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Life Sciences and
Health Care Horizons

2019



Welcome

Innovation in the life sciences and health care industries is occurring at a dizzying pace. Five years ago, anti-PD-1 antibodies from Merck and BMS had yet to be approved, CAR-T therapies were still in small-scale clinical trials, and digital health was seen as electronic step counters and little else. Today, cures are being found for diseases and conditions once considered life threatening or permanently debilitating.

All of this is happening within a regulatory environment characterized by constant turmoil, and the reality that for better or worse, innovations in medicine and health care lead to legal uncertainty. The market is striving to keep pace with novel technologies while also grappling with changes in the macro- and micro-political climate, including Brexit, GDPR and responses to a nationwide opioid crisis.

Our global Life Sciences and Health Care team—comprising more than 500 lawyers around the world who support more than 1,000 clients — helps chart safe passage through the uncertainties that exist at the intersection of business and government.

In the following pages, our team identifies a number of current and evolving trends that are shaping the future of the industry. We hope that you find our view of the horizon thought-provoking. We also want to thank you for your continued innovation for the purpose of improving human health. In many cases, it is your efforts to make the world healthier, and our work alongside you that allows us to better navigate the uncertain, but exciting future.



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Asia

Navigating China's expanding and evolving drug market

2019 is set to be a milestone year for China's drug regulatory and health care reform. The China drug regulator changed its name, again, in 2018 to become the National Medical Products Administration (NMPA), but the pace of regulatory reform has not been interrupted. In July 2018, NMPA implemented a new policy that a clinical trial application or CTA (similar to a U.S. IND) will be considered automatically approved, unless NMPA responds with any questions within 60 working days of filing.

In November 2018, in an unprecedented regulatory action, NMPA called on global pharmaceutical companies to bring innovative drugs to China, which are viewed to be urgently needed in China and have already been approved and marketed in the U.S., EU or Japan. In December 2018, China's approval of roxadustat, a new anemia drug for kidney patients from AstraZeneca and FibroGen, marks the first time the country's drug regulator approved an innovative drug before any other country. Looking forward, we expect NMPA will continue to reform its drug regulatory regime to be in line with the International Council for Harmonisation (ICH) guidelines and provide more incentives for pharmaceutical companies to bring their innovative products to China.

With the opportunity for global pharmaceutical companies to gain new access to the Chinese innovative drug market presenting itself like never before, generic drug manufacturers should expect fierce competition in China. Significant news broke in December 2018 regarding a newly implemented pilot centralized drug procurement program (the "4+7 city centralized procurement program"). Under the new program, the government will award a contract to the lowest bidder, who will be guaranteed a sale volume of around 60-70% of the total market in 11 major metropolitan areas for a year. The program marks a significant change in how generic drugs are priced and procured in China. After the first bidding, which took place on-site in Shanghai, the average price dropped 52%, with the highest price reduction being 96%.



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China pushing for internet powered medical services

On 14 September 2018, the Chinese regulators released three trial measures addressing telemedicine, internet diagnostic services and internet hospitals matters. Below please find a summary of key takeaways from the three trial measures.

Telemedicine services

Telemedicine rules clarify that telemedicine, which is “hospital to hospital” (H2H) medical activities, mainly covers two scenarios:

- a host medical institution directly invites other medical institutions to provide technology-based support to diagnose and/or treat patients; and
- a medical institution or a third party establishes a telemedicine platform on which other medical institutions register so as to render remote medical consultation services at the request of host medical institution or through matching services.

Medical institutions involved in telemedicine services are not subject to extra ex-ante approval, but they must obtain consent from treating patients and be ultimately responsible for the diagnosis and treatment of patients.

Internet diagnostic services and internet hospitals

Internet diagnostic services are “hospital to patient” (H2P) medical services, which means remote return visit services for certain common or chronic diseases or a family physician’s services

provided by physicians. Eligible providers of such H2P services include (i) bricks-and-mortar medical institutions; and (ii) internet hospitals formed by a tie-up between a provider and an external bricks-and-mortar medical institution. A bricks-and-mortar medical institution intends to provide internet diagnostic services or operate an internet hospital must apply to add “internet diagnostic services” or “internet hospital” to its current Medical Institution Practicing License, while the establishment of a pure internet hospital is subject to prior an administrative approval. Very likely, the regulatory pathway of internet hospitals would follow that of bricks-and-mortar medical institutions, which mean, for foreign investors, internet hospitals may only be established in the form of joint venture with a 70% shareholding ratio limitation for foreign investors.

The three trial measures are helpful to gain certainty when market players make use of advanced technology for internet-based medical services, but we believe more rules will be promulgated in 2019 to address many important yet unanswered issues (e.g., the reimbursement mechanism for the cost of internet-based medical services).



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New Hong Kong listing regime proposals for biotech companies

In late April 2018, The Hong Kong Exchanges and Clearing Limited (HKEx) adopted new rules to expand the current listing regime to attract more companies from emerging and innovative sectors to list in Hong Kong. The new regime, incorporated into the Main Board Listing Rules as Chapter 18A, allows some biotechnology companies which would have previously been unable to conduct an IPO in Hong Kong (e.g., those without profit or revenue) to be listed on the HKEx's Main Board.

To qualify under the new regime, the biotech applicant should have:

- its current line of business (under substantially the same management) for at least two financial years;
- primarily engaged in R&D of its core products for at least 12 months prior to listing;
- registered patent(s), patent application(s) and/or intellectual property over its core product(s);
- obtained meaningful investment from at least one sophisticated investor six months prior to listing; and
- upon listing, a market capitalization of at least HK\$1.5 billion (approx. US\$190 million and €150 million).

Regarding its core products,

- they can be pharmaceuticals, biologics, medical devices (including diagnostics), or other biotech products considered on a case-by-case basis;
- they must be regulated by the U.S. Food and Drug Administration (FDA), China Food and Drug Administration (CFDA), European Medicines Agency (EMA), or a competent authority acceptable to the HKEx and Hong Kong Securities and Futures Commission; and
- the R&D of at least one product is "beyond the concept stage."

Companies may submit a formal listing application under the new regime. As of February 2019, five biotech issuers have listed under Chapter 18A and eight others have submitted their listing application. These changes facilitate more early-stage capital raising and retail investor participation. We expect the number of life sciences and health care companies choosing to list on the HKEx to grow as awareness of the implementation of the new regime increases.



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Biologics and biosimilars in Japan

Japan is the world's third largest pharmaceutical market and commentators currently expect it to reach a value of US\$105 billion by 2021 (and US\$109 billion by 2026). With an average life expectancy of 85 years, the rapidly aging nation is experiencing health care cost pressure that is pushing the increasing use of biosimilars, both through domestic development and increased investment by international companies.

Beginning with the approval of Sandoz's growth hormone treatment Somatropin BS in June 2009, the Japanese regulator has approved nine biosimilars, including granulocyte colony-stimulating factor, erythropoiesis stimulating agent, and insulin and tumour necrosis factor-inhibitor. Two of the most recent approvals are Nichi-Iko Pharmaceutical's Infliximab BS treatment for Crohn's disease, rheumatoid arthritis, and ulcerative colitis in September 2017; and Mochida Pharmaceutical's Etanercept BS treatment for rheumatoid arthritis in January 2018.

Historically, Japanese pharmaceutical companies have focused their R&D efforts on small chemical molecules. But due to increased government pressure, attention is now shifting towards more biosimilars. Recent press reports suggest that in addition to partnering with international companies, Japanese biosimilars manufacturers are also seeking to acquire relevant secondary patents. This strategy may help strengthen Japanese companies' negotiation position—especially with respect to potential cross-licensing arrangements—and enable them to be more nimble when entering the fast-growing biologics market. As the push for increased biosimilar availability in Japan continues, more competition, collaboration and challenges are expected to follow.



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Ranked Band 1 for Life Sciences – Japan

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Digital Health

Overview

Technology is rapidly changing the way the health care industry operates, introducing unique solutions for challenging issues and creating potentially enormous business opportunities. From standalone software that analyzes consumer electronic data to detect disease, to novel wearable sensors, complex predictive analytics and advanced digital therapeutics, the technological landscape is evolving at an unprecedented speed.

As novel technological solutions make their way to market, changes to the legal and regulatory landscape have slowly begun to take shape. Innovators are required to simultaneously understand and navigate the existing frameworks, while working actively to anticipate new developments. From increasingly complex global privacy regulations to novel reimbursement models and evolving product safety and medical device regulatory paradigms, companies must be ready to engage in nimble compliance approaches. Concurrently, these products raise new questions of liability and intellectual property protection.

At the same time, due to the enormous promise of digital health solutions, the digital health sector has continued to see enormous investment, reaching a record reported US\$8.6 billion in 2018.

