our products: in cases where doctors prescribed herbal drugs to treat cholesterol, these products have demonstrated concrete results,” he assures.

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Bertrand de Lavenne, general manager, Mylan

permit the introduction of substitutable generics, the drug must explicitly be listed on a special registry of products known as the ‘repertoire,’” explains Bertrand de Lavenne, general manager of Mylan. “In this way, paracetamol is deemed off patent and can be produced by anyone in France, but, at the pharmacy level, paracetamol from generic players cannot be delivered because it is not listed,” he elaborates.

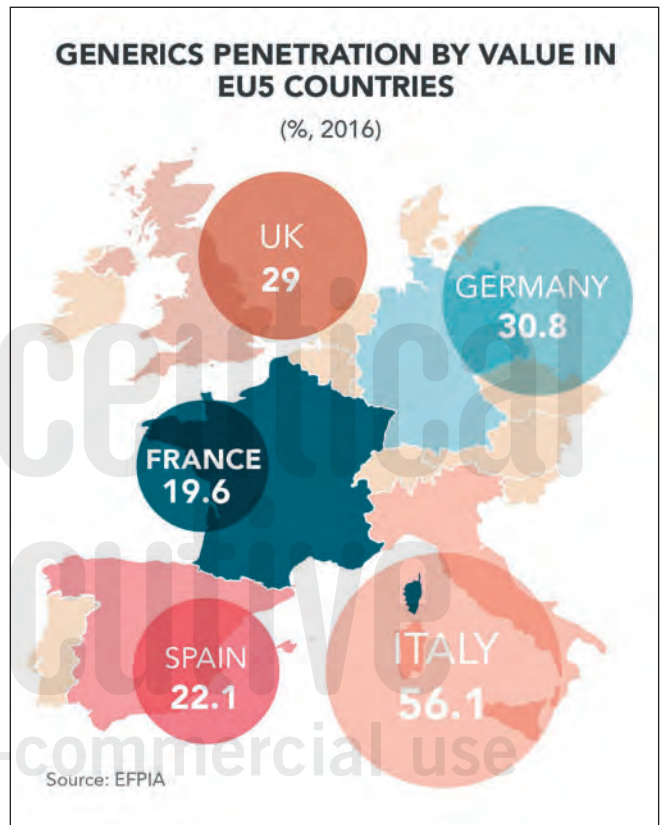


Pascal Brière, president, Biogaran

Others also perceive a lack of clear incentives on the part of the physician to opt for generic substitution. “The statistics show that 53 percent of prescriptions written by French physicians are for originator products that are not accessible as generics and this is because, contrary to many other European markets, French doctors are not subject to the same financial constraints and thus naturally manifest a high partiality towards pricey novelty therapies,” argues Pascal Brière president of Biogaran, the leading domestic player in generics.

“When generics were initially launched, France was actually a bit late to the party compared to some other countries and, in an attempt to cut corners and catch up, a policy decision resolved to deal with substitution at the pharmacy level rather than with the physicians at the point of prescribing. Not only did this mean physicians had little motivation to control costs, but it also brought the complication of triggering skepticism among the patients as they arrived at pharmacies with prescriptions from their doctors, only to then be given a different product that they did not understand,” recalls Teva’s general manager, Jean-Louis Anspach.

Interestingly the pharmacists themselves do appear to be enthusiastic to switch to generics whenever possible and it is the limited scope of the ‘repertoire’ that is ultimately artificially depressing volumes. “The statistics show that substitution at the point of sale is occurring almost 90 percent of the time for items on the list so there’s actually very little real leeway left for pharmacists to do better... it’s obvious that the only real way to release the brake on generics penetration is to



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extend out the repertoire to cover other products,” argues Vincent Pont, president of Laboratoire Arrow, the French subsidiary of Aurobindo.

“Indeed, pharmacies are already working well to substitute what they can and policy reform is going to be needed if the large, untapped savings potential that French generics represent can be truly unlocked,” concurs Jean-Louis Anspach.

While, like many of his peers, he is lobbying for a broadening out of the registry, Anspach is nonetheless much encouraged by the Macron administration’s moves to normalize physicians’ prescribing behavior. “While other European countries have successfully applied pressure on physicians via financial penalties, our government is thankfully looking to foster greater generics usage by reducing the number of ‘do not substitute’ prescriptions available to physicians and determining a reimbursement cap,” he observes.

Many welcome these developments. “We are broadly optimistic because we are gradually seeing more general practitioners prescribing by International Nonproprietary Name (INN) and the change in the regulation that the authorities are working on would mean doctors would have to justify ‘non-substitutable’ prescriptions something they are not obligated to do by today’s standards,” affirms Mylan’s Bertrand de Lavenne.

