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2022 Life Sciences and Health Care Horizons

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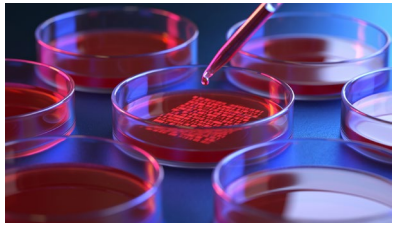

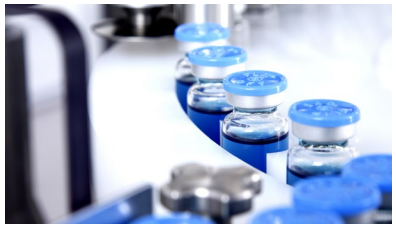

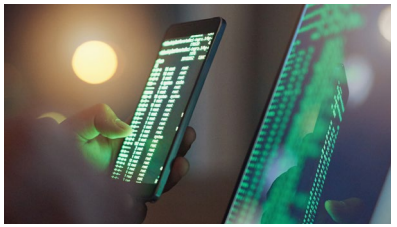

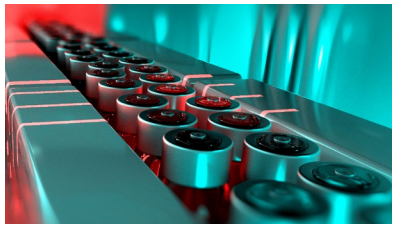

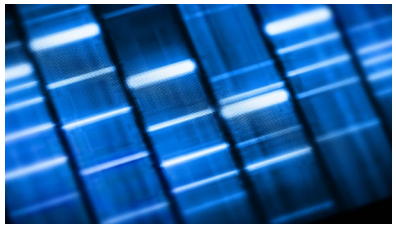

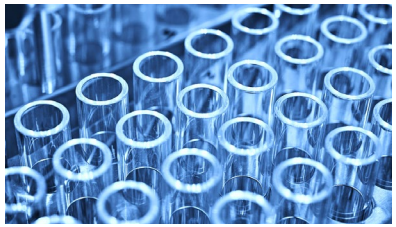

Welcome

The Covid-19 pandemic remains a dominant theme in our forward looking view for companies in the life sciences and health care industry, as the past year has continued to create challenges and a seemingly endless stream of lockdowns and viral surges. While uncertainties abound, we remain hopeful that the innovations necessitated by our collective pivot to pandemic life will become a part of our new normal.

The worldwide vaccine rollout enabled the gradual easing of Covid-19 mandates, but with a watchful eye on the evolution of new variants. The pandemic continued to drive the development and adoption of new technologies and innovations resulting in massive investments into AI, virtual health solutions, telehealth products, and related cybersecurity measures. It also spurred increased scrutiny by regulatory authorities over supply chain reliability, and we expect to see continued activity in this area with the enactment of new diligence obligations, return to in person inspections, and overall manufacturing accountability. Precision medicines continue to provide opportunities within evolving regulatory frameworks that are as complex as their innovative technologies. Moreover, advanced analytics are enabling the incorporation of data collected outside of a traditional clinical setting and regulators are taking note. The need for rapid response and working with regulators to expedite development and review processes will continue to be crucial for the life sciences and health care industry for many years to come.

In the transactional space, we also see increasing complexity, as partners develop innovative terms and payment structures to account for long development timelines and allocation of manufacturing risk for bespoke therapies. While investors may continue to take a cautious approach towards IPOs, indications point to a robust M&A and partnering market in 2022 as many large companies have amassed significant amounts of cash. We believe that innovators having strong data and sound fundamentals will continue to attract investments. We also continue to advise clients on innovative alliances between government, industry, and academia. Conversely, we also see an increase in arbitration, particularly involving cross-border contractual disputes.

In addition to the seismic shifts stemming from coronavirus, life sciences and health care companies are affected by specific issues in each geographic region. In the United States, data collection continues to attract the interest of state regulatory bodies in addition to meeting federal requirements. This is similarly true elsewhere in the Americas, where we see cybersecurity and privacy concerns raised in the context of new digital health offerings in Mexico. The UK is developing new legislation in areas such as medical device regulation, balancing increased flexibility post-Brexit with aligning closely with EU and other major international regulatory systems. In the EU, our life sciences and health care clients are also navigating changing legislation with the introduction of new regulations on clinical trials and medical devices, and proposals for new legislation on artificial intelligence. Companies are also watching the coming implementation of the Unitary Patent Court and its impact on existing systems in Member States. These themes also carry over to Asia-Pacific markets, from regulators watchful of PPE in Australia to recent patent reforms having significant regulatory impacts elsewhere in the region. We have been advising clients doing business in China on new regulations on the use of human genetic resources and the implementation of amendments to the patent law, with significant implications for patent linkage and future marketing authorizations. Patent linkage also continues to be an important topic in Japan, along with the evolution of suitable pricing models for access to innovative therapies. Last but not least, the challenges faced as life sciences companies interact with local third parties in India is also emblematic of these within- versus cross-border tensions.

These are just some of the current and evolving trends that are shaping the future of the industry, which we discuss in the following pages. Hogan Lovells' global Life Sciences and Health Care team — comprised of more than 500 lawyers around the world who support more than 1,000 clients in the industry — stands at the ready to provide you with creative strategies for your most promising opportunities and integrated solutions that protect and support your business when issues arise. We hope that you find our view of the horizon thought-provoking. We look forward to working together, and hopefully seeing each other again soon.

Global Co-Heads, Life Sciences and Health Care Industry Sector

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Next

1 Precision and Regenerative Medicine

Precision and Regenerative Medicine

CTGT transactions: Beware the ripples in the safe harbor

We increasingly encounter research and development collaboration partners relying on various research tools, cell lines, and other technologies to develop products and therapies within the cell, tissue, and gene therapy (CTGT) field. These research tools, cell lines, and other technologies, many of which are patented, are useful for but separate from the product or therapy being developed. When the question of third-party patent rights is raised with respect to such patented technologies, many partners dismiss the concern on the ground that the development of the product or therapy is being conducted in support of a Biologics License Application to the FDA, and therefore is immune from an infringement suit pursuant to the development safe harbor.

Indeed, in the United States, Section 35 USC § 271(e)(1) expressly exempts certain otherwise infringing acts if conducted solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or biological products.

Similar exemptions exist under the laws of many other jurisdictions. Historically, this safe harbor, also known as the Bolar exemption, has been broadly construed in the U.S. However, as recent case law indicates, where a patented research tool, such as a cultured host cell useful in the manufacture of a gene therapy product or a fluorescent protein, is itself not subject to FDA premarket approval, the safe harbor may not apply.

As additional patented research tools become available, developers of CTGT products would be prudent to include any potential development technologies as part of their freedom-to-operate analysis moving forward. And in development collaboration arrangements, companies should ensure that their partners engaged in development work have secured the appropriate licenses for the conduct of such development activities.

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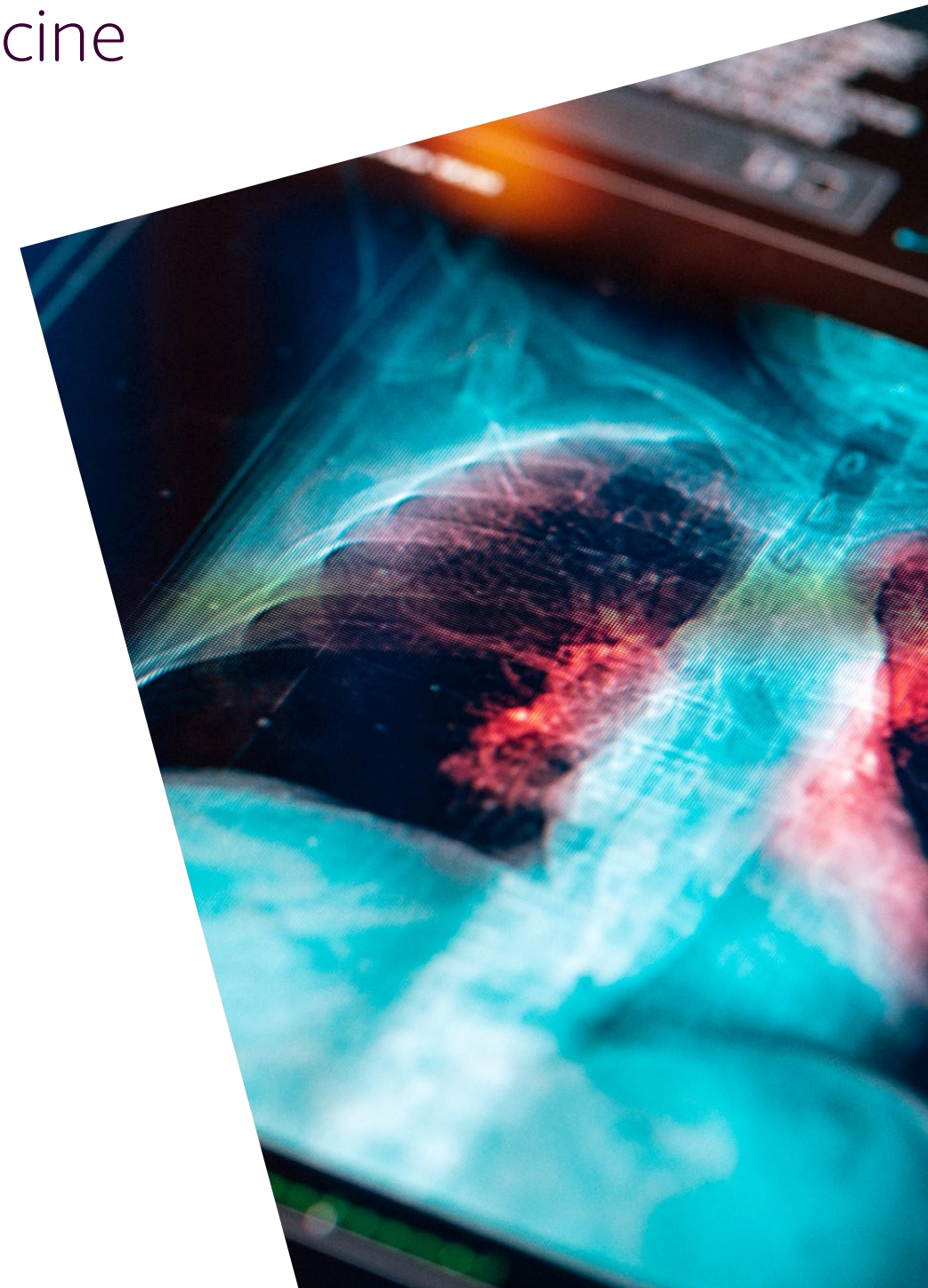