Continued technological advances, ever-increasing adoption of wearables, and growing health insurer interest in digital health intervention has helped to fuel digital health M&A at unprecedented levels. The coming year promises new opportunities in AI, robotics, and development of technologies in areas ranging from mental health, diabetes, therapy adherence, and support for aging adults.

As telehealth and other novel health care delivery models grow in prevalence, the need for digital health solutions that are clinically meaningful will also grow. Companies looking to develop or leverage these new technologies will need to keep pace with the evolution of technology and regulation. Optimal business planning requires understanding the issues as they exist today and anticipating how they are likely to evolve in the future.



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Artificial intelligence: the future of drug design

2018 has seen a surge in interest in the use of artificial intelligence (AI) in the pharmaceutical industry. Garnering particular interest is the growing number of cases where AI is being used in drug discovery successfully. This advance is already disrupting long-standing ecosystems in the industry, and prompting important debates about how AI-derived innovations should be regulated.

In drug discovery, AI is promising to cut the time and costs of generating a hit to candidate, from around five years to one or less.

Specifically, AI is being used to identify and plan the synthesis of new molecules or known molecules for new uses, by analysing vast amounts of public and proprietary data. The use of AI in drug discovery is already having a tangible effect on the industry's long-standing ecosystems. Companies wanting to take advantage of the opportunities offered by AI are having to seek expertise from, and divest some of their R&D to third parties, including novel players in the field such as tech start-ups. AI is also prompting the rise of much smaller – typically tech – companies.

The use of AI in drug discovery is prompting important questions about how AI, and AI-derived innovations should be regulated. Earlier this year, the European Patent Office (EPO) held its first ever conference on AI. The EPO has since updated its guidelines on patenting, to include a new section on AI. For the time being at least, the usual rules on patenting algorithms will apply to the AI. The picture is less clear for AI-derived innovations. If an AI invents a new compound for medical use, who is entitled to the IP? What IP would vest in something that has been created by a machine?

For companies collaborating over AI, these questions could prove more challenging to answer. Companies will need to think about these questions now, to prepare for the future. Keeping the human central to the drug design process could prove key to ensuring that IP is generated and vested in the right parties.



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Digitization of the supply chain

The digital revolution is poised to create sweeping changes for life sciences companies—helping them better understand patients, but also transforming their manufacturing and supply chain operations. Machine learning and autonomous machines will change views on regulatory responsibility and liability in contracts, particularly given the absence of guidance documents from European or national authorities on the implications of digitization.

Pharma and med tech companies face growing challenges: globalization, personalized medicine, increasing supply chain complexity, and price and cost pressure. Digitization of the supply chain holds enormous potential in helping companies cope with these challenges and gain competitive advantage. Integrated digital supply chains will allow companies to improve planning accuracy, manufacturing efficiency, productivity, inventory levels, and service levels.

Sharing digital data throughout the entire supply chain (starting with the patient and ending with the supplier) may allow continuous manufacturing instead of “siloes” batch manufacturing. However, these new data streams raise critical legal questions: How do you create a GMP digital supply chain if there is not yet regulatory guidance? Who is responsible if machines are making autonomous decisions? How do companies separate and define responsibilities in contracts?

As automation in the supply chains becomes critical for remaining competitive, these questions, and many other surrounding the future of regulation, will come into focus.



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They display brilliant teamwork and their strategies are very pragmatic. They are very good on tactics and they work fast, all with a good sense of humour which is always very refreshing.

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Health technology assessment in the EU

In many European member states, reimbursement of new health technologies—namely medicinal and pharma products and, increasingly, medical devices—is linked to a health technology assessment (HTA) which is the payer's prior assessment of additional patient value compared to other existing technologies. In the past, various HTA bodies have cooperated to some extent, but this has proven largely inefficient. A proposal for a new regulation submitted by the European Commission to streamline the HTA process may help change this.

Each member state typically conducts its own HTA. The result is multiple assessments, often with divergent outcomes. Moreover, HTAs are not well aligned with the regulatory requirements for product approval, which means uncertainty for pharma and device companies as well as significant financial and administrative burdens.

The new regulation (Regulation on health technology assessment, 2018/0018 (COD), 31 Jan. 2018) stipulates that the clinical part of the HTA exercise be conducted just once and steered by a newly established coordination group of HTA bodies. The outcome of this type of joint clinical assessment would then form the basis for reimbursement and pricing decisions by the respective member states. They are not to repeat the joint HTA assessment or to deviate from its clinical outcome.

It is also proposed that manufacturers be entitled to joint scientific consultation. There, the parameters and requirements for the respective technology will be determined uniformly for the upcoming joint HTA and can even align with the scientific meeting at the European Medicines Agency (EMA). These measures, along with the cooperation of individual HTA bodies, are likely to result in a more streamlined process, and further alignment for reimbursement across the EU as new and novel technologies continue to expand.



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Telehealth: the challenges ahead

Telehealth gives rise to new and complex technological, business, legal, and regulatory issues which cannot be addressed within the borders of our traditional areas of law and local regulation. To date, there is no unified legal framework for telehealth in Europe.

The launch of a telehealth solution in one or several Member States will require addressing a variety of legal topics:

- **Classification of the solution:** telehealth services are made possible thanks to software and connected devices. Such software may classify as a medical device. The design of the solution must include from the outset the constraints resulting from medical device regulations.
- **Practice of medicine and telemedicine:** a telehealth solution aiming at performing medical acts will fall under national regulations on the practice of medicine and raise several structural regulatory questions, ranging from pricing and reimbursement and use of AI to advertising and the corporate set up of the legal entity (or entities) hosting the business.
- **Data protection:** telehealth technologies must comply with the EU General Data Protection Regulation since 25 May 2018.

- **Advertising:** telehealth solutions may be a vehicle to promote products, disease awareness or carry out institutional advertising. Content provided in this context must be assessed under EU laws regulating promotional activities.
- **Interactions with Health Care Providers (HCPs):** an increasing trend of regulations restricting or organizing such interactions, coupled with transparency requirements, will need to be taken into account.
- **Telecom and e-commerce regulations:** telehealth is subject to regulations applicable to online platforms and communications. These include regulations on encryption, import/export controls, telecoms regulations, or consumer regulations applicable to e-commerce.

As tools powered by AI, data management through blockchain, and other new technologies burst into the heavily regulated health industry, mapping out the regulatory framework of each project and related risk exposures will remain of utmost importance in 2019.



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Data breaches

With the media regularly reporting on cyberattacks and data breach investigations, and calls for increased regulation growing louder, the existence of cyber threats to digital health businesses cannot be ignored. Legislators and regulators around the world are enacting data breach notification laws and the trend toward imposing industry-specific cybersecurity standards is expected to continue. The EU General Data Protection Regulation (GDPR) and California Consumer Privacy Act (CCPA), for example, both include key provisions requiring data breach reporting and imposing security obligations.

Hackers view health systems and medical devices as high value targets. Liability for class action and shareholder suits, regulatory penalties from enforcement actions, and reputational damage associated with health data breaches continues to grow. Threats to health information include increasingly sophisticated ransomware and phishing attacks, insider threats, connected devices, and lost or stolen equipment and data. Increasingly larger data sets also raise heightened risks. Digital health organizations must account for the unique and heightened risks associated with health information, and implement programs for ongoing cyber risk identification, management, and protection that go beyond “check-the-box” compliance efforts.

Every digital health organization should have an Incident Response Plan (IRP) ready and rehearsed. It may be advisable to maintain playbooks for different stakeholders as well as addressing particular threat scenarios (such as ransomware). Effective preparation for managing a data breach helps ensure a swift and coordinated response that can minimize harm to patients and consumers as well as reduce reputational impact and potential legal liability. As the threat of cyberattacks continues, nearly every digital health organization will be faced with a cybersecurity incident. Organizations that have plans in place to mitigate the risks will be better positioned to survive and thrive.



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Regulatory outlook

Pricing and reimbursement in the U.S.

The cost of pharmaceuticals and issues of patient access will remain at the forefront of the policy landscape in 2019. The Trump administration continues to focus on drug pricing issues, and state legislatures continue to propose new drug price transparency legislation. At the same time, innovative new therapies, such as one-time treatments for cancers, pose challenges to the traditional public and private payer reimbursement models, and manufacturers likely will remain motivated to consider innovative, value-based pricing arrangements in 2019.

Federal agencies are expected to propose significant reforms to the existing system of drug pricing and reimbursement in 2019. For instance, Centers for Medicare & Medicaid Services (CMS) has announced plans to issue a proposed rule in spring 2019 that would refer to drug prices charged in other countries to set reimbursement rates for Medicare Part B drugs in the U.S. Additionally, on 31 January 2019, the Department of Health and Human Services Office of Inspector General (OIG) proposed changes to the Anti-Kickback Statute safe harbor rules, which would effectively preclude manufacturers from offering rebates to Medicare Part D and Medicaid managed care plans.