Moreover, “as the new regulations are put in place, the patients might well be pushed to pay the difference in price. Our understanding is that drugs could be reimbursed up to the price of the most expensive generic, but if a customer insists on the specialty brand, the shortfall will become an out-of-pocket expense, so it’s going to be rather



Jean-Louis Anspach, general manager, TEVA;
Vincent Pont, president, Laboratoire Arrow



interesting to see how patients react,” predicts Pont.

DIFFERENTIATION RULES

As it stands, the French generics market remains a challenging domain where robust returns hinge upon having a well-defined, balanced and adeptly differentiated business model. “Teva sees decent opportunities to develop in the local market, but not at any cost... at the end of the

day this is a segment that is rather fragile in terms of profitability after repeated price cuts and cost increases so it’s necessary to tread carefully and wisely,” confides Anspach.

Indeed Teva’s local footprint is surprisingly heterogeneous. “Although we are often assumed to be a pure generic player, the reality in France is that Teva maintains a 50/50 split between its specialty and generic business activities. One of our core strategic objectives is to manage a relatively mature portfolio with key specialty brands like Copaxone® in neurology while simultaneously preparing for the arrival of Fremanezumab®, a new biologic to treat migraine,” he reveals.

Mylan’s formula, meanwhile, is not entirely dissimilar in the sense of spreading risk exposure. “In France, we are neither a generic company, an OTC outfit, or a Rx entity, but rather a healthcare organization encompassing all these elements. In 2018, we actually sold around 400 million units meaning that, in general, any French patient will have six Mylan products in their home!” opines de Lavenne. “We thus feel we have a major role to play as one of the key actors interacting across the entire health ecosystem: for instance on top of our strong track record supplying a wide range of antiretrovirals for AIDS patients, we simultaneously enjoy the distinction of having been the



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Redefining the Boundaries in Neurovascular Therapy

The USD 2.5 billion global neurovascular market grows by between 15 and 20 percent every year, making it a particularly profitable therapeutic area for those companies at its forefront. Yet overall potential is even higher. As Pascal Girin, CEO of French interventional neuroradiology specialist BALT, deftly points out, “If every patient in developed health markets in this field were treated, the market could blossom to USD 12 billion in size.”



Pascal Girin,
CEO, BALT

Girin continues, “Stroke is the second largest cause of death in the world and many patients are not being well treated. Although much progress has been made, there is still a huge unmet medical need. Ischemic stroke accounts for 85 percent of stroke patients and up until recently, there were no effective treatments outside of a six-hour window.”

However, with developments in technology, this window is increasing in size. Girin posits that “the latest clinical studies show that with the treatment options that neurovascular companies like BALT can provide, patients can

now be treated up to 16 or 24 hours after onset. Developments in hospital and healthcare infrastructures can also be attributed to this improvement in stroke treatment.”

The technology needed to facilitate this improvement is not, though, easy or quick to produce. Girin describes how, “The creation of BALT’s microcatheters and implants is an extremely delicate process that requires a high level of precision and manual skill” and adds,

“The number one problem of BALT today is meeting market demands.”

To counter this issue, BALT has invested in a new facility in the US with large production potential and is now looking to bolster its French manufacturing operations as well. Girin states, “our factory here in Val-d’Oise is excellent at producing small series batches, but we need to transform this site into a large-scale operation. Therefore, this January we initiated an investment program to double our capacity in France through the modernization of equipment and application of lean principles to the production process.”



Claude Le Pen,
healthcare
economist, IQVIA

first company to launch the Autotest VIH®, the first self-test for the detection of HIV.”

Arrow Labs, for their part, have gone down the route of aligning their offering with specific needs in the French hospital sector. “We have pioneered unique unit dosage blister packaging. A standard product has a name, batch number, and expiration date on its blister, which allows for the secure tracking of each drug as it is distributed through the hospital.

By pairing our generic products with this technology, we are managing to offer added value,” confesses Pont.

“Another of the ingredients of the affiliate’s success is having the flexibility to opportunistically in-license products which were not developed internally. For example, in 2016, Arrow acquired the Orocal® brand of Teva only in France and this has been generating good results,” he adds.

GROWING EXPECTATIONS FOR BIOSIMILARS

Biosimilars constitute yet another potentially prospective arena for generics companies operational in France. As part of the recently unveiled ‘Ma Santé’ reform, the Macron administration has already set an aggressive target of achieving 80 percent uptake of biosimilars by the end of 2022. “We commend the highly ambitious goals set by the government in its National

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Health Strategy and calculate that the ecosystem is stable enough to accept biosimilars so long as a bespoke regulatory framework specific to the products is implemented,” asserts de Lavenne, noting that Mylan has been one of the early movers in this space locally having successfully launched Hulio™ (adalimumab) in February.