Precision and Regenerative Medicine

The rising complexities of harnessing genomic data

Genetic and genomic information is facing a rapidly changing and uncertain regulatory environment. State legislatures have continued to enact laws and put forth policies that protect the privacy of genetic and genomic information in ways that may complicate its collection and use. For example, at the state level, Florida and California, two of the most populous states in the U.S., enacted laws that may require health and life science organizations that process genetic information to reassess their policies and procedures. At the federal level, and in response to the evolving genomic research landscape, the National Institutes of Health (NIH) is continuing to revise its Genomic Data Sharing Policy, which sets guidelines for ensuring appropriate and timely sharing of genomic research data generated from NIH-funded or conducted research.

The effects of these developments are felt by various players in the life science industry who generate, receive, and rely on genetic information as a core, or even tangential, part of their business model. For example, direct-to-consumer (DTC) genetic testing organizations have direct obligations under state laws, including notice, consent and consumer rights obligations. Pharmaceutical companies who may want to obtain genetic information – from DTC companies or other entities holding genetic data – to advance goals of transforming genomic information into innovative diagnostics and therapies will need to reassess their deal-making strategies with such companies. Medical centers and other organizations participating in research involving genomic data may also have new direct or indirect obligations as new requirements are implemented.

As a result of this ever-evolving regulatory landscape, health and life science organizations are tasked with creating flexible privacy frameworks to maneuver these developing and increasingly complex regimes. A thorough understanding of the ways in which genetic and genomic information may weave in and out of regulatory frameworks will help health and life science organizations to harness the benefits of genetic and genomic information for much-needed and innovative treatments and medical technologies.

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Precision and Regenerative Medicine

Gene and cell therapeutics and advanced therapy medicinal products (ATMP) in Europe

Gene and cell therapeutics are currently the most innovative area in the treatment of patients. While the EU provided a harmonized legal framework with the ATMP Regulation (No. 1394/2007) in 2007, there are still many pitfalls for launching them. Local laws of the EU Member States also provide a layer of complexity. We remain constantly engaged with the agency on behalf of our pioneer clients to make sure the science and the law add up.

In many therapies, cells are taken from the patient in clinical centers, are reengineered and then administered as autologous products. This manufacturing process can present several legal challenges:

- Cell collection may in many jurisdictions be regulated as a (first) manufacturing step, thereby requiring a manufacturing license or the need to act under the control and the license of the engineering manufacturing site such as the cell/tissue or blood collection center. This has a material impact on the GMP requirements that the company must secure with collection centers (e.g., sample testing against infectious diseases).
- The cells can be regulated as tissue or as blood and this may vary between countries. For example, stem cells from blood are regulated differently in different member states. The procedures applied in local markets need to be adapted accordingly.
- Shipping cells and autologous product across EU borders or even within the EU may trigger import/export issues and notification/authorization requirements.
- Supply chain from cell collection to treatment of autologous products must be properly designed from a privacy standpoint due to sensitive health data being processed (e.g., controller-to-controller (C2C) or controller-to-processor (C2P) structure, info notices, contract clauses).
- Packaging and labelling of ATMPs must comport with specific guidelines.
- In view of the above, unique liability risks may arise (see separate write-up).

Gene and cell therapeutics are often curative but their personalized nature can also make them expensive.

Pricing and reimbursement can be a challenge:

- Will clinical collection centers be paid by health insurance or by the company?
- The company should not pay for efforts which are supposed to be covered by insurance reimbursement.

Finally, companies may see competition from clinical centers. Particularly in certain Member States, academic or non-industrial ATMPs may provide alternative services under interpretation of the 'hospital exemption rule' (see write-up below).

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Visit our website to learn more about our Cell, Tissue, and Gene Therapies work.

Precision and Regenerative Medicine

Potential liability risks associated with administration of gene therapies and ATMPs in Europe

The advent of products that use gene therapy, somatic cell therapy and engineered tissues for preventing, treating or even curing human diseases represents a new era in medicine, and probably the biggest innovation in the pharmaceutical industry since the introduction of biologic medicines in the 1980s. The treatment with Advanced Therapy Medicinal Products (ATMPs) brings with it unique and novel legal issues and liability risks particularly for those who manufacture and supply ATMPs.

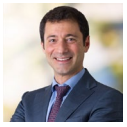
Unlike conventional therapies, ATMPs generate intrinsic and peculiar risks for patients, which are associated with the use of human biological material and with its potential for stimulating immune reaction. The supply chain management of ATMPs, which involves several stakeholders, and the lack of standardization in manufacturing procedures regarding those products are additional critical factors.

The traditional model of the relationship between manufacturer and customer has been a simple transaction point in which the customer pays for a manufactured good and, provided that the good is fit for purpose and as described, the responsibilities on both sides are rather easy to define. With the advent of ATMPs the boundaries are less well defined especially as more players may be involved.

The question “where does the manufacturing begin and end?” is not an easy one to answer. The manufacturing process for a medicinal product using autologous cells indeed involves several steps, including initial harvest of cells from the patient tissue, isolation of cells from that tissue, transfer of the construct to the clinic, removal of construct from the carrier container, preparation of the implant site, final preparation (such as by trimming) of the construct, and implantation. Which of these steps actually constitutes manufacturing? The manufacturer is in any case just one of the key players as the role of health care practitioners and hospital teams is pivotal. The outcome of the procedure can be adversely affected at each step through the introduction of adventitious microorganisms, contamination, or inappropriate manipulation such as over-trimming or poor temperature control. The liability for successful outcome is therefore shared between the legal manufacturer of the ATMP, the contract manufacturer or other service providers, and those who harvest the tissue and who carry out the implantation.

ATMPs moreover raise specific issues concerning data management and data privacy. This may include data from hospital electronic health records, generation of patient related data for end product, data in CAD files describing the end product, etc. These all challenge the existing regime for patient data protection because customization and traceability for product safety make patients identifiable, anonymity difficult, and data can be breached and stolen.

The development of more personalized treatments thus requires an individual analysis of each situation, at the intersection of general liability regimes (tort liability, contractual liability) of each EU member states and specific regimes concerning product liability, clinical trials or data protection deriving from EU legislation.



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Precision and Regenerative Medicine

Product sameness in an increasingly complex environment: Considerations for cellular and gene therapy products

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Whether a product is the "same" as a previously approved product impacts a number of important regulatory decisions, including exclusivity awards and approval actions. Increasingly complex and innovative products in the cellular and gene therapy fields have challenged FDA's traditional sameness standards, but the agency has made strides in addressing this gap.

- In 2021, FDA finalized a guidance document regarding the determination of sameness for gene therapy products for rare diseases, for purposes of orphan-drug designation and exclusivity. Although the guidance provides that sameness is based on transgene and vector characteristics, the inherent complexity of gene therapy products means that this general standard will continue to be refined on a case-by-case basis.
- For biosimilar products, a showing of similarity to the reference biological product is a critical first step towards approval. Here, again, cellular and gene therapy products raise novel issues for FDA and sponsors to navigate. For example, CAR-T therapies involve harvesting a patient's T cells and genetically modifying them ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR). The CAR-T cells are then expanded and infused back into the patient. FDA recently issued a draft guidance document regarding the development of CAR-T products, which discusses principles to show high similarity after a manufacturing change. It remains to be seen how FDA will implement those principles to usher in the next generation of biosimilar products.

The evolving regulatory landscape requires that cellular and gene therapy product manufacturers consider whether and how to engage with regulators to assist in the development of favorable policies and guidance.

2 Clinical Trials

Clinical Trials

Diversity in clinical trials

The Covid-19 pandemic illuminated health and health outcome inequities in the United States. Pharmaceutical industry stakeholders, from government to manufacturers, have begun to recognize that meaningful representation of diverse participants in clinical trials can address health inequities facing historically underrepresented populations. Several bills that promote the inclusion of underrepresented groups in clinical trials have been introduced in Congress. The proposed legislation takes many approaches to increasing diversity, from requiring sponsors to report clinical enrollment targets to the FDA to directing and the Department of Health and Human Services (HHS) to develop guidance about patient recruitment and leveraging decentralized clinical trials to promote diversity.

FDA has also continued to prioritize efforts and initiatives to address clinical trial diversity. As an important preliminary step, FDA issued a guidance document in November 2020 on Enhancing the Diversity of Clinical Trial Populations. More recently, FDA issued guidance on the use of digital health technologies in remote clinical trials and highlighted digital health technologies as a tool to increase the inclusion of diverse populations in clinical trials. Earlier this year, FDA's Center for Devices and Radiological Health also released its Health of Women Program Strategic Plan to address sex- and gender-specific data gaps. We expect Congressional and agency focus on diversity to persist and will keep clients abreast of this everchanging policy landscape.

Many sponsors have independently announced goals to increase the recruitment of underrepresented minorities in clinical trials. With our knowledge in clinical trials diversity initiatives, we advise clients on balancing their clinical trial diversity goals with compliance with legal requirements and bioethical standards pertaining to patient recruitment and outreach, data analysis, protocol design, and more.