States are seeking to pressure manufacturers to offer more substantial rebates when drugs are reimbursed by state Medicaid programs, and certain states are considering regulatory approaches that would establish limits on Medicaid payments for certain categories of therapies. With the court challenge to California's drug pricing transparency law still underway—and with drug price transparency bills expected in Maryland, Oregon, and Massachusetts, among others—states show no sign of slowing their legislative efforts related to drug prices.



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Pricing and reimbursement in the EU

Reimbursement of medicinal products in the EU is handled on a country-by-country basis. But because in many EU nations health care is provided and financed directly by the government through tax payments, challenges tend to be similar from country to country. Innovative medicines, such as gene therapies, now pose new questions around the future of reimbursement.

Seeking budgetary relief through a spending review is no longer sufficient. Increasingly, the focus is shifting to health technology assessment (HTA) and new pricing strategies. The concept of “pay per value” continues to be relevant, the idea being that reimbursement is not one-size-fits-all. As a result, payments for results, as well as mechanisms for sharing the costs and the risks with payors, are becoming popular.

What should innovators do? Real-world evidence is the key and cannot be limited to considering a therapeutic comparator that is considered as a reference for assessing the added value that a medicinal product may provide as against available alternatives. In the case of universal health care coverage systems like those the EU, many authorities may also consider the indirect cost-saving and social benefits associated with new therapies.

Unexpected or out-of-control costs are the main concern. How to address them is not only a matter of price: in some instances, precision medicine and new tools (e.g. diagnostic companions) may help to define the target and may become part of the answer.



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Federal funding for cutting edge research

Policymakers are increasingly focused on leveraging a combination of government and private resources to accelerate innovation and improve health outcomes. In the last few years, several high profile public-private initiatives have emerged:

- The US\$500m CARB-X program — dedicated to enhancing antibacterial research to tackle drug-resistant bacteria.
- The NIH BRAIN Initiative — a US\$500 million investment in neuroscience research.
- The Precision Medicine Initiative and the Cancer Moonshot — both featuring dozens of collaborations across industry and academia.

While the government encourages industry participation in these programs, regulatory complexities abound in federally-funded research projects. For example, protection of intellectual property and valuable data may be in tension with the principles of transparency and openness in federal research.

Pressures on corporate budgets and perceptions of value have companies paying increased attention to opportunities to partake in federally-funded initiatives. University-industry compacts also are on the rise, and the government has shown willingness to support them through federal grants and cooperative agreements. But companies that receive federal funds as recipients, subrecipients, or contractors have important obligations; some of these obligations extend to participation in federal projects even without receipt of federal funds.

Strict cost accounting requirements apply to recipients and subrecipients, and to the contribution of private funds as “cost share” to a federal project. The government’s regulation of intellectual property, data sharing, and research misconduct may reach companies working on these programs. Federal audit and inspection rights related to financial and scientific performance are also factors as industry involvement in these programs surge.

Alliances between government and industry are imperative in the modern research environment. To the government’s credit, myriad programs are helping to nourish and expand these interactions. But the government has limited regulatory flexibility in these projects, and companies must be attentive to the downstream implications.



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Complex generics

Scott Gottlieb, Commissioner of FDA, is rallying his staff to “crack the code” on complex brand-name drugs that have frustrated the generic drug industry. Gottlieb speaks frequently on using FDA’s scientific and gate-keeping roles to lower drug prices. Widening the array of products available as generics is one way to do that.

These complex products fall into three categories:

- Active ingredients (e.g., drugs derived from natural sources, peptides, and drugs that incorporate novel chemistry complexes, shared salts, and encapsulated compounds).
- Drug delivery (e.g., products that incorporate device components such as auto-injectors and inhalers).
- Bioequivalence (e.g., implants and long acting depots with months-long dosing intervals).

FDA has now hosted several public meetings on solving the “problem” of complex products and is applying user fee funds (per agreement with the generic industry) to develop alternative methods for demonstrating equivalence. One area of research focuses on advanced metrics for characterizing factors that govern drug release and correlating those factors with in vivo pharmacokinetics. The idea is to use in vitro release measures as a proxy for in vivo testing.

On the drug-device side, FDA is focusing on whether products with different designs may nevertheless be used with no greater error rate than the pioneer. Recent approvals of a generic emergency use autoinjector and a generic dry powder inhaler show that FDA believes it has a workable framework even for the more challenging integrated drug-device combination products. Whether this framework can be applied to some of the more complex products being developed, such as drugs integrated with digital health tools, requires close attention. We are monitoring this area closely for our pioneer clients.



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OTC drugs

We expect major changes to unfold in the way over-the-counter (OTC) drugs are regulated by Food and Drug Administration (FDA). The regulatory scheme that governs the marketing of OTC drugs is now widely recognized as outdated and inadequate. Last year, Congress came very close to passing legislation that would have overhauled the 45-year old OTC drug monograph system. We believe that similar legislation is likely to pass in 2019.

FDA has complained publicly that the monograph system is cumbersome and impedes prompt agency action on safety issues. The draft legislation is designed to expedite agency action on evolving science and safety issues and to create new incentives for innovation, including a new exclusivity provision. The new system is expected to result in opportunities for marketing OTC drugs with new ingredients and dosage forms, including some that were previously only available overseas or by prescription.

FDA is also developing a regulation — under its formally known as the Non-Prescription Safe Use Regulatory Expansion (NSURE) program—to expand the types of drug products that may be considered OTC. Such OTC conditions of safe use might include consultation with a pharmacist on the use of a self-selection algorithm in the retail pharmacy setting, or even a mobile medical app. Using these new technologies and other conditions, certain products now available only by prescription will become more widely available as OTC drugs.



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Right to try

In May 2018, the federal Right to Try Act, was signed into law. This was the culmination of a multi-year effort by Right to Try advocates to enact this legislation at the federal level. Key elements of the Right to Try Act include the following:

- Companies can make unapproved drugs available to patients with life-threatening diseases without FDA's authorization.
- Drugs must only complete one Phase I trial before becoming eligible for right to try use.
- As a general rule, FDA may not use clinical outcomes from "right to try" patients during the new drug review processes.
- Manufacturers cannot be held liable for making their drugs available on a right to try basis.
- Companies may be able to charge patients for certain costs of drugs provided under right to try.

Importantly, for patients seeking access to unapproved drugs, the provisions of the Right to Try Act set up a parallel track with FDA's existing Expanded Access regulations. And for drug companies willing to consider compassionate use requests, these competing laws put them in the position having to determine if they will make their drugs available under Right to Try, Expanded Access, or both.

Since the enactment of the Right to Try Act, there have only been a very small number of publicly reported cases where investigational drugs have been made available to patients under Right to Try. Many pharma companies are hesitant to consider the Right to Try pathway because they would rather have FDA included in the decision-making process for compassionate use cases through the Expanded Access process. In the meantime, FDA has largely avoided making any definitive statements about the Right to Try Act, and instead has urged patients to speak with their doctors if they wish to explore the use of an investigational product under Right to Try.

Pharmaceutical and biotechnology companies will need to carefully consider whether they should make their investigational therapies more widely available under the Right to Try Act. Doing so could pose significant risks (such as undermining their relationships with FDA), but may also lead to substantial benefits (including obtaining broader patient experience outside of the framework of clinical trials).



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Medical products with military application

The Food and Drug Administration (FDA) has launched a new program to expedite development and review of certain products designed to address unmet medical needs. The program — which expands upon recently enacted legislation that helps accelerate availability of medical products for the U.S. military — follows earlier enactment of a new priority review voucher for material threat medical countermeasures.

Starting with blood products designated as high priority by Department of Defense (DoD), the program will significantly increase collaboration between FDA and DoD. It will eventually expand to include other DoD priorities, including vaccines, regenerative medicine and other medical products. The program includes involvement of senior FDA leadership, enhanced communication with FDA and extensive manufacturing and clinical advice — all aimed to encourage FDA to treat DoD priority products at least as favorably as “breakthrough” therapies.

We anticipate that, starting in 2019, FDA will take this new program beyond its current military context . Based on FDA’s initial work plan, FDA aims to expand the program beyond the battlefield to include other products for “austere environments” and other “front–line conditions” that may provide collateral benefits for military personnel, and in turn, the general population.



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For more on regulatory-related issues,
download our recently published 2019
Regulatory Insights for Life Sciences and
Health Care Investments



Government enforcement

IWCF developments in life sciences

The Department of Justice's (DOJ) industry-focused investigation into allegations that pharmaceutical companies violated the False Claims Act by paying kickbacks to Medicare patients through charitable foundation disease funds continues. United Therapeutics' US\$210 million settlement in 2017 was exceeded by Actelion's recently inked US\$360 million resolution. Moreover, disclosures by other pharmaceutical companies suggests that additional resolutions are likely in 2019.