Others, however, remind that the fledgling biosimilars market in France is still pretty lopsided as companies wait for the regulatory landscape to shore up. “Biosimilar products are gaining momentum quickly in hospital settings through tender offers, but have so far struggled in the community pharmacy space,” analyses IQVIA’s Claude Le Pen.

“Biosimilars have already achieved nearly EUR one billion (USD 1.1 billion) in turnover in the hospitals and, after going through the public tender, these drugs can take up to 50 percent share in the market quite quickly, especially in areas like oncology. In retail settings, by contrast, the law passed to allow pharmacists to substitute with biosimilars, but the decree defining the necessary conditions has not and this is holding back the development,” he clarifies.

At the same time companies are experimenting with different business strategies as they jockey for position in securing a foothold in this emerging niche. One debate raging is whether companies should have fully integrated, internal capabilities to develop, manufacture, and market biosimilars, or if it is instead preferable to create collaborations to share these burdens among partners. “What Biogaran has chosen to do is enter into licensing partnerships as we have done with our first three products from Celltrion from Korea and hopefully a fourth with Rovi in Spain... We are picking



Pierre Banzet, CEO, Synerlab; David Lescuyer, managing director, Skyepharma



up assets on a product-by-product basis, which is increasing our chances of being a first mover in the biosimilars market. Companies like Sandoz manage biosimilars entirely in-house and on their own, but because of that, they may not be the first to reach the market. To me it is clear that when a biosimilar is not first-in-line its value plummets terribly so I am banking on flexibility, adaptability, and speed as being the key assets to ensure leadership,” reasons Pascal Brière.

“Certainly you would expect players to be trying to mitigate and limit risk exposure,” muses Le Pen. “Given the complexity and sheer expense of the developmental process, I would estimate that biosimilars should normally not be discounted by much more than 30 percent, but in France let’s not forget we’re seeing the drug developers having to absorb a reduction of almost double that!”

THE RISE OF THE SPECIALTY CDMO

Another part of the value chain adapting its service model is the contract-manufacturing segment. On the face of it, the local CMO industry is booming, but that is only part of the picture. “We have perceived some similarities between pharma and other business sectors such as the electronics and automotive industries where there has been a steady divestment of non core activities which are instead outsourced to service providers, which for Big Pharma means R&D, manufacturing and even regulatory functions,” reckons David Lescuyer, managing director of complex oral solid dosage form specialist, Skyepharma.

“France’s CDMO space is dynamic and has been enjoying a CAGR of between four and ten percent over the past

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few years, but this has simultaneously occurred in tandem with a bit of a filtering out of the weaker CMOs that are not managing to make the leap to CDMO and are finding themselves left behind,” he perceives.

“A good portion of this growth is being driven by pharma multinationals selling off their production facilities to instead be managed by CDMOs,” notes Pierre Banzet, CEO of Synerlab.

“On the one side, these clients are often keen to streamline the number of contract manufacturers that they work with so as to easily ensure quality control. On the other hand, as pharma M&A activity heats up and clients mass scale, we are witnessing the volume of production for a single customer shooting up...This, in turn, is altering the client-provider relationship with greater attention to auditing and also encouraging the CDMOs to become more specialized and diversified,” he believes.

Consequently, Synerlab, in an attempt to carve out its own niche, has been investing heavily in soft gelatin capsules and lyophilization conscious of the paucity of competitors in those areas. “We are detecting considerable demand for outsourced biologics production as well, because, similar to lyophilization, there is a shortfall of certified manufacturing capability for biologic products, but the only way to break through into that niche would be to build a brand new, expensive facility from scratch and that represents a significant barrier to entry for a mid-sized CDMO,” he admits.



Michel Spagnol, CEO, Novasep; Patrick Mahieux, general manager, ABL Europe



One contract manufacturer that has been bold enough to take the plunge is molecule production and purification player, Novasep. “Looking at the maturity curve of some of these biologics, demand for monoclonal antibodies has been skyrocketing, antibody drug conjugates have been gaining momentum and gene therapies are increasingly in vogue,” suggests CEO, Michel Spagnol. “The latter is an area in which Novasep waded

on several years ago and it fortunately turned out to be the right bet. At the time we made this decision, gene therapies were still an uncertain playground as there were only a small handful of products that had actually gained FDA approval,” he recalls. “However, we can clearly understand today that biologics are becoming the shapers of the industry.”