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Visit our website to learn more about our Clinical Trials work.

Clinical Trials

Clinical trials regulation

New clinical trials regulation brings possibilities, but also new challenges for pharmaceutical companies conducting clinical trials in the European Union and European Economic Area (EU/EEA): Since the end of January 2022, clinical trials with medicinal products in the EU/EEA are governed by a new regulatory framework, the EU Clinical Trials Regulation (Regulation (EU) No. 536/2014, CT Regulation), which begins replacing the prior EU Clinical Trials Directive 2001/20/EC (CT Directive). The CT Regulation aims to create a harmonized regulatory environment favourable for conducting clinical trials in the European Union. While the CT Regulation is directly applicable in the member states, national laws are still required to fully govern clinical trials.

Possibilities, but also challenges, arise for pharmaceutical companies conducting clinical trials in the EU/EEA, including:

- The CT Regulation brings certain procedural innovations as, even in a multinational trial, the sponsor will only be required to file one request for authorization of the clinical trial. The involved member states will assess the authorization request in a coordinated procedure with each member state providing one approval covering the approval by the national competent authority and the ethics committee/institutional review board.
- The management of the clinical trial and all communications between the sponsor and the involved member states will be done throughout the complete life cycle of a clinical trial in a new online portal, the Clinical Trial Information System (CTIS). The CTIS will be used, e.g., for the authorization requests, any required changes to the clinical trial, any requests by the member states or the submission of annual safety reports as well as of the clinical trial results. One aim of the CTIS is also to increase transparency in clinical trials to the general public. Therefore, sponsor(s) need to carefully consider which information in the CTIS should instead remain confidential.
- The concept of co-sponsorship is formally introduced recognizing that a clinical trial can have more than one sponsor and stipulating the requirements the co-sponsors have to observe.
- The CT Regulation provides a transitional period allowing pharmaceutical companies to continue, to commence (for a limited time), and to finish clinical trials under the prior CT Directive framework and implementing national laws. All clinical trials conducted under the CT Directive with at least one active site in the EU will have to be transitioned to the CT Regulation by 30 January 2025 triggering the need for a new authorization under the CT Regulation.

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Clinical Trials

A comparison of clinical trials litigation risks: U.S. and EU developments

On 31 January 2022 Regulation EU/536/2014 (CT Regulation) governing clinical trials with medicinal products in the EU eventually became applicable. The CT Regulation will fully replace Directive 2001/20/EC (CT Directive) and the implementing laws in the member states.

The CT Regulation is directly applicable in the member states. Having said that, it is important to note that national laws are still required to fully govern clinical trials.

One important part is damages compensation, as the applicable system shall be regulated by the Member States. The CT Regulation explicitly requires Member States to ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted in their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk. Certain exceptions may apply for low-intervention clinical trials. The applicable system shall follow the form appropriate for the Member State concerned where the clinical trial is conducted. Information about the applicable damage compensation system is to be included in the informed consent.

In the United States, FDA regulations set forth specific requirements for informed consent, including the requirement that the consent must explain whether there is compensation available in the case of injury, which is typically required by institutional review boards that are responsible for ensuring the adequacy of the information in the consent document. Further, the consent document cannot waive or appear to waive the rights of the study participant or appear to release those conducting the study from liability for negligence.

While it is best to strive for global consistency in clinical trial documentation, when possible, it is important to adhere to any local requirements. Regardless of the local requirements, companies should ensure the coverage is defined specifically, including the types of expenses that will be reimbursable and the requirement that the expenses be directly caused by the experimental product.

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Clinical Trials

Risk management for the handling of Human Genetic Resources in China

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With the Biosecurity Law, the Personal Information Protection Law and the Criminal Law taking effect in 2021, China is striving to emphasize the safety of human genetic resources (HGR). The Human Genetic Resources Administration of China (HGRAC) also continues to play an active role in interpreting relevant regulations. Multinational life sciences corporations need to be cautious when dealing with HGR in clinical trials and other research programs in China, and comply with the appropriate regulatory procedures outlined below.

- Collaboration with Chinese Parties. Foreign parties are prohibited from collecting, preserving, or supplying HGR in China with only limited exceptions. Therefore, foreign parties will need to collaborate with Chinese medical institutions in the handling of HGR. The local Chinese institutions shall be the ones involved in collecting HGR, substantively involved in the whole process of clinical trials and research programs, and able to access the full HGR records and data. The relevant trial data backups shall also be provided to HGRAC.
- Record-Filing/Approval from HGRAC. Different activities are subject to different administrative requirements, specifically:
  - Prior record-filing is needed for the international clinical trials conducted for product registration and the exportation of HGR data.
  - Prior approval is needed for the international collaborative scientific research and the exportation of HGR materials.
- IP Sharing. Patent rights generated during international collaborative scientific researches need to be jointly applied and owned by the foreign and Chinese parties.
- Informed Consent. An appropriate “separate consent” mechanism needs to be included in the informed consent form to be signed by the data subjects for handling of the non-anonymous HGR data.

3 Digital Health and AI

Digital Health and AI

Global virtual medicine

Demand for virtual medicine is surging across the globe. Driven by the pandemic, refugee crises, public health necessity, or visions of revenue generation, health care providers increasingly reach across sovereign borders using technology to provide medical services directly to foreign patients. Physicians often ask – May I diagnose and treat a patient in another country entirely via internet platforms? May I deliver a remote second opinion to a physician in another country to benefit a local patient there?

While international medical activity is nothing new for hospitals, universities, research institutions, and health care companies that have long been engaged in global health endeavors, modern telecommunication technology has forever changed the delivery model.

Although the practice of medicine is regulated across the globe, the practice of telemedicine does not always fit within the traditional areas of law and regulation applicable to the medical profession. And where countries do regulate telemedicine – which is a growing trend – such laws do not necessarily address the circumstances in which a foreign physician sitting outside the country may render remote services into the country. As more and more providers seek to serve patients and clinicians across borders, counsel is increasingly called upon to address difficult questions of foreign regulation.

Remote medical practice raises myriad complex topics:

- Practice of medicine: physicians and institutions that are considered "engaged" in the practice of medicine in a particular state or country may have licensure/registration requirements or face limitations on the precise services that can be rendered lawfully from a remote location.
- Privacy and data protection: regulation of patient medical information and data varies significantly from country to country. Processing health data must rely on a solid legal ground which will often be the patient's consent.
- Billing and reimbursement: whether, and under what circumstances, virtual medical services can be covered and reimbursed by government and other third party payers varies. Health care providers that receive reimbursement for services provided in a country may then be subject to various regulatory requirements imposed by that country.

Other challenges include liability and malpractice, e-commerce regulation, advertising constraints, intellectual property protection, and tax compliance.

As global regulation strains to keep pace with modern practice of medicine, the regulatory scene is a blurry patchwork from country to country.

William Ferreira
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Digital Health and AI

Health care digitization creates new FCA risk

The recent and rapid expansion of telemedicine and electronic health records (EHR) – and associated potential for new types of fraud – has caught the attention of the Department of Justice (DOJ) and the qui tam relators' bar, resulting in increased use of enforcement tools like the False Claims Act (FCA).

As early as 2019, DOJ pursued enforcement actions in the telehealth space like "Operation Brace Yourself," which targeted a fraud scheme concerning kickbacks to prescribe medically unnecessary braces involving over $1.2 billion in loss. More recently, the Covid-19 pandemic has prompted a dramatic rise in telemedicine, creating new opportunities for potential fraud and abuse. DOJ has demonstrated resolve to use the FCA to crack down on illicit orders for medically unnecessary braces and cancer genetic testing in operation "Happy Clickers." We expect more to come.

Since 2009, EHR use has also rapidly expanded, encouraged in part by over $30 billion in Congressional incentive payments to physicians and hospitals to make meaningful use of EHR. With this new technology has come new potential avenues for fraud. For example, Practice Fusion paid US$145 million to resolve criminal and civil allegations of extracting kickbacks from pharmaceutical companies in exchange for shaping electronic clinical decision support alerts that encouraged prescriptions for their drugs, and Coffrey Health System paid US$250,000 to settle claims it misrepresented its eligibility for EHR incentive payments.

Despite shifts in technology reshaping patient care and records, the FCA continues to be DOJ's "go-to" and increasingly utilized enforcement tool to root out alleged fraud associated with these new technologies.

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View the full False Claims Act guide

Digital Health and AI

Distribution of prescription medical devices, including digital therapeutics and diagnostics

Medical device manufacturers who distribute prescription medical devices are subject to complex and varied state licensing requirements that can attach to their manufacturing and/or distribution activities, most of which are set up for the distribution of traditional physical products. Further, many manufacturers partner with third-party logistics providers (3PL) that are also subject to separate state licensing requirements. Licensing rules vary by state as well as between prescription and OTC drug or device types, recipient, and facility/entity location. Adding to the complexity, most state licensing paradigms were developed to handle prescription drugs and controlled substances and, consequently, are not always suitable for the distribution models used for prescription medical devices. Further still, while distribution models are well developed for distributing tangible things, they are often not well suited for digital therapeutics and diagnostics for which there is no physical product, including software downloads of applications and provision of access codes. While some states do not have any licensure requirements for prescription medical devices and similar products, such as digital therapeutics, many states do.

In the last few years we have seen an uptick in state Boards pursuing prescription medical device manufacturers and distributors for failure to secure the necessary licenses. We expect this trend to continue.

Looking forward, changes to how manufacturers and distributors are licensed are coming that may affect medical devices. When the Drug Supply Chain Security Act (DSCSA) (Title II of the Drug Quality and Security Act (DQSA)) was enacted, it included a provision intended to harmonize rules for drug distribution across the states by establishing standards. FDA recently issued a proposed rule, National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers, 87 FR 6708 (Feb. 4, 2022) intending to provide clarity and consistency for wholesale distributors and 3PLs desiring licensure.