As discussed in the previous section, DOJ has announced opioids as its highest enforcement priority. In 2017, it settled Controlled Substances Act civil penalties with distributors Cardinal & Kinray (US\$44 million) and McKesson (US\$150 million) for alleged failure to report suspicious orders. McKesson agreed to an independent monitor and Drug Enforcement Administration (DEA) compliance program, the first of its kind with a distributor. Opioid manufacturer Mallinckrodt paid US\$35 million to settle alleged failures to report suspicious orders. It agreed to monitor and report to DEA suspicious chargeback volume in its distribution chain, the first time a manufacturer has been asked to monitor and report such chargebacks at a lower level in its distribution chain.

DOJ is scrutinizing electronic medical records software used in medical practices when physicians receive HiTech Act incentives for adopting electronic recordkeeping and communication with hospitals, labs, and other health care providers (HCP). The US\$155 million eClinicalWorks civil False Claims Act settlement and Corporate Integrity Agreement in 2017 demonstrate that software companies are expected to comply with the Anti-Kickback Statute, and ensure that their testing, certifications, and functionality meet the Health and Human Services (HHS) Office of National Coordinator regulations. These require software to meet "meaningful use" standards for their HCP customers. We expect more scrutiny in this arena by DOJ, HHS-OIG and the ONC.



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Patient Support Programs

As health care systems around the world have gotten more complex and treatments more costly, navigating access to treatment has become a major challenge for patients. Pharmaceutical, biotech and device manufacturers increasingly have stepped into the breach with a variety of Patient Support Programs (PSPs) aimed at helping patients better understand their treatment options, secure insurance coverage, and afford the out-of-pocket costs of treatment. More advanced PSPs provide nurse education and adherence monitoring services to maximize the benefits of advanced therapies. It's no exaggeration to say manufacturer-sponsored PSPs have improved and saved the lives of millions of patients.

PSPs that involve direct interactions with patients and/or health care professionals are impacted by a variety of regulations, and recent digital tools enhancing these programs have brought their share of new legal developments. Data privacy requirements are triggered when collecting patients' information and advertising law restrictions may apply when communicating on a specific medicinal product. Telemedicine and medical device regulations set boundaries on how PSPs operate, how the tools used are to be legally classified and whether they require regulatory approval. Direct engagement with patients also brings increased product liability risks. And the participation of health care professionals is key to PSPs, but related incentives need to be carefully assessed in terms of compliance with applicable conflict of interest, disclosure and anti-kickback laws. Deploying global PSP policies and programs require a

holistic approach on these topics and awareness of local differences in regulatory treatments of PSPs, notably in the U.S. and the EU.

In the U.S. in particular, manufacturer PSPs have been the subject of intense government scrutiny and enforcement actions over the past several years. Recent efforts by the U.S. Department of Justice to dismiss a series of high profile whistleblower cases challenging nurse education and insurance authorization support as unlawful kickbacks to prescribers, however, suggests government support for PSPs that are properly structured in accordance with government guidance and industry best practices

Life sciences companies must legally anticipate, address, and mitigate these legal risks when launching PSPs to prevent any subsequent liability claims, as well as regulatory and reputational risk exposure. PSPs have the indisputable potential to improve clinical, adherence, and cost outcomes, but it's essential that they be carefully structured to comply with the myriad laws and regulations that govern their operation.



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Yates memo

On 29 November 2018, Deputy Attorney General Rod J. Rosenstein announced long-awaited revisions to the Yates Memo — a directive from 2015 that provides guidelines focused on prosecuting culpable individuals within entities, rather than just the entities themselves.

Codified in § 4-3.100 of the Department of Justice's (DOJ) "Justice Manual" (previously known as the U.S. Attorneys' Manual), the new policy draws sharper distinctions between criminal and civil investigations of corporations in which individuals may be held accountable. While reiterating the DOJ's priority of pursuing individual accountability for corporate wrongdoing, the new policy affords DOJ civil attorneys some discretion to negotiate civil releases of liability for individuals who do not warrant further investigation or civil prosecution. The previous policy set forth in the original Yates Memo expressly excluded any releases of individuals in all corporate resolutions.

Recognizing the impractical nature of the previous requirement that a corporation identify every individual involved in the wrongdoing in order to receive cooperation credit in a civil investigation, the new policy sets forth a sliding scale of cooperation credit a corporation may receive in a civil investigation measured by how much "meaningful assistance" the corporation provides to the government. A corporation may receive maximum cooperation credit by doing a "timely self-analysis," proactively disclosing wrongdoing, and identifying "all individuals substantially involved in or responsible for the misconduct." However, DOJ civil attorneys can exercise their discretion and still offer "some

cooperation credit" to a corporation that has meaningfully assisted the investigation without meeting the requirement for full credit.

As with the prior policy, the extent of the credit earned depends on the timeliness of the cooperation, the diligence, thoroughness and speed of the internal investigation and the proactive nature of the cooperation. Of course, in criminal investigations companies must still provide information on all individuals who were substantially involved in the conduct at issue in order to receive cooperation credit.

According to DAG Rosenstein's comments introducing the new policy, the DOJ hopes to achieve faster resolutions of civil investigations as a result of the new discretion afforded the civil DOJ attorneys to negotiate releases of individuals and award cooperation credit on a more flexible basis.

The eCW settlement is unique in that the DOJ, in addition to requiring the company owners to admit joint and several liability for the settlement payment, required three lower-level employees to pay relatively minor sums (US\$50,000 for one individual and US\$15,000 for the other two) to resolve their liability in separate settlement agreements apart from the company. This appears to be a departure from previous experience where the DOJ only pursued high level employees, officers or owners of companies who directly benefitted from the alleged conduct.



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Precision medicine

Gene therapies

The FDA approved the first gene therapies in 2017, marking a new era in precision medicine. Gene therapies are beginning to deliver on their promise of eradicating the underlying causes of diseases, and we anticipate continued progress throughout the coming year.

The FDA has approved Luxturna, a treatment for a rare, blindness-causing genetic mutation, and Yescarta and Kymriah, two gene-based blood-cancer treatments which are CAR-T immunotherapies. Gene therapy is also being developed for more prevalent diseases, such as hemophilia, Parkinson's disease, Huntington's disease, and cystic fibrosis.

Despite new opportunities bolstered by FDA announcing that gene therapies may qualify as Regenerative Medicine Advanced Therapies, challenges remain. Thoughtful clinical trial design continues to be a critical component. Small patient populations and serious and progressive symptoms in diseases targeted by gene therapies create barriers to generating the robust clinical evidence needed for both FDA approval and reimbursement decisions by payers.

There is also uncertainty and concern around long-term outcome durability, dangerous immunogenicity reactions and unique manufacturing challenges. Government policy continues to evolve on issues like reimbursement and the regulation of diagnostic devices often needed to personalize therapies.

Gene therapies will play a growing role in medicine in the decades to come, but important challenges will need to be addressed before their full potential can be realized.



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Regenerative medicine

Regenerative medicine — which includes breakthroughs like stem-cell-regenerated organs and personalized gene therapies— has been recognized by the Food and Drug Administration (FDA) Commissioner as one of the “most promising fields of science.” To support innovation, the FDA has issued four guidance documents designed to clarify how it will apply the existing regulatory framework to these therapies. This framework includes the Regenerative Medicine Advance Therapy (RMAT) designation program, which offers sponsors more frequent interactions with FDA during product development.

These guidelines attempt to clarify which human cellular and tissue products (HCT/Ps) may continue to be marketed without prior FDA approval. FDA announced that it will not enforce its stricter interpretations until December 2020, but has recently been urging companies to approach the agency for product-specific input. An uptick in FDA enforcement action against certain currently-marketed HCT/Ps has demonstrated that those HCT/Ps promoted for serious or life-threatening diseases (e.g., cancer) or with high risk routes of administration (e.g., intra-ocular injections) will not be insulated by this enforcement moratorium.

For regenerative medicines that will require FDA pre-approval, the FDA may consider innovative approaches adapted to the revolutionary nature of these products. FDA outlined some of these approaches in six draft guidance documents on gene therapies in July 2018, and has promised more. Sponsors may also benefit from enhanced collaboration with the FDA and expedited review in obtaining pre-market approval.



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Personalized medicine

Personalized medicine seeks to precisely target therapies to the specific characteristics of individual patients. Rapid advancements in genetic and molecular testing have improved the ability to select the right therapy at the right dose for the right patient. Other forms of personalized medicine, such as 3D printing of individually matched implants, also promise to improve targeted treatments. While initial developments in companion diagnostics and personalized devices have proven promising, these technologies are only at the very beginning of their opportunity.