The bottom line therefore is that the new breed of CMOs are having to get creative and adapt to the evolving marketplace if they are to remain ahead of the game. Advanced BioScience Labs (ABL Europe) an Institut Mérieux-backed CMO, for instance, not only developed mastery in the highly specialized viral vector niche where there are fewer than 20 peer outfits in the world, but also devised a solution to one of the drawbacks of the classic pharma model. “We were attentive to ensure that there is no segregation between product development and GMP manufacturing – a practice which does not exist in big pharma organizations,” says general manager, Patrick Mahieux.

Skyepharma, for its part, leverages its own patented technologies – Geomatrix®, Geoclock®, and Soctec® – to deliver a strong differentiation from its competitors. “These platforms allow us to build controlled release formulations to adapt to patient dosing schedules or adjust API intake. Such technologies allow us to better manage side effects, which is a capability much prized by our clients,” says Lescuyer.

BRACED FOR CHANGE

All in all, hopes and expectations are thus riding high right across the life science value chain as France enters this exciting new period in its development trajectory when the rules of the game are being reshuffled and in which fortunes can be established (or indeed surrendered). “We are manifestly living through unprecedented times when the wave of innovation in life science is absolutely exceptional... and France’s own internal transformation is absolutely tapping in to this vibe,” exclaims the president of Novartis’ affiliate, Frédéric Collet. 🌟

FMD: Survival of the Fittest

In accordance with the Falsified Medicines Directive (FMD), all drugs were to be serialized across the EU by February 2019. “I would say that the FMD presents CDMOs with parallel opportunities and threats resulting in a natural selection of actors, between those who are prepared to meet the regulatory requirements and those which are not,” reflects Skyepharma’s David Lescuyer, pointing out that remaining compliant with the regulation will be a repeated cost each year and that without a sufficiently big enough scale and resource pool, firms might struggle to adapt. “For a company possessing the size and capabilities of Skyepharma, however, serialization and aggregation represent favourable entry doors to expanding client networks and we will thus be looking to leverage the incoming regulation to fashion new business activities such as supply chain improvement projects,” he remarks.

Investors like to put their money behind people as much as ideas, so building the right team at the right time is ultimately the most critical factor in determining the success or failure of a new venture. And it is crucial for startup companies in the life sciences. The question is, who should emerging biopharma entrepreneurs be targeting to give their missions the greatest chance of success, and how should they go about attracting the talent?

The light-bulb moment

Anyone can have a great idea, but it's how that idea is executed that makes the difference. Successful evolution relies on brilliant people. One person alone is unlikely to secure an entrepreneur the investment they need in order to make a success of their venture. Put simply, if you don't add scale to your team, you won't add scale to your idea.

Build a board

Before seeking out series A funding, entrepreneurs should build their own personal advisory board. There is no substitute for experience when it comes to giving a startup the best chance of success. These board members should have experience in scaling up products and teams from concept through to commercialization. If you can present to investors an ex-CEO who has been through all the challenges, who understands the full product life cycle and all the regulatory hurdles, then your business proposition becomes significantly more attractive.

The benefits of building a team early aren't restricted to investors, either. The sooner you have access to quality advice and decision-making, the greater

Building the Startup Dream Team

your chances of a fast route to successful launch.

Assembling your roster

So you have your idea, your advisors, and your plan to build a team. Now the hard work really begins: How do you attract top talent to a startup? Many industry veterans can be tempted to take a risk if they believe they'll be a part of something really big. That doesn't simply mean persuading them of the superiority of your product or drug candidate—it's about empowering them to see how their experience and gravitas will be crucial to securing the company's future.

It is also important to treat each position in a fledgling business as a specialist role. Allotting more than one area of responsibility is a typical approach to help save costs, but this can make it difficult for people to focus, causing burnout and ultimately, it can dilute your resources of expertise.

And, while building a great culture will future-proof your business, don't fall into the trap of hiring a "type." The most successful businesses are usually those who bring diversity of background, ideas, and working approaches to the table.

The hiring process

At interview time, pitch the company vision first. If a candidate is not excited about this, you'll know straight away that they are not going to be right for you. Passion—and a shared vision—is absolutely critical to success.


It can be a mental hurdle for many, but don't be afraid to hire

someone with more experience, who is more renowned or better paid. Don't lose sight of the fact that you are building the dream team who can bring your vision to life. It's also important not to dismiss candidates who may have previously worked for a startup that failed. It doesn't mean the failure was their fault; moreover, they may know what mistakes to avoid.

Great candidates are a precious commodity. If you have a candidate on hold, don't assume there is a better one—you just might risk losing the perfect new addition to your board. Experienced C-suite professionals in fields like medtech and biotech always have lots of options, so speed is essential. If you leave a candidate hanging, it could detrimentally affect your reputation as an employer.