The DSCSA by its terms does not apply to medical devices; however, because the DQSA and the proposed rule seek to establish consistent standards and drive uniformity for drug state licensing, we also anticipate changes in how state Boards will regulate the wholesale distribution of drugs and 3PLs. And because medical devices are largely regulated under states' drug licensing authorities, we expect the impacts of many of the drug distribution regulations to spill over to medical devices, possibly resulting in higher standards or additional licensure requirements.

It is therefore critical for prescription medical device manufacturers to secure necessary state licenses and also monitor the impact of these rules on medical devices, once implemented. Digital therapeutic and diagnostic companies should also consider whether there is an opportunity to shape the proposed rule to carve out their products or establish different standards. Companies should expect an impact in the renewal process and the need to address new or different infrastructure requirements, or secure new licenses to comply with states that newly elect to require licensure of medical device distributors.

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Digital Health and AI

Coverage and reimbursement challenges for digital health services

The development and use of digital therapeutics (DTx) has grown exponentially in recent years, and the Covid-19 pandemic has accelerated both interest in, and adoption of, these technologies by providers and patients alike. DTx are used to treat a wide range of conditions, including substance use disorders, pain, chronic conditions like diabetes, and mental health diagnoses. However, regulatory agencies and payers continue to struggle with how to regulate DTx, and whether and when to cover and reimburse them.

DTx typically fall under FDA's software-as-a-service medical device category, but FDA's approach continues to evolve. They also don't neatly fall under any Medicare or other payer benefit category, with some DTx companies seeking to fit them into existing drug or device paradigms, and others likening them more to durable medical equipment (DME). At the moment, most DTx companies are negotiating with payers and pharmacy benefit managers one at a time, and making the case that DTx can bridge gaps in access to clinicians, and provide care that is both better and more convenient, or more cost effective.

Legislation has been introduced in Congress that would expand Medicare and Medicaid coverage to include prescription DTx meeting certain criteria. In the meantime, new DTx services continue to be approved by FDA and come to market, and DTx companies are collecting real-world data to demonstrate their value to patients, clinicians and payers.

Brooke Bumpers
Counsel, Washington, D.C.

Visit our website to learn more about our Digital Health capabilities

Digital Health and AI

Speeding medical device approval and reimbursement

The FDA's Breakthrough Devices Program, finalized in 2018, continues to gain traction, with the numbers of requests and devices granted this designation steadily increasing. While the benefits for the FDA clearance/approval process are attractive, the primary driver seems to be the reimbursement benefits, which are of substantial interest to investors driving innovation.

The program is intended to speed development and review of devices which provide for more effective treatment/diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Features of the program include increased interaction with FDA, including mechanisms for quicker interaction like Sprint Discussions, and prioritization of the submission in the review queue. Sprint Discussions are a particularly useful feature that allow companies to obtain agency feedback in half the time of a traditional pre-submission.

However, it is becoming apparent that FDA cannot grant breakthrough status to all devices which may be eligible, especially in review groups where most devices would qualify (e.g., cardiovascular). Given the increased competition to obtain breakthrough status, it is critical that companies present their strongest case in their application. Key considerations include the timing of the breakthrough request in the development program, and justification for meeting the eligibility factors, especially showing the device is reasonably expected to be "more effective" than the standard of care. This last criterion is the one most cited when applications are denied by FDA.

Obtaining breakthrough device designation has tangible benefits from a Medicare payment perspective, and perhaps for other payers. From a Medicare payment perspective, having breakthrough designation makes it easier to qualify for special, additional reimbursement. Under Medicare's inpatient hospital payment system, hospitals may receive extra payment for technologies that qualify for new technology add-on payments (NTAP). An FDA designated breakthrough device is deemed to meet the most difficult two of the three criteria to qualify. Similarly, under the Medicare hospital outpatient payment system, devices are eligible for separate payment if they qualify for pass-through status. Breakthrough designation means that the device automatically meets the difficult "substantial clinical improvement" criterion. Thus, breakthrough designation facilitates the ability to obtain these special additional payments.

The Centers for Medicare & Medicaid Services (CMS) issued a final rule in 2021 that would have allowed for four years of national Medicare coverage for breakthrough devices under the Medicare Coverage of Innovative Technologies (MCIT) pathway. However, that rule was subsequently withdrawn and CMS is considering avenues to facilitate Medicare coverage for new technologies, which may or may not be applicable to breakthrough devices. It is unclear when CMS's consideration will yield a coverage policy proposal.

Given the FDA regulatory and reimbursement benefits, we only expect competition to increase for breakthrough status in the coming years. For devices which do not qualify for this program, there may be an opportunity to qualify for FDA's Safer Technologies Program (SteP), which was finalized in January 2021, for devices targeting non-life-threatening conditions; however, there are no similar reimbursement benefits for this program.

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Digital Health and AI

Coding and medicare benefit category determinations for medical devices and AI

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Medicare is the largest health insurance program in the U.S. It is a defined benefit program, meaning that items and services are only covered if they fall within a statutorily defined benefit category. For medical devices that are used by patients in the home, including artificial intelligence (AI)-based devices, the Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) benefit most often applies and itself includes several different benefit categories. In the past, the Centers for Medicare & Medicaid Services (CMS) informally made benefit category determinations for medical devices as part of the Healthcare Common Procedure Coding System (HCPCS) process. However, based on the Agency's reading of the Supreme Court's 2019 decision in Azar v. Allina Health Services, it ceased making these benefit category determinations until a process was established through notice and comment rulemaking.

Unfortunately, CMS did not finalize a benefit category determination process until 28 December 2021, when it issued the DMEPOS Final Rule. Thus, for more than two years, innovative new medical devices have come to market with no way to obtain a benefit category determination and, consequently, no way to be covered by the Medicare program as the Durable Medical Equipment (DME) Medicare Administrative Contractors (MACs) declined to make specific coverage decisions in the absence of a national benefit category determination.

With a benefit category determination process in place for 2022, we hope to see the backlog of devices that came to market in the last two years clear, finally affording Medicare beneficiaries access to these devices. However, we also expect to see a reckoning in terms of how CMS categorizes innovative devices under the rigidly defined statutory benefit categories. In many cases, this will truly be an exercise of fitting a square peg in a round hole. It will be up to developers and manufacturers to ensure that they clearly lay out for CMS why their innovative device/technology fits within the archaic benefit categories of the Social Security Act and to familiarize themselves with the new Medicare benefit category determination process.

Digital Health and AI

Outlook on the proposed Artificial Intelligence Act on medical devices in the EU

The implementation of artificial intelligence (AI) is often seen to have great potential to advance health care. However, the ability of an AI system to further develop, optimise and adapt itself is one of the biggest challenges for smart medical devices with regard to regulation and liability law – because such "learning" is currently not provided for in medical device legislation.

Self-learning AI software in Europe requires a CE marking under the European Union Medical Device Regulation (EU MDR) - as for any medical device. However, two worlds collide: According to Annex I, section 17.1 EU MDR, software must be designed to ensure "repeatability, reliability and performance in line with their intended use". For "locked" algorithms, which provide the same result each time the same input is applied, this is not a problem. However, continuously learning and adaptive algorithms, especially software based on a "black box" model, are by definition not supposed to deliver repeatability.

Unlike in the U.S., where the FDA takes a sector-specific approach on AI, the European Commission plans to create a general regulatory framework for AI across all sectors and published a proposal for an Artificial Intelligence Act (AIA). Under the proposal, AI applications in medical devices within the meaning of the EU MDR, or those which constitute a medical device themselves, would be considered as "high-risk AI systems" and require a conformity assessment by a "notified body". Conformity assessments for AI medical devices would continue to be conducted in accordance with the EU MDR, while certain additional provisions of the AIA would also apply.

Whether and when a self-learning AI medical device would need to undergo a new conformity assessment would depend on whether a certain change to an algorithm and its performance has been pre-determined by the provider and assessed at the moment of the initial conformity assessment. Accordingly, if a certain change was "pre-determined", it would not constitute a substantial modification and would not require a new conformity assessment. However, the question of what "pre-determined" means, and how specifically it needs to be described in the technical documentation, is still open and will need to be clarified at some point in time.

In addition to opportunities and innovations, the use of AI also creates the risk of damage caused by machine intelligence. The principle that liability follows from responsibility reaches its limits in artificial intelligence. Therefore, manufacturers must address these issues as early as during the device development phase and contractually regulate as many potential risks as possible.

The regulatory landscape is evolving now, but eventually, regulators have to develop certification processes to handle adaptive AI systems and to approve not only an initial AI model but also a process for adjusting an AI model over time.

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Digital Health and AI

Software as a medical device and its regulatory treatment in Mexico

As part of the digital revolution in health care, software has become a game-changing element in Mexico. Software is shifting how medical services are provided, how health information is managed, how new devices are developed, and how stakeholders of the industry interact.

It was not until December 2021 that the Mexican government expressly included more clear guidance for software as a medical device (SaMD).

SaMD is that used for medical purposes, which does not need to be part of the hardware of the medical device. It is capable of running on general computing platforms and can be used alone and/or in combination with other software. Mobile applications meeting this definition are also considered SaMD.

Validation (technical and analytical) requirements, more clear requirements to be met in all stages of the device's lifecycle, good documentation practices and principles associated with GMP and risk management, are now contemplated as part of this regulatory improvement.

Key risks and challenges include: Cybersecurity and Privacy matters (to prevent and manage cyber risks); Managing of Health Data (i.e., use of sensitive information by non-health professionals); and Clear and Complete Regulation (advocating for more developed regulations and better governmental policies and consistent criteria by the authority, and to converge with global principles).

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4 Privacy and Cybersecurity

Privacy and Cybersecurity

Complexity of privacy implications for clinical research increases

U.S. data collected and created in research studies can be subject to a multitude of privacy laws and requirements. These laws can impact the collection, use and disclosure of identifiable health information (and what is considered de-identified information), notification requirements in the event of a data breach, consent/authorization and sharing requirements, as well as future research uses and activities. Research sponsors, study sites, and other entities involved in research should be aware of the scope of these laws to determine whether compliance is required.

There are requirements under the Federal Policy for the Protection of Human Subjects (the "Common Rule") that impose requirements on sites that have a federal wide assurance and the FDA Protection of Human Subjects Regulations (FDA Regulations) that would be applicable to certain research studies and certain sponsors. In addition, in the absence of comprehensive U.S. federal privacy legislation, states continue to enact broad laws governing personal information which could be applicable. Such laws, including in California, Colorado, and Virginia,[1] impose GDPR-like obligations on businesses, but generally include some exemption for research information typically provided the research is conducted in accordance with the Common Rule and/or FDA Regulations. Some states (e.g., California) even have their own laws governing research.

Other state health information privacy and sensitive condition laws govern health information generally and certain sensitive conditions (e.g., genetic information, HIV/AIDS, substance abuse, STDs). Covered entity sites also are typically subject to privacy, security and breach notification regulations under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as modified by the Health Information Technology for Economic and Clinical Health (HITECH) Act, which will impact the requirements governing the use and disclosure of protected health information for research. State data breach laws could apply to a breach involving research data, depending on the nature of the data and the scope of the incident. Finally, Institutional Review Boards (IRBs) may impose additional privacy requirements on research under their review and oversight and certain NIH policies (e.g., the NIH Genomic Data Sharing Policy) also may apply depending on the nature of the research. Accordingly, entities involved in research should be careful when navigating the varying federal and state privacy laws as such could impact research activities and the ability of sites and sponsors to use and disclose health information collected, including for future research.

[1] California Consumer Privacy Act of 2018 ("CCPA") as codified at Cal. Civ. Code Part 4, Division 3, Title 1.81.5, § 1798.100 et. seq., as amended by the California Privacy Rights Act of 2020 ("CPRA") as codified at Cal. Civ. Code Part 4, Division 3, Title 1.81.5, § 1798.100 et. seq.; Colorado Privacy Act, Cal. Rev. Stat. § 6-1-130 et seq (effective July 1, 2023); and Virginia Consumer Data Protection Act, Va. Code § 59.1-571 et seq.

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Privacy and Cybersecurity

Ransomware attacks are on the rise

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According to a recent report, 2021 saw a 755% increase in attacks on health sector organizations operating within the sector, making them a board-level threat.

Such incidents can have a systemic impact on technology infrastructure, resulting in critical systems being unavailable for prolonged periods. In a health care setting this can directly impact patient safety and create substantial risks of regulatory action and litigation.

This was recently highlighted by the serious attack on the Irish health care service (HSE), which resulted in delayed Covid-19 testing, cancelled appointments and impacted frontline services.

HSE's post-incident report recommendations illustrate many of the steps that we commonly recommend organizations take to guard against and prepare for ransomware attacks, including:

- **Develop incident response and business continuity plans**, which can provide a reasonably detailed outline of how the organisation will respond as well as promptly recover impacted systems, particularly taking into account potential large-scale loss of functionality across global operations.
- **Test plans through tabletop exercises** that help ensure that plans work in practice, relevant stakeholders across the organisation understand their roles, and any identified weaknesses can be addressed in advance.
- **Understand technology and cybersecurity risk profile**, including through periodic assessment and corresponding risk management activities.
- **Confirm appropriate executive leadership and corresponding Board oversight** such that senior management is intimately involved in driving ongoing enhancements and overseeing how the organisation's cybersecurity standards address increasingly wide-ranging regulatory requirements across jurisdictions.

Privacy and Cybersecurity

What can I do?: With shifts in U.S. legal landscape, use of clinical data for R&D is a big question

Clinical data maintained by U.S. health care providers (Providers) has significant value, but how can it be used for research and product development? The answer to that enduring question continues to get more complicated and there are no one-size-fits-all answers.

Consider consent. With notable exceptions, Providers may use and share patient health information for treatment, payment, and certain operational purposes without obtaining consent. However, the rules for using that same data for research can be stricter, often requiring consent or institutional review board approval, sometimes even for de-identified data. This can raise issues for Providers wishing to perform research using data originally obtained for treatment. In some cases, obtaining consent may be near-impossible. For example, indirect Providers, such as laboratories, encounter additional challenges, as they rarely have the opportunity to obtain consent directly from a patient.

To unlock the promise of clinical data, Providers must adeptly navigate consent and other issues under rapidly shifting federal and state privacy, consumer protection, and research laws. Beyond longstanding laws like the Health Insurance Portability and Accountability Act (HIPAA) and state health privacy laws, Providers need to assess compliance obligations under a growing patchwork of state consumer privacy laws. These include generally applicable laws, such as the California Consumer Privacy Act (CCPA), and more narrowly targeted laws, such as those regulating genetic testing information. Further complicating matters, the Department of Health and Human Services is evaluating potential updates to HIPAA and the Federal Trade Commission has signaled that it will begin enforcing its long dormant breach notification rule for incidents involving non-HIPAA covered data.

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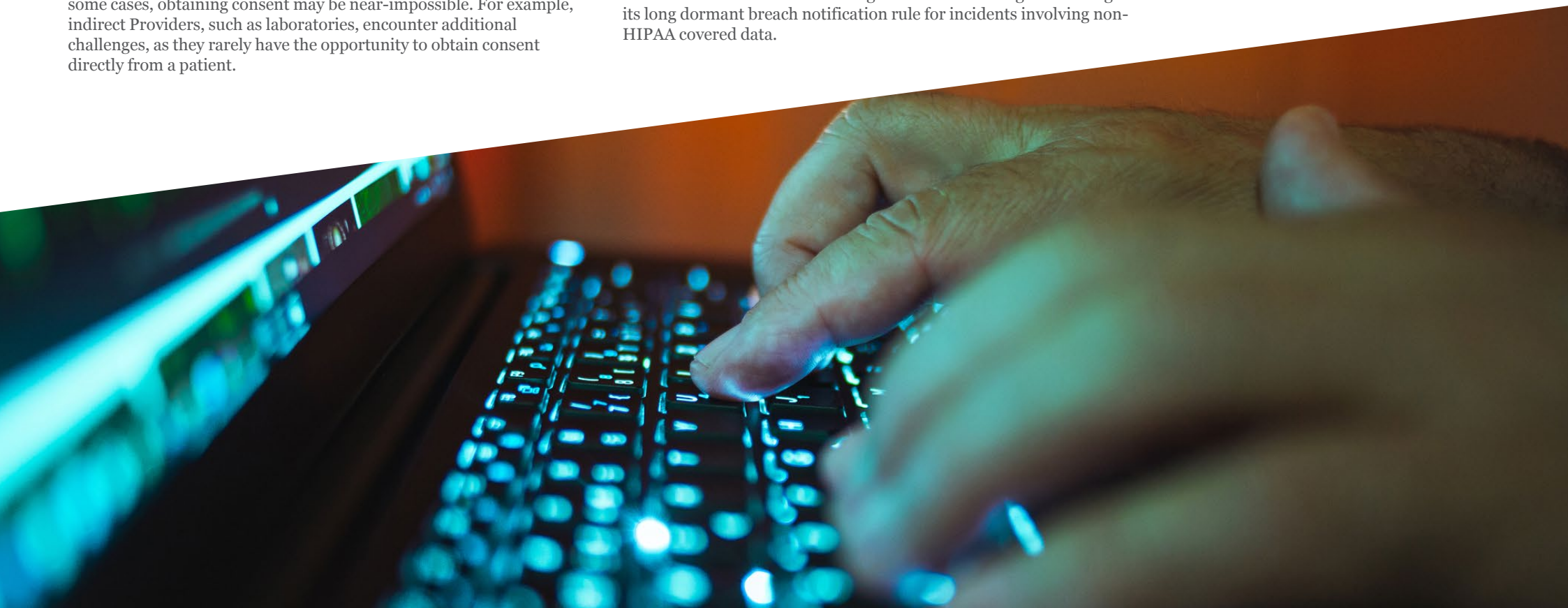

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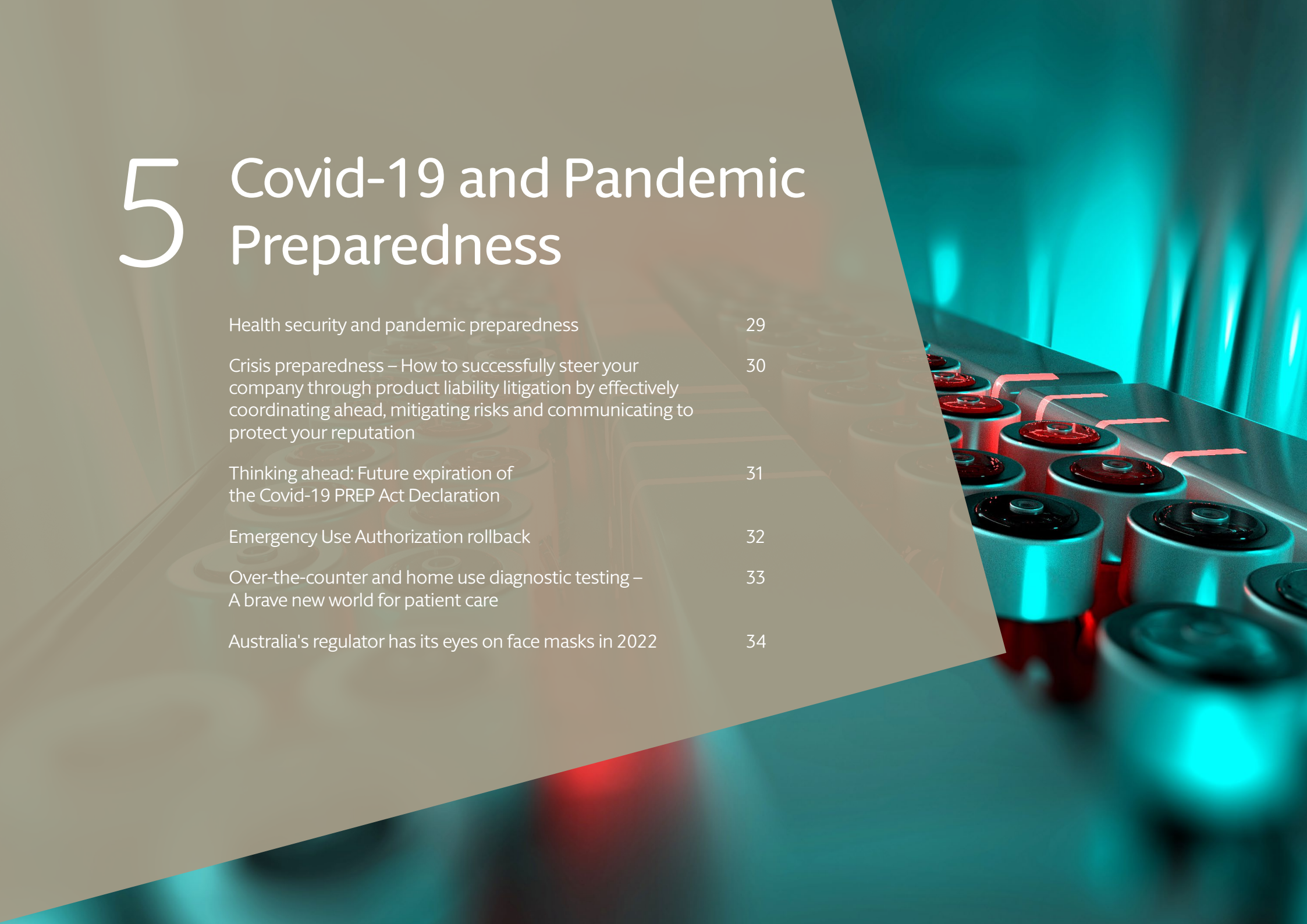

Covid-19 and Pandemic Preparedness

Health security and pandemic preparedness

As the Covid-19 pandemic continues to evolve, we expect life sciences companies to remain laser focused on health security and pandemic preparedness. Initiatives targeting existing infectious diseases including Covid-19, influenza, and HIV and other serious conditions, readily cross product categories, including therapeutics, vaccines, diagnostics, devices, and digital health technologies. Similarly, preemptive medicine initiatives, focused on extending healthy lifespan and improving the wellbeing of a growing global population, cross traditional regulatory paradigms and provide new opportunities to integrate previously siloed interventions (e.g., behavioral, advanced diagnostics, agricultural biotechnology) to create sustainable solutions to global challenges.

Moving forward, we see a unique opportunity for emerging companies and their investors in these cross-functional areas. Early stage innovators can move quickly to leverage advanced technologies such as artificial intelligence/machine learning (AI/ML) platforms for early detection or even to prevent the progression of chronic conditions. Supply chain resilience will also continue to be front and center across the life sciences sector. We expect continued investments in manufacturing capacities, advanced manufacturing, and strategic onshoring efforts to prevent shortages of essential medicines and inequitable distribution. Opportunities in plant- and microbial-based ingredients and processes for food production are also abundant.

We see additional opportunities for companies to benefit from strategic and interactive engagement with FDA and other agencies early in product development allowing innovators to prioritize investments on scientific, design, manufacturing, or other critical considerations. FDA likely will continue integrating lessons made necessary by the current pandemic to streamline review processes and to advance real-world evidence and patient-generated data to support or enrich regulatory decision-making. These opportunities highlight the significance of having, at the outset, a fully integrated team that understands the science, data, and the law and regulations that govern them.

We look forward to partnering with our clients as we prepare, together, for advancing technologies for improved health security.

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Visit our website to learn more about our Emerging Companies and Investors work.

Covid-19 and Pandemic Preparedness

Crisis preparedness – How to successfully steer your company through product liability litigation by effectively coordinating ahead, mitigating risks and communicating to protect your reputation

The life sciences industry is a complex litigation environment for businesses and their products.

In the face of product issues, consumer groups, plaintiffs' bar and regulators may aim at taking over the steering wheel. To limit fallout of technology failure, businesses want to remain in the driver's seat – before a crisis, while navigating through it, and when successfully leaving it behind.

The earlier that businesses seek product liability advice, the better prepared they will be.

Make your business "product liability-proof"

Despite widespread awareness of product liability threats, many businesses do not invest enough in mitigating them. Preparation often remains fragmentary and product liability counsel is regularly involved too late.

Key elements of becoming "crisis-ready" include:

- Building and training the right teams (collaboration of management, technology, communications, legal and internal/ external key stakeholders)
- Keeping updated crisis-management playbooks with guidance for product issues, ensuring an effective, consistent and global approach
- Preparing real-time product "bibles", identifying and addressing critical issues and potential risks
- Monitoring media, plaintiffs' bar and consumer groups
- Maintaining good relationships with regulators
- Reviewing company communication culture and messaging

Engage cautiously and consistently

The spread of (mis-)information on the product can be challenging. It significantly impacts litigation risks.

Keeping engaged in on-going conversations on the product is vital. Facing product issues, regulators, (social) media and consumers should not be left alone. They need to be consistently informed and educated.

Avoiding communication may erode reputation and trust. To the public eye, businesses should own the narrative of their products. They should be perceived as collaborative and as a reliable source of information.

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Covid-19 and Pandemic Preparedness

Thinking ahead: Future expiration of the Covid-19 PREP Act Declaration

Since the start of the pandemic, we have published various articles regarding the Covid-19 Declaration (Declaration) issued by the Secretary of the Department of Health and Human Services (HHS) pursuant to the Public Readiness and Emergency Preparedness Act (PREP Act). The Declaration provides certain "covered persons" with immunity from liability arising out of or related to the manufacture, distribution, administration, or use of certain "covered countermeasures." The immunity provisions triggered under the Declaration are set to expire on 1 October 2024. However, the Declaration provides an additional twelve months of liability protection at the conclusion of the effective period to allow manufacturers to "arrange for disposition of the Covered Countermeasure" and for covered persons to take any other actions "as are appropriate to limit the administration or use of the Covered Countermeasures."[1]

While it is possible the expiration may be extended, in the event that it is not, those covered persons continuing to engage in activities involving covered countermeasures should consider taking steps to mitigate potential future liability risks, including, for example:

- Ensure accurate tracking measures are implemented and/or maintained for relevant products to facilitate the return and/or destruction of those products upon expiration of the immunity period;
- Ensure any existing protocols pertaining to covered countermeasures are placed under review to confirm compliance with all applicable laws; and
- Consider liability insurance issues as appropriate.

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[1] 42 U.S.C. 247d–6d(b)(3)(B) and (C).

Covid-19 and Pandemic Preparedness

Emergency Use Authorization rollback

The Covid-19 Pandemic has impacted the world in a way that no one could have predicted and required all stakeholders to step up to confront the many challenges that emerged, including manufacturers, health care providers, government agencies and entities who never envisioned themselves as life sciences companies.

Manufacturers from many industry sectors responded and developed products to contribute to the pandemic response and the FDA leveraged rarely used emergency use authorization (EUA) and enforcement discretion policies across technologies to bring much needed personal protective equipment (PPE) and medical devices to the market. Now that we are trying to return to normal, how do we handle the impressive number of products that were released under emergency use pathways?

Companies were permitted to market products under EUAs and enforcement discretion for the duration of the public health emergency without obtaining the premarket clearances or approvals that are typically required. Because they are not marketed under a full approval, their market authorizations are limited in scope and duration. In general, an EUA product's special status terminates upon the public health emergency coming to an end, a change in the approval status of the product, or if there are other circumstances that make revocation appropriate. Such "other" circumstances may include:

- Significant adverse inspectional findings;
- Reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product;
- Product failure; or product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" for its intended purpose under the EUA), among other things;
- Company proactively requests that FDA withdraw the EUA;
- Umbrella revocation; and
- Failure to follow requirements mandated in the Emergency Use Authorization letter.

FDA is supposed to work with manufacturers to figure out the appropriate disposition of products that were released under emergency use. FDA has started the process of revoking some authorizations for example due to how ubiquitous they now are in the marketplace (e.g., Non-NIOSH-Approved or Decontaminated Disposable Respirators) and the launch of other authorized products with superior performance as is the case with some Covid-19 tests.

FDA's guidance indicates that products must be cleared or approved to be marketed after the emergency declaration terminates and companies will need to be prepared for that day to come . . . and come it will. For those companies who have already submitted their application for full marketing authorization, FDA has indicated informally that it will not require companies to withdraw products that have already been released while the application is pending. For those companies that have not yet submitted and/or do not have plans to submit, they should be prepared for the possibility that FDA may well demand that products released during the pandemic be withdrawn once the public health emergency comes to an end. Either way, as we are emerging from the pandemic, now is the time for companies to start to plan for the next phase of operations.

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Covid-19 and Pandemic Preparedness

Over-the-counter and home use diagnostic testing – A brave new world for patient care

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Over-the-counter (OTC) assays are tests sold directly to the consumer, for use at home, and do not require a physician prescription. During the Covid pandemic, both rapid antigen and molecular tests have been authorized for emergency use as OTC tests, and have played an important role in helping manage patient care. Other kinds of diagnostic tests (such as glucose monitoring devices, drugs of abuse tests, cholesterol tests, and pregnancy and ovulation tests) are not OTC devices, require a prescription, but can still be used at home.

As technology has advanced and assays have become more accurate, patients have asked for and companies have been developing more tests for use in home environments, especially for infectious diseases and chronic conditions where testing has historically been performed only by prescription and in clinical laboratories. The public health successes of OTC Covid tests has highlighted the technical feasibility of OTC testing and increased the public's interest. Patients are seeking more active participation in their health care. Given the growing trend of telemedicine and interest in home testing, we expect an increasing number of OTC and at home tests for a wide variety of infectious diseases and other conditions.

Manufacturers need to be strategic in developing tests and engage with FDA early to align with FDA's expectations and concerns. Companies will need to follow the evolving regulatory environment and standards, and help shape developing regulatory standards to advance home diagnostics, to meet the growing consumer need.

Covid-19 and Pandemic Preparedness

Australia's regulator has its eyes on face masks in 2022

Personal protective equipment (PPE) are classified as medical devices in Australia and include a variety of devices such as surgical and isolation gowns, surgical suits, gloves and face masks. PPE have come under increased regulatory scrutiny amid the Covid-19 pandemic and heightened demand for such products.

Australia's Therapeutic Goods Administration (TGA) is paying much closer attention to the registration of PPE, in particular face masks, and sponsors are being faced with increased inquiries by the TGA, including information and document requests, in order to substantiate registrations on the Australian Register of Therapeutic Goods (ARTG).

Face masks and the ARTG

Face masks meet the definition of a medical device, and are regulated by the TGA, when the following claims are made:

- the face masks are used for the prevention of the transmission of disease between people; or
- the face masks are suitable for 'therapeutic use', such as in surgical or clinical settings, for medical use, or use in other health services.

Face masks meeting the definition of a 'medical device' must be included on the ARTG before import and/or supply in Australia. Compliant registrations on the ARTG are the responsibility of the sponsor of the face mask.

Multiple companies have been issued with infringement notices by the TGA for, amongst other things, importing face masks that were not included on the ARTG, including Target Australia Pty Ltd which was fined AU$13,320.

By contrast, face masks which are non-sterile and are not intended by their manufacturer to be used for the prevention of the transmission of diseases between people are excluded from regulation by the TGA under the Therapeutic Goods (Excluded Goods) Determination 2018.

Post-market Review

The TGA is undertaking a post-market review of face masks included on the ARTG. The review has resulted in several face masks being cancelled from the ARTG for non-compliance with the TGA's Essential Principles, highlighting the need for sponsors to ensure their products meet the required evidentiary and testing standards.

Issues identified in the TGA's review include, amongst other things, insufficient evidence to support claims and incorrect labelling. The TGA has also issued product recalls for certain face masks claiming to meet certain standards (such as 'N95' or equivalent standards) without appropriate evidence to justify such claims.

TGA Requirements

All medical devices registered on the ARTG must undergo conformity assessment procedures and comply with the TGA's Essential Principles for safety and performance. As the majority of face masks are categorised as Class I medical devices, most applications to include a face mask on the ARTG will be required to provide a manufacturer's Declaration of Conformity as part of the conformity assessment procedures.

In addition to the Essential Principles, conformity assessment and general requirements regarding ongoing quality and risk management and labelling, face masks and respirators must demonstrate that they meet standards for certain performance parameters, including:

- Surgical and medical face masks must demonstrate that they meet appropriate standards for fluid resistance, bacterial filtration efficiency, and breathability; and
- Respirators must demonstrate that they meet appropriate standards for particulate filtration efficiency, breathability, fit and head strap strength. Surgical respirators are also required to demonstrate an appropriate level of fluid resistance.

Sponsors and manufacturers should maintain documentation regarding the ongoing conformity of their products with the requirements, as the TGA may request the provision of this information within a specified timeframe. Failure to comply with the information request may result in enforcement actions, which may include fines, infringement notices, and further civil and criminal penalties.

Aidacare Pty Ltd was recently issued with two infringement notices and fined AU$26,640 for failing to respond to information requests, while Life Biotech Pty Ltd was issued with eight infringement notices and fined AU$106,560 for failing to provide information and face mask samples, and for providing false and misleading information to the TGA.

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6 Transactions

Transactions

Unique issues in cell and gene therapy transactions

Cell and gene therapy transactions have significantly increased over the last few years in number and complexity and give rise to a number of issues that merit further attention. Due to concerns oover cell and gene therapy pricing, there is a growing sentiment that pricing should be based to some extent on patient outcomes. Typically, "Net Sales" definitions permit deductions for rebates and chargebacks, but further modifications may be necessary to ensure that a licensee is permitted to recoup/offset against future royalty payments any refunds or payments to insurers/payors as a result of negative patient outcomes.

Typically, royalty terms continue until the later of expiration of (i) the last valid patent claim, (ii) a period (typically 10 to 12 years) following first commercial sale, and (iii) regulatory exclusivity. Because of the complexity of the manufacturing process associated with cell therapy (which in itself could provide de facto market exclusivity), some companies are pushing for royalty terms to extend until there is some biosimilar market entry (or, a longer period).

With respect to the manufacturing process, given the high cost of materials (plasmid DNA/cell banks), their long lead times and limited high spec manufacturing facilities, careful planning of manufacturing capacity is also key. The impact on platform technologies of adjustments to specification/process, particularly with respect to evolving products such as MRNA based vaccines may also need to be factored in.

We also see differences in the exclusivity provisions. Where cell and gene therapies are based on platform technologies it may be necessary to limit the rights being out-licensed to preserve flexibility and maximize the value of the technology for future deals. We have seen exclusivity being limited to certain indications, or rights preserved to the licensor to use the target or binders for other collaborations. Obviously this has implications both from a regulatory perspective (risk of data contamination) and the risk of funding technology that could compete with the collaboration.

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Transactions

Application of 'commercially reasonable efforts' to life sciences transactions and disputes

'Commercially reasonable efforts' clauses are frequently included in licensing, distribution, and other life sciences contracts. These clauses, like 'best efforts' and 'reasonable efforts' clauses, set a level of effort a party is expected to exert in performing its contract obligations, such as developing or commercializing products. As the Southern District of New York recently reiterated in *Alto v. Sun Pharmaceuticals Industries, Inc.*, Case No. 1:19-cv-09758-GHW, 2021 WL 4803582, at *41 (S.D.N.Y. Oct. 13, 2021), though, under New York law, "[t]here is no settled or universally accepted definition of the term 'commercially reasonable efforts."

Courts applying New York law, however, will enforce definitions for 'commercially reasonable efforts' agreed by the parties. For this reason, where the parties attempt to agree on a definition in their contract, consider the following points:

- Avoid inconsistent terminology (e.g., using 'commercially reasonable efforts' and 'best efforts' for different obligations).
- Where possible, include metrics such as minimum expenditure requirements or other objective parameters.
- If regulatory approval is required, specify what steps need to be taken and any necessary timetables.
- Identify any applicable objective industry standards against which efforts will be measured.
- Include contract language stating that parties' obligations extend beyond just the specified metrics or parameters to all commercially reasonable efforts to allow for flexibility.
- Maintain a detailed record of the negotiation of the clause in case of future disputes regarding its interpretation.

Defining 'commercially reasonable efforts' this way will help provide predictability when performing under a contract and in any potential dispute. However, in certain scenarios, it may be in a party's interest not to include such specificity in order to maintain flexibility in how it meets its diligence obligations.

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Transactions

Using CVRs to bridge valuation gaps in life sciences M&A transactions

The past three years, have witnessed significant expansion in the use of contingent value rights (CVRs) in acquisitions of publicly-held life sciences companies. Buyers have increasingly turned to CVRs to bridge the valuation gap that arises when a buyer is reluctant to value a target company's products as highly as the target company believes warranted based on its own projections. Particularly for publicly-held life sciences companies with clinical stage products, CVRs may effectively serve as a form of earnout to address the inherent uncertainty that arises when a buyer seeks to value the future performance of a product.

CVRs allow former target company shareholders to participate in the future value created by a specific product if that product achieves some or all of the target company's expectations. To that end, CVRs in life science transactions are generally milestone-based: target company shareholders are entitled to additional post-closing payments if one or more milestones are achieved within a specified period of time. These milestones may include, for example, clinical trial developments, regulatory approvals, sales targets, or receipt of third party payments.

Like earnouts, however, contractual provisions relating to CVRs must be carefully drafted and negotiated (with particular focus on the buyer's obligation to seek to achieve milestones, avoiding individual actions by CVR holders, and describing milestones clearly) to reduce the likelihood of litigation.

Despite the need for cautious drafting, we anticipate that CVRs will remain a key tool for bridging valuation gaps and offering compelling acquisition proposals to public life sciences companies.

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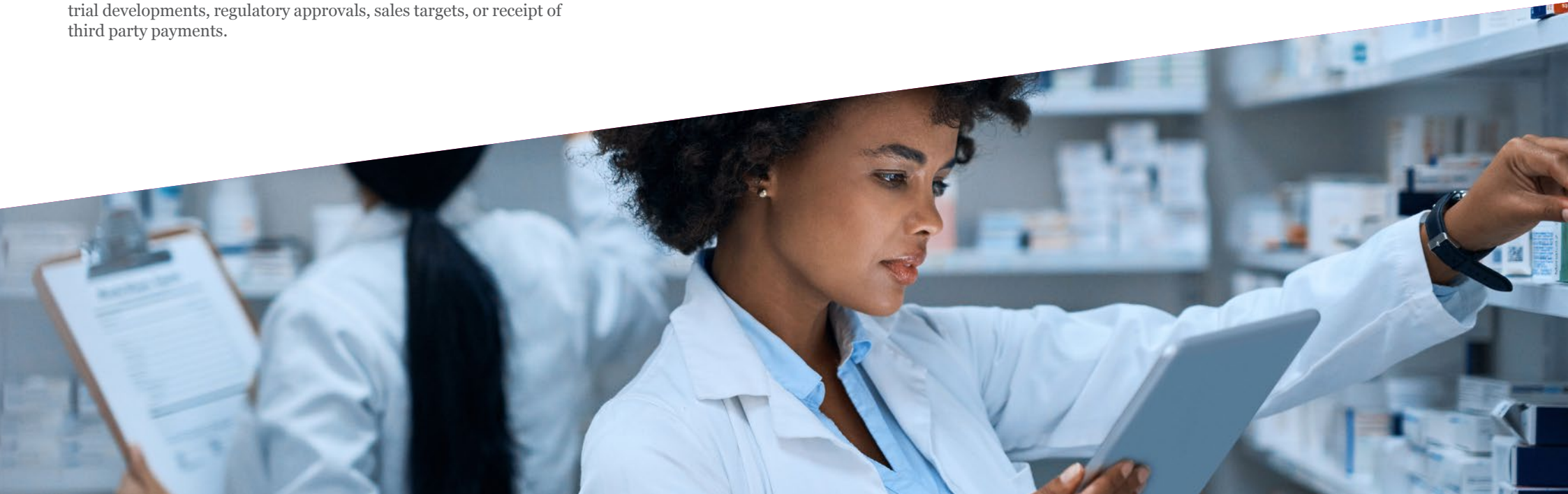

Transactions

Arbitrating post-M&A disputes in life sciences

Essentially all players in the life sciences sectors are or have been involved in large-scale M&A transactions. Parties cooperate on the basis of a range of contractual arrangements, such as R&D agreements, co-promotion contracts, or joint ventures. They may engage in the sale/acquisition of product portfolios or individual products. We have seen both asset and share deals, or a combination of the two.

Disputes arising from M&A transactions notably arise in connection with breaches of warranties, or the earn-out. A leading insurer recently reported a “rising tide of large claims” under policies for warranty and indemnity insurance. In almost 20% of the deals a claim was notified. Another frequent scenario are breaches of disclosure obligations in the pretext of the transaction, particularly where the seller has failed to disclose information relevant to the target's performance and/or the purchase price.

Arbitration has become the mechanism of choice for resolving post-M&A disputes. Sources report that approximately 90% of all arbitrations are post-M&A arbitrations. In arbitration, parties may choose a neutral venue, select arbitrators based on their familiarity with the relevant factual and legal issues, tailor applicable rules and proceedings to their needs, and agree on complete confidentiality.

Also – unlike court judgements – arbitral awards may be enforced virtually around the globe under the New York Convention.

These advantages of arbitration are a particular fit for post-M&A disputes in the life sciences sector. Many global players cooperate with Asian partners, in which case arbitration may provide the only enforceable means of dispute resolution. Moreover, post-M&A disputes in the life sciences sector often involve complex questions of cGMP, product quality, and the robustness of manufacturing processes or, in terms of damages, a prognosis of the market development and/or questions of substitutability. With any of those issues, it is key to be able to select decision-makers and skilled experts familiar with the industry.

In our experience, clients in the life sciences sector typically follow a forward-looking, business-oriented approach, bringing about a certain reluctance to pursue claims arising from past transactions. Those claims, however, may be significant. Please let us know if you would like us to test and assess potential post-M&A claims.

Inken Knief
Partner, Munich

Thomas N. Pieper
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7 Patents, Litigation, and Beyond

Patents, Litigation, and Beyond

Patent settlements in the pharmaceutical sector: The Court of Justice refines the applicable legal test

In the pharmaceutical sector, originators and generics producers may frequently litigate over patent infringements which can be resolved with patent settlements (PS).

However, the European Commission considered in several cases that some PSs amounted to market-sharing agreements violating competition law "by object" i.e., an agreement that by its very nature is anti-competitive.

In 2020 and 2021, the Court of Justice provided clarifications on the legal test applicable to such analyses.

First, a PS does not restrict competition if the parties are not competitors or potential competitors. For instance, if the generics manufacturer has not taken preparatory steps to enter the market or is not a credible new entrant on the market because of insurmountable barriers to entry, there is no potential competition. However, the mere existence of a patent is not sufficient to create insurmountable barriers.

Second, payment should not compensate for the absence of market entry and should be directly proportionate to the purpose of the dispute. For instance, the amount cannot be set by reference to the expected benefit that a manufacturer could have expected, had it entered the market.

Last, pro-competitive effects may rebut the presumption of a violation by object if they are demonstrated, relevant, specific and sufficiently significant to create a reasonable doubt as to the purpose of the PS. Such a rebuttal would force antitrust authorities to go through a detailed assessment of the effects of the PS.

Further developments on this interesting question are to be expected in 2022 when the Court of Justice rules on another PS in the *Servier* case.

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Patents, Litigation, and Beyond

Compliance issues unique to life sciences companies

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With combating bribery and corruption set as an important Biden administration foreign policy priority, you can count on the U.S. Department of Justice (DOJ) enhancing its investigatory coordination with foreign governments and increasing its scrutiny of potential Foreign Corrupt Practices Act (FCPA) activity.

This will greatly impact multi-national life sciences companies, which should review, update, and enhance their FCPA compliance programs accordingly. Companies that determine they have an issue will also have to grapple with the ever-present and problematic question of self-disclosure under the FCPA Corporate Enforcement Policy if they seek to gain the putative benefits of cooperation.

Several factors unique to multi-national life sciences companies should be kept in mind, including:

- The multitude of touchpoints life sciences companies have with government officials;
- Overseas clinical trials, often under the auspices of foreign officials;
- Sponsorship of educational speaker programs overseas that involve HCPs working for nationalized health systems; and
- Extent of reliance on overseas third parties.

If issues are identified, be sure to consider the following questions:

- Does self-disclosure in the United States trigger disclosure obligations elsewhere?
- What is the true cost-benefit of self-disclosure?
- What happens if, despite a company fulfilling all the elements of the disclosure policy, DOJ pushes for a criminal conviction? Is exclusion a live issue?

Because the risk profiles for life sciences companies are unique, they need to ask themselves a very different set of questions when determining whether and when to self-disclose.

Check out the Global Bribery and Corruption Outlook 2022 for more information.

Patents, Litigation, and Beyond

Complex generics

There is a large and diverse class of innovative drug products that share one common denominator: they are extremely difficult to copy. These products (Complex Generics) include (1) Complex Active Ingredients, such as low molecular weight heparin, peptides, nanoparticle iron, complex mixtures, natural source products: (2) Complex Formulations, such as liposomes, microspheres, copolymers, (3) Complex Routes of Delivery/Locally Acting Drugs, and (4) Complex Drug-Device Combinations.

As innovation advances in the direction of increasingly complex, multi-component systems, we have been monitoring and analyzing whether FDA has the backing of science and law to accommodate generic versions of these complex systems. Complex Generics have gained attention from high-end generic sponsors, who see an opportunity to enter as a lone generic, or a lone 505(b)(2) competitor, where the norm for most generics is to enter as one of many in a crowded field. Funded by user fees from Generic Drug User Fee Amendments (GDUFA II), FDA has invested substantial research dollars into the development of new scientific tools and new forms of scientific and regulatory thinking to adapt – if possible – the generic drug approval system to fit these complex products.

Pioneer sponsors who develop products in this area understand that they can be extremely difficult to manufacture and characterize, and that proposed generics may need extensive data to show "sameness" to the pioneer: pharmacokinetic studies, *in vitro* release studies, physicochemical comparative studies and, in some cases, comparative pharmacodynamic or clinical endpoint studies. FDA, in response, is examining whether alternative testing models can predict *in vivo* release and bioavailability of complex products, to relieve generics from having to conduct lengthy *in vivo* studies. However, the validity of these models remains unresolved. In addition, many complex products (e.g., drug-device combinations) raise difficult comparative device performance issues.

We remain constantly engaged with the agency on behalf of our pioneer clients to make sure the science and the law add up.

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Patents, Litigation, and Beyond

The Netherlands: Liability towards health insurers for patent enforcement against generics

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The Dutch Courts are expected to continue dealing with issues relating to patentee liability towards third parties for patent enforcement against another party. On 28 December 2021, the Court of Appeal of The Hague held that AstraZeneca (AZ) was not liable towards health insurer Menzis for the enforcement of a patent infringement injunction against a generic company, where the patent was later held invalid.

Menzis alleged that it had suffered damages by having to reimburse the price of the originator product rather than the price of a generic product. The Court of Appeal considered that there must be some form of culpability on the part of AZ in order for liability to arise. The Court did not need to answer the legal question whether AZ would have been liable against Menzis if AZ had known or should have known that there was a serious chance that the patent would be revoked, as it was considered that AZ did not know nor should have known this. The mere fact that the patent was later revoked did not mean that AZ knew or should have known that the patent was invalid.

The Court of Appeal did not establish what the legal test would be for establishing patentee liability towards a third party for enforcement of an injunction against another party. Nevertheless, it follows from the Court's decision that liability against a third party is not easily accepted. The decision is open to Supreme Court appeal.

Patents, Litigation, and Beyond

Using arbitration to protect IP rights within life sciences and health care

International arbitration is becoming more popular in resolving disputes in the life sciences sector in recent years. Disputes have been driven by increasing medical demand, accompanied by growing profitability for the industry's players, and a proliferation of cross-border collaborations between these players. Many life sciences disputes concern Intellectual Property (IP) rights, which are one of the most valuable assets of these companies.

Arbitration, unlike litigation, allows the parties to retain more control of the process, including the choice of an arbitrator with expertise and familiarity with IP disputes and the life sciences industry. The ease of enforcement of arbitral awards, coupled with confidentiality of the arbitral proceedings, are also particularly attractive since IP disputes invariably involve trade secrets or sensitive information. Further, arbitration can unify applicable law in contracts with different contracting parties and thereby avoid parallel court proceedings in different jurisdictions, which is common in patent litigation.

Life sciences companies should bear in mind investment treaties when structuring cross-border deals involving valuable IP rights. These often refer disputes to