Given these developments, personalized medicine is also changing the way therapies are developed. Collaboration between pharmaceutical and diagnostic companies allows for the design and use of companion diagnostic assays early in the development of novel therapies. This approach allows therapeutic manufacturers to better target optimal patient populations, potentially increasing efficacy and reducing side effects.

While these medical approaches are revolutionizing certain areas of medicine, they also require adjustment of traditional legal and regulatory frameworks. Companion diagnostics and their associated pharmaceutical products must be approved by the U.S. FDA in parallel, requiring close collaboration between companies.

Similarly, a complex framework of reimbursement is slowly developing and traditional models of laboratory regulation are melding with diagnostic product regulatory requirements. Given these novel regulatory and reimbursement issues, agreements governing the relationships between pharmaceutical and diagnostic companies must establish a framework for the companies to cooperate and share data as they pursue regulatory and reimbursement approvals, and address contingencies such as clinical holds, approval delays and protracted reimbursement negotiations.

As these technologies grow in prevalence, questions surrounding the legal issues – and the strategies for addressing them in the collaboration context – will continue to evolve as well.



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Regulatory framework for genetic testing

We are presently witnessing the rapid development of biomedicine, including genetic testing which serves the diagnosis, management, and treatment of conditions possessing genetic components. The role of genetic testing is expected to increase, in particular in view of the development of personalized medicine.

Among the main concerns on how best to ensure the safety and quality of genetic testing are: personal data protection, medical supervision, genetic counselling, direct-to-consumer genetic testing (DTC), requirements for medical laboratories and health care providers, appropriate assessments of product safety and efficacy, and authorities' supervision over genetic testing.

There is no uniform or comprehensive regulatory framework concerning genetic testing in Europe. Genetic testing is, to a large extent, regulated at a national level, and different countries implement different approaches. Some states have adopted biomedical regulations, or specific acts concerning genetics, while others have included different aspects related to genetics within general health care laws. Notably, there are countries that restrict or essentially prohibit DTC genetic testing (e.g. Germany or France).

Certain issues connected with genetic testing are governed by EU and international laws. Most notably and recently, the GDPR, in terms of data privacy, and the In Vitro Diagnostics Regulation (IVDR), with respect to genetic tests, have a substantial impact on the industry, although the latter to a smaller extent than initially planned. Moreover, the Council of Europe's Additional Protocol on Genetic Testing of 2008 finally entered into force in 2018.

In 2019, one could expect that, in view of safety and quality concerns, the innovative character of the industry, and the increasing popularity of genetic testing, new laws will be adopted in countries that are currently lacking specific regulations, and that the existing laws will be subject to changes. For instance, in Poland, in July 2018, it was announced that a draft law on genetic testing and biobanks will be published in the near future.



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M&A

Pharma and biotech M&A

2018 started out with great promise for the life sciences M&A market. With tax reform and many of the other uncertainties driven by the new presidential administration in the U.S. having been resolved at least in the short term, and many buyers having significant amounts of cash to invest, 2018 seemed primed for robust M&A activity. In fact, a number of sizable transactions in the early part of the year seemed to portend just that. However, that early momentum did not continue. A strong stock market and competition for biotech assets in hot areas such as oncology and orphan drugs combined to drive valuations to a level that caused many buyers to sit on the sidelines. A continuing refrain we heard from clients was that they were in the market but prices were just too high.

In the early part of 2019, many of the same dynamics that we saw at the start of last year seem to be in play. Pharmas and the big biotechs have cash on the balance sheet and are strongly motivated to add new products and technologies to their platforms. Prices are generally thought to have come down to more reasonable levels and CEOs were again heard at the annual JPMorgan Healthcare conference in January to be intent on being active in the M&A market. Several significant transactions have already been announced, including the US\$74 billion acquisition of Celgene by Bristol-Myers Squibb (BMS) and Roche's US\$5 billion acquisition of Spark Therapeutics.

Will we see this momentum continue? Deals of the BMS/Celgene magnitude are always difficult to predict. However, our clients are very actively looking at smaller and mid-size "bolt-on" deals and we do expect 2019 to be a strong year for those deals. Potential threats to this increase in activity include market volatility of the type we saw in late 2018 and whether boards of directors will be comfortable selling at today's prices with significantly higher valuations still clearly in the rear view mirror.



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Transfer Pricing

As the life sciences sector continues to evolve, adopt new technologies, and seek new growth opportunities, Transfer Pricing (TP) and tax and supply chain planning will continue to play a very important role in 2019.

The use of technology and the fragmentation of IP make it increasingly difficult to determine where value creation is. What's more, an increase TP focus on the location of people involved in the development, enhancement, maintenance, protection, and exploitation of IP, means that companies aren't able to operate in many jurisdictions without people on the ground.

Tax authorities are becoming more aggressive, and businesses should expect new legislation on IP and an increased number of TP audits.

M&A, JVs, and collaborations are often common in life sciences as a way to grow product lines, market products, or divest from mature markets and products to focus on new opportunities. Assessing risk and identifying opportunities through supply chain planning can generate significant financial benefits for businesses in this sector and mitigate tax and TP risk.

If carefully planned and aligned with commercial strategy, TP can enable businesses to achieve their strategic goals and become more efficient. But if ignored, it can result in significant cost and reputational damage.



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Milestone payments as tool to bridge the valuation gap

In the past, milestone clauses were only known from license agreements. Now, they are virtually the norm in U.S. life sciences M&A transactions and are seen more and more in European life sciences M&A transactions. They provide for purchase price payments which are contingent on certain events, the milestones. These can be financial figures like annual revenue or EBIT (financial milestones), regulatory events like the granting of a marketing authorisation for a medicinal product in a certain country (regulatory milestones), and/or other milestones like the granting of a patent.

Milestone clauses make deals possible that would otherwise not happen, but they are prone to dispute, in particular if the milestones are not clearly defined. According to a U.S. study, approximately 30% of all milestone clauses used in private U.S. M&A agreements lead to a legal dispute of some kind.

For financial milestones, digital clauses (all or nothing) are not advisable from the seller's perspective, because then the buyer has a strong incentive to manipulate the figures so that they remain just under the relevant threshold. A sliding scale within a certain corridor makes more sense. Other protection clauses for the seller pertaining to financial milestones are difficult to negotiate because they impair the ability of the buyer to manage the target company as he or she sees fit and to realize synergy effects.

The efforts the buyer needs to undertake in order to achieve regulatory milestones, the so-called diligence obligations, are typically heavily negotiated. Often "commercially reasonable efforts" are agreed, but it should be further defined what that means. If the up-front payment is high enough, the buyer might be able to avoid diligence obligations. The absence of such obligations should then be clearly stated in the agreement.

Listed contingent value rights which certify milestone payment claims have recently been rarely seen in the U.S. and never in Europe.

Milestone clauses are here to stay, in the U.S. as well as in Europe. It can be expected that they become more common in Europe – which is good news, because milestone clauses bridge the valuation gap and therefore increase the number of successful life sciences transactions.



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Hospital M&A

Hospitals and health care providers are continually asked to do more with less: improve efficiency and quality of care delivery (while bearing some or all of the financial risk), and at the same time contend with decreases in U.S. government reimbursement. To respond to this challenge, health systems must acknowledge a need for better management of health within the populations they serve — driven by access to services across the continuum of care.

In 2019, health systems will continue the search for partners that can assist with these goals. New relationships will take on a host of forms with increasingly complex legal and regulatory issues that set them apart from transactions in other industries. And because most U.S. health systems operate as nonprofit corporations, governance, culture, and community-dynamics provide an additional level of complexity.

In the coming year, we expect to see:

- a host of transaction structures, including joint ventures, joint operating agreements, member substitutions, co-management agreements, and all-out acquisitions;
- a range of targets and combinations spanning the continuum of care;
- increased attention to the tax and finance implications of these structures; and
- continued, heightened attention from antitrust enforcement agencies to competitive effects of these deals.



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The firm has extremely intelligent attorneys who offer sage advice. They are available at a moment's notice, and are deftly able to summarize a legal issue and offer several potential solutions with probabilities, strengths and challenges. The client service is exceptional too.

*Client, Healthcare,
Chambers USA, 2018*

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Europe

Brexit

Brexit continues to create significant uncertainty for the life sciences industry, with no clear answers yet as to whether the UK will leave the EU with a withdrawal agreement in place or not, nor on the details of the future longer term trading relationship between the EU and UK.

If the Withdrawal Agreement, which sets out the terms on which the UK will leave the EU, is approved there will be a transition period until the end of 2020 during which EU law will continue to apply in the UK and the details of the future EU/UK trading relationship will be negotiated. If the Withdrawal Agreement is not approved, referred to as a “no deal” scenario, the default position is that the UK will leave the EU with no transitional arrangements in place and no bespoke long term trading relationship, unless a different outcome is subsequently agreed. Then there is still the outside possibility of a delayed exit date or second referendum.

Whatever the immediate outcome, the life sciences industry in both the EU and UK are agreed on the need for close cooperation and alignment of the future UK and EU regulatory regimes for medicines and devices — and the overarching need to ensure patient safety and supply continuity.

Life sciences companies across the world with operations, third party manufacturers, suppliers, customers, or clinical trials in the UK need to urgently assess the legal and business risks resulting from Brexit and prepare on the basis of a “no deal” scenario. This includes reviewing the company’s regulatory position, batch release activities, supply chains, key contracts, customs arrangements, and data flows.

While many companies have or are in the process of implementing changes to safeguard their ability to develop, manufacture, and supply products post-Brexit, not all have done so yet and with the UK scheduled to leave the EU at 11:00 p.m. GMT on 29 March 2019, time is running out.



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MDR and IVDR

In 2017, after much discussion, the Medical Devices Regulation and In Vitro Diagnostics Regulation were adopted at the EU level. These regulations, which include changes in classification of medical devices—as well as the conformity of assessment processes that will precede their CE marking, marketing in the EU and related clinical data requirements—are likely to result in major changes to EU regulation of medical devices.

Although the Medical Devices Regulation will not officially come into effect until May 2020 and the In Vitro Diagnostics Regulation will not begin until May 2022, manufacturers are already facing the impact of the upcoming changes, including in their interactions with authorities and notified bodies.

A number of notified bodies have decided either not to seek licenses to the MDR and IVDR or to limit the scope of these licenses. Consequently, these notified bodies will either cease to exist or have a reduced capacity to issue CE Certificates of Conformity. As a result, manufacturers are facing the prospective of losing their notified body and the CE Certificates of Conformity that is essential to marketing of their medical devices in the EU.

The European Commission has prepared several guidance documents to address a variety of issues including transition periods related to public procurement, import and export of medical devices and the validity of CE Certificates of Conformity during the transition period. These documents are useful in light of the fact that, during the transition periods related to the MDR and IVDR, medical devices with CE Certificates of Conformity issued on the basis of the old and the new rules will be available on the EU market simultaneously.

Further guidance documents are expected from the European Commission in 2019. These will include guidance intended to anticipate gaps in alignment with other legislation, such as environmental compliance legislation.



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Regulatory exclusivities in the EU

Regulatory exclusivity rights in the EU were originally developed to incentivize the industry to continue development of innovative medicinal products, including for the treatment of rare diseases and for use by children. In an effort to further promote development of these innovative treatments, the European Commission continues to consider the legal environment and its effects on innovation, as well as, now, pricing.

In the EU, innovative medicinal products can be protected by several regulatory exclusivities including regulatory data protections that safeguard data contained within marketing authorization dossiers and market exclusivity protections for orphan drugs. Pediatric extension of SPCs or of orphan exclusivity is also available in return for conducting pediatric studies.

With continued emphasis on innovative drugs, governments in the EU have been considering to what extent the legal framework for regulatory exclusivities is successful and how regulatory exclusivities relate to pricing and affordability of medicinal products.

The European Commission has recently launched several projects to evaluate the legislation on regulatory exclusivities. In 2018, the European Commission started its evaluation of the legislation on medicines for children and rare diseases.

Although debate around efficacy of regulatory exclusivities will surely continue in 2019, several court decisions in 2018 – both by the Court of Justice of the EU and by national courts in the UK and the Netherlands – confirmed the exclusivity rights for innovator pharmaceutical and biotech companies.



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Excessive pricing in the pharmaceutical

An issue of increasing importance for competition authorities

Competition authorities have historically been reluctant to investigate cases of excessive pricing and to appear as price regulators. However, developments over the past few years, at both the EU and the national level, suggest that the tide is turning.

Excessive pricing can constitute a breach of competition law under certain circumstances. Under Article 102 of the Treaty of the Functioning of the European Union (TFEU) dominant firms are prohibited from “directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions.”

In recent years, national competition authorities in EU Member States have vigorously pursued cases against pharmaceutical companies. Recent examples include the Aspen case (September 2016) in which the Italian Competition Authority fined Aspen €5.2 million for abusing its dominant position in Italy by charging unfair prices for four off-patent cancer drugs, and the CD Pharma case (January 2018) in which the Danish Competition Authority found that CD Pharma, a pharmaceutical distributor, had imposed excessive prices for Syntocinon, a drug preventing excessive bleeding during childbirth.

In addition, several excessive pricing investigations are currently underway in the pharmaceutical sector, initiated notably by the UK Competition and Markets Authority (CMA) (Actavis, 2016 / Concordia, 2017) and the European Commission (Aspen, 2017).

However, the most recent excessive pricing case to reach the courts may have cast a shadow over these successes. In Pfizer/Flynn Pharma (June 2018), the UK Competition Appeal Tribunal (CAT) held that the CMA had misapplied the legal test for excessive pricing when it fined Pfizer and Flynn Pharma over GBPE89 million for charging unfair prices for an anti-epilepsy drug. The CAT’s judgment is damning. It states that “cases of pure unfair pricing are rare in competition law” and that such cases should only be brought where they are “soundly based on proper evidence and analysis.” The CAT also warns that competition authorities should be “wary of casting themselves in the role of price regulators.”

It is unclear whether the Pfizer/Flynn Pharma decision will deter competition authorities from bringing excessive pricing cases in the future. The CMA has already announced that its ongoing investigations in this area are likely to be “severely delayed” as a result of the CAT’s decision. However, the excessive pricing landscape is likely to continue to evolve in 2019 as competition authorities grapple with the difficult task of balancing, on the one hand, the need to crack down on the abusive charging of high prices by dominant companies, and, on the other hand, the recognition that high prices are necessary to reward the investment and innovation of such companies. The pharmaceutical sector is likely to remain at the centre of this debate.



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Is the EU regulatory system being set aside?

The debate about drug pricing and perceived “excessive pricing” has prompted political debate in some EU member states about possibilities to apply cheaper alternatives such as off-label use, pharmacy compounding, personal import from outside the EU, or even compulsory patent licenses. However, some of these suggestions may be questionable from an EU pharmaceutical regulatory law perspective, which requires a marketing authorization based on an appropriate data package in order to place a medicinal product on the market.

The debate regarding “excessive prices” is not new. However, over the last years there is an increase in political pressure and subsequent measures that could change or even undermine the EU regulatory system. In light of the more advanced novel products (e.g., gene therapy) that are increasingly entering the market, it is expected that such pressure will build even more.

The basic rule is that no medicinal product may be placed on the market in the EU without a prior marketing authorization granted by the European Commission or by the competent authority of the EU Member State. Certain exceptions apply, e.g., compassionate use, named patient use pharmacy compounding and off-label use. Although such exceptions should be interpreted strictly, we note that use of such exceptions has increased and that this is often promoted by governments and payers justified by cost-cutting arguments.

We note an increased interest and push from governments and payers regarding pharmaceutical compounding whereby the pharmaceutically compounded product effectively serves as a less costly alternative to an authorized medicinal product with an allegedly high price. The same applies for the use of a medicinal product for a use not covered by its marketing authorisation (off-label use) as an alternative for the use of a medicinal products authorized for such use which has a higher price. The latter was recently deemed acceptable by the European Court of Justice.

Medicinal products may benefit from certain regulatory exclusivity rights in the EU (e.g., regulatory data protection, orphan exclusivity, paediatric SPC extensions, etc). In recent years, a number of reports have been published on an EU level investigating such exclusivity rights, such reports may be the starting point for a review of the current system of exclusivity rights and potentially amendments to such system. Similarly from a patent perspective there is an increased interest in compulsory licensing. These developments are encouraged and initiated by governments under political pressure following the pricing debate and the allegedly excessive prices.



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R&D in the EU

The promotion of R&D in the EU is aimed at ensuring the continuous development of treatment methods, as well as the appropriateness, affordability, and accessibility of medicinal products.

Certain steps have been taken at the EU level, for example:

- **Innovative Medicines Initiative:** a public-private partnership between the European Commission and the pharmaceutical industry offering grants for innovative research.
- **Horizon Europe (in 2021-2027):** the new European Innovation Council will fund fast-moving, high-risk innovations.
- **InnovFin Infectious Diseases:** the European Investment Bank supports projects related to innovative vaccines, drugs, medical and diagnostic devices, and novel research infrastructures for combatting infectious diseases.

Individual countries are also taking action, for example:

- **IP Box:** a preferential tax rate for revenues generated by IP rights covering innovations. This has been introduced in several EU countries, for instance, in the UK (a reduced rate of 10%), Luxembourg (80% of revenues exempted from taxation). Poland introduced a reduced 5% tax rate starting in 2019.
- **Medical research entities:** supporting innovations and sponsoring medical research, especially those that do not generate an easy profit. These include the Medical Research Council in the UK, the Danish Medicines Agency, and Inserm in France. In Poland a Medical Research Agency is being created.
- **Preferential reimbursement procedure:** Poland announced work on an innovative

procedure for development which would provide companies that manufacture or invest locally in R&D preferential treatment in reimbursement proceedings (e.g. partial or total exemption from fees, or a shortening of procedures).

However, since many patients and countries cannot cover the costs of innovative treatment, various countries have started negotiating reimbursement deals in groups:

- **BeNeLuxA:** Belgium, the Netherlands, Luxembourg, and Austria.
- **Valetta:** Italy, Spain, Greece, Portugal, Cyprus, Malta, and Romania.
- **V4 Plus Fair and Affordable Pricing:** Poland, Lithuania, Slovakia, and Hungary; the Czech Republic is an observer.

The overall trend is observed towards the stimulation of innovation and competitiveness. The EU searches for new long-term solutions. In 2019, more initiatives on the national-level and continuous growth of funding are expected, facilitating R&D activities of the industry within the EU.



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Aggregate consumer actions in Europe

2019 will bring a new level to product litigation in Europe. Legislation adds a new layer of actions with a potential for life sciences companies.

With the introduction of Musterfeststellungsklage on 1 November 2018, there is now a kind of collective procedure available in Germany. Consumers can register claims that are similar to the subject matter of a representative action in a public litigation register. Defendant to the representative action as well as the registered consumers will be bound by the ruling on the representative matter. Legal or factual elements of civil claims in consumer matters can be subject matter of the representative action. The first of these new actions are pending and made public in the litigation register.

More than 100,000 consumers are said to have registered claims already. While registered, consumers cannot bring their own actions against the defendant. These consumers can bring follow-on actions once the representative action is res judicata. Non-registered consumers can bring their own action. Other countries such as the Netherlands and Italy are also amending their existing collective redress legislation.

Another legislation project might bring a further development as the topic of collective redress recently picked up speed at the EU level – although with an uncertain outcome: in April 2018, the European Commission proposed a directive on representative actions for the protection of the collective interests of consumers. Qualified consumer organizations across the EU would be enabled to bring representative actions for an injunction and for compensation in case of infringement of EU consumer legislation. Several legislation of concern for the life sciences industry would be within the scope of the action. The Committee on Legal Affairs of the European Parliament has proposed changes in December 2018 which will be further discussed in 2019. The future timeline is somewhat uncertain with elections to European Parliament coming up in May 2019. Nonetheless, this is a development to look out for.



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Emerging markets

Africa

South Africa's proposed National Health Insurance scheme (NHI), once implemented, will represent a new paradigm in how health care is funded and procured in South Africa. The government intends to formulate a comprehensive legislative framework for the full implementation of the NHI by 2026.

Despite the perceived benefits of NHI adoption, many questions remain, and there is uncertainty regarding matters such as funding, administration, legislative reforms, and the future of private health care. Government has not provided any concrete indication regarding projected costs of the NHI or the manner in which it will be funded. Current funding options include payroll taxes, surcharges on taxable income, and/or increases in VAT.

The future of private medical schemes once the NHI has been implemented is also uncertain. It is conceivable that medical schemes may be rendered redundant by the NHI or that they may be prohibited from funding health services covered by the NHI. There is also concern that implementation of the NHI may adversely impact private medical schemes.

In light of these uncertainties, the 2026 implementation timeline is widely regarded to be ambitious.



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Health care innovation: the view for Latin America

Transnational companies from the sector will continue to view Latin America and its emerging markets as attractive for expanding their activities and businesses. Some of the factors key to Latin America's appeal include:

- Increasing growth and expansion of health infrastructure and services aimed to better cover the population's needs.
- Innovative but not yet fully explored business and regulatory models aimed to improve access to innovative technologies, therapies, and products.
- Regulatory frameworks which in some jurisdictions aim to simplify the launch of drugs and devices.
- Jurisdictions where various factors – including location, costs, population, and health infrastructure – are highly conducive to conducting clinical trials.
- Adoption of specific recognition agreements between certain Latin American countries aim to expedite regulatory processes.

New regulations and trends related to regulatory enforcement, competition, and consumer protection are also emerging in several Latin American territories. Key issues in the region in 2018 include general compliance, data privacy, competition, and health regulation (which include innovative therapies, digital health, and clinical trials). Strategic investments and

divestitures adopted globally are delineating new business trends and models for the further expansion of the life science industry sector throughout the region.

Mexico

Mexico will face the adoption of a new public policy and approach by the new Federal Administration regarding the provision and access of health care services and products.

Changes to the Mexican Health Law and related provisions are expected towards a federal control of all health services and for the procurement of health inputs (all medicines, devices, and products), which will have an impact for the Mexican industry.

Mexico has adopted a new anticorruption system that has impacted the way in which the supply and performance of certain activities (i.e., public procurements, and interaction with HCPs) are carried out by the sector.

Also, Mexico has set the grounds for adopting a new framework concerning the legalization of activities and products involving cannabis. Important development of activities and investments has started to occur.



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On the horizon

Closed loop systems

Combining the power of real-time sensing, novel therapy delivery tools, and complex control algorithms to automatically deliver optimized therapy, so-called “closed loop” systems sit at the forefront of cutting edge technology. Early versions of some closed loop systems are already available, such as artificial pancreas systems, which combine glucose sensing technology, insulin delivery tools, and automated control algorithms.

As novel wearable sensors come to market, the opportunity to leverage real-time physiological information to optimize therapy delivery presents new opportunities for personalized medicine. From drug delivery to electrical stimulation, these tools leverage automation to help manage complex diseases, alleviating some of the self-management burden on patients and potentially improving outcomes.

Complex systems like artificial pancreas products require innovative regulatory approaches, nuanced privacy strategies and long-term reimbursement plans. They are also an area to watch because development often involves strategic partnerships between multiple companies. This requires that deals be structured to provide long-term benefit to all of the players.

While some initial technologies have already been released to the market, innovation promises to bring continued improvements.



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They have great legal and regulatory knowledge, as well as litigation capabilities both at a national and international level. They are incredible and their technical understanding is fantastic.

*Client, Life Sciences,
Chambers Global-wide, 2019*

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3D printing in the EU

3D printing is quickly taking hold in the medical devices market and poised to change how we think about health products, manufacturers, and the legal issues they create. While medical devices like implants, prostheses, and even bones are already being produced by 3D printers, Medical Device Regulation, which has not yet even come into force, is outdated in this area.

Until now, 3D printing has largely been unregulated, despite multiple legal issues. For example, if an implant is 3D printed by a hospital, who is responsible? The supplier of the printer, the supplier of the CAD files providing the blueprint for the implant, or the hospital itself? Is the implant a customized device? Which manufacturing standards and regulatory requirements apply? Do exemptions apply for devices made in health care institutions or are they manufactured on an industry scale?

The answers to all these questions have to be found by interpreting laws which do not explicitly regulate this new area of technical developments. Additional questions also arise from the direction of the machinery directive, the REACH Regulation, data privacy, intellectual property, and product liability.

These issues also impact the pharmaceutical industry, as 3D printers may soon be used to manufacture drugs. For traditional manufacturers, utilizing 3D printers compliance with GCP is in focus. However, 3D printers may soon be used by hospitals to print their own medicinal products or to do patient-individual compounding. Questions arise as to whether a hospital/pharmacy is allowed to manufacture outside the scope of pharma laws, and what traditional manufacturers can do about it.



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CRISPR controversy: what next?

In 2018, cell and gene therapies continued to dominate the headlines. In November, experts were gathering in Hong Kong for the second international summit on human genome editing. They were due to discuss scientific advances in the field, ethical concerns over gene editing and debate how governments and regulators should respond. Shortly beforehand, the news broke that a Chinese researcher, He Jiankui, had apparently used CRISPR to create the first gene-edited babies who were resistant to HIV infection. Jiankui was due to present his research at the summit and it quickly turned into a media fire storm.

Jiankui's research has yet to be published but what is apparent is that many of the concerns surrounding CRISPR have been demonstrated by his work. He chose to edit the CCR5 gene – mutations in this gene have been associated with resistance to many strains of HIV infection. However, it also leads to an increased susceptibility to West Nile virus and to more severe cases of flu. It is also not clear what the new mutations introduced into the CCR5 gene will do.

What does this mean for those developing therapies based on CRISPR? Clearly they will need to show robust evidence not only that the expected genetic change has occurred but that as far as possible there are no off-target effects. For individuals with life-limiting or terminal conditions, off-target effects may well be an acceptable risk. The choice of gene target is also crucial. Would there have been the same reaction to He's work if he had chosen to eliminate a disease such as Huntington's? The scientific community will be watching with great interest for the results of the first clinical trials due in 2019, as will regulators.



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The application of blockchain to life sciences

The life sciences and health care sectors have issues with data storage due to the huge volume and need for interoperability across different organisations. When patients move between different health care providers, their medical data has to be transferred to different organisations making medical records difficult to track and trace. The data must be accessible by each organisation, which requires consistent methods of storage and access.

The use of blockchain technology would allow patients to have a unified medical record that can be accessed from a decentralized store. Systems such as the MedRec prototype, which uses blockchain smart contracts to create a decentralised data-management system, are set to improve the way that patients' medical records are stored and accessed.

One of the biggest challenges that will be faced by blockchain technology will be compliance with GDPR. A patient's medical records constitute sensitive personal data, which by the very purpose of a blockchain system, would be transferred to other users of the system. This conflicts with the objective of GDPR, which requires the party controlling personal data to safeguard the security and privacy on behalf of individuals. Systems will have to implement safeguards to ensure that data security and privacy is maintained. This could take the form of restrictions on jurisdictions that can participate in the system. Systems could also ensure that medical records are not stored on the blockchain themselves, but instead the blockchain holds a reference to where each medical record can be accessed.



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For more information

Life Sciences and Health Care Horizons provides only a snapshot of some issues the industry will face in 2019. Our team is focused on tackling these issues to provide our clients around the globe with valuable and innovative solutions to their most complex challenges — present and future.

To learn more about our team or any of the issues covered, please contact Asher Rubin, any of the authors in this publication, or one of the partners you regularly work with at Hogan Lovells.



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Life Sciences and Health Care Horizons – Global Event Series

From spotting trends in digital health innovation to breakthrough cures and navigating fluid regulatory landscapes, the Hogan Lovells' Life Sciences and Health Care Horizons event series will span three continents and feature cutting-edge analysis, engaging panel discussions, and featured keynote speakers.

Save the date:

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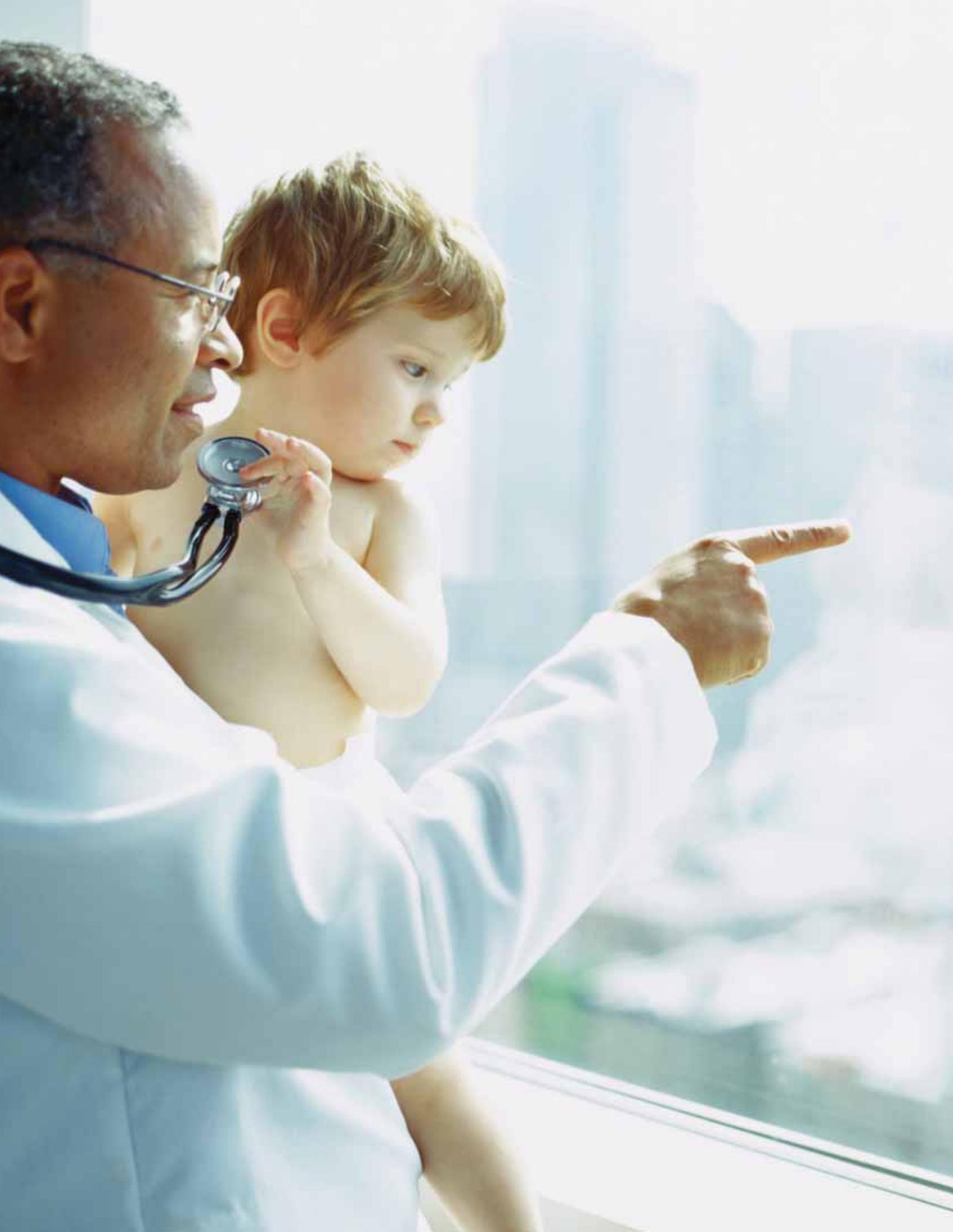


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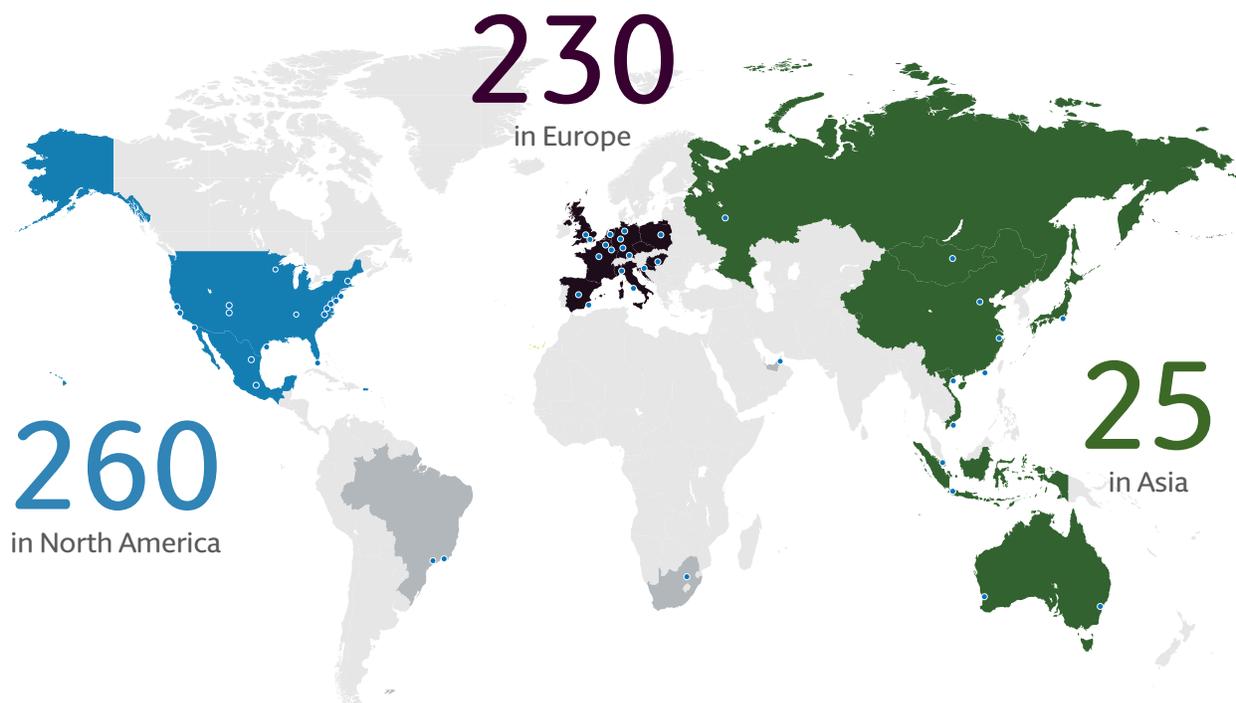
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