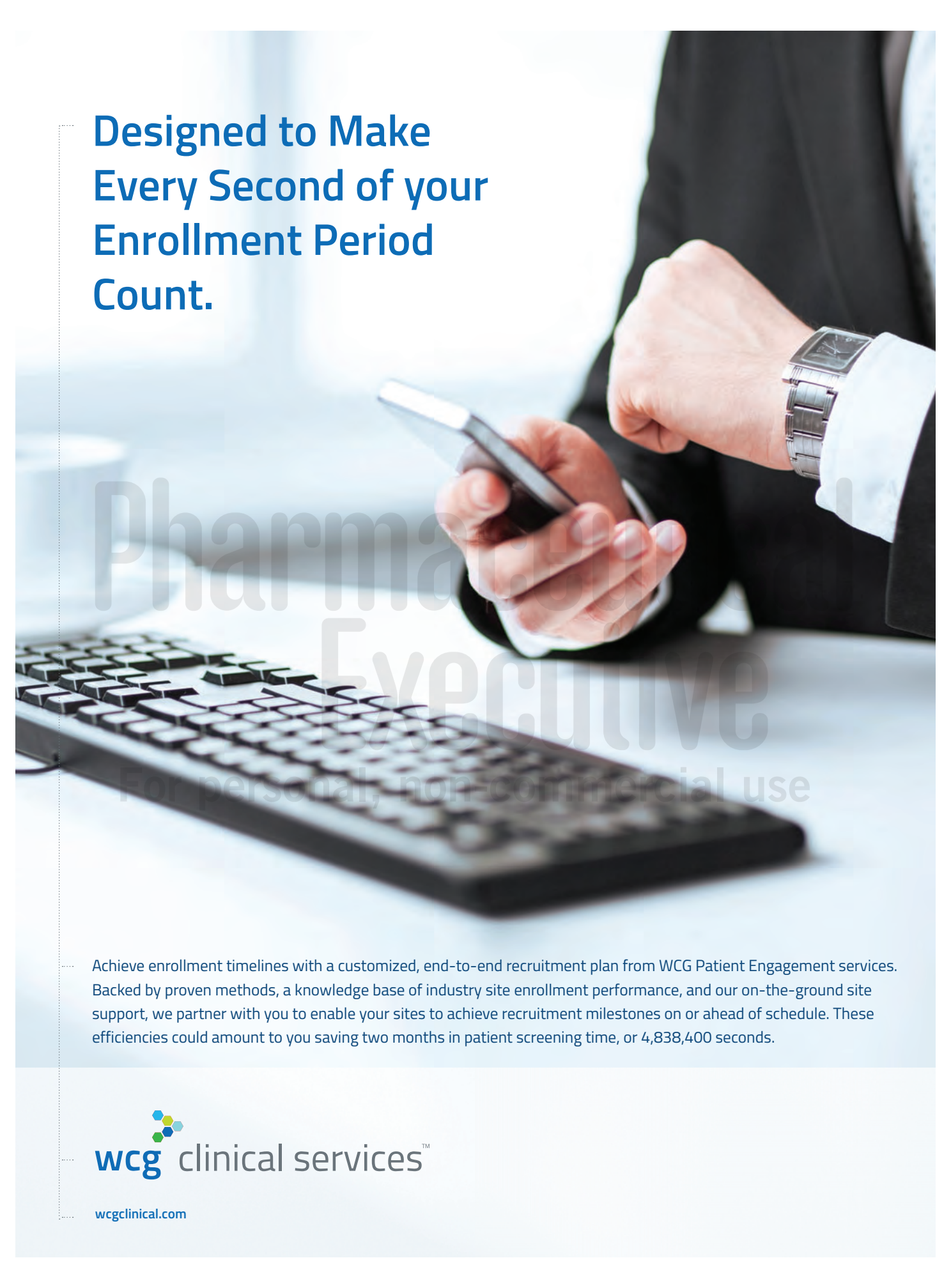
When it comes to salary, it is important to remain open-minded yet realistic. Don't pass on an interview with a potential candidate just because of their salary. Salary is rarely a candidate's only consideration when deciding whether or not to accept an offer. Neither is equity. Factors such as work-life balance and internal culture are increasingly important to today's executives.

Finally...

It is easy for biotech entrepreneurs to fall into the trap of devoting all of their attention to their big idea, thereby failing to focus on the human component of success. The initial investment in human capital may create nervousness, but if there's inherent belief in the company's vision, then the risk will undoubtedly be worth it. 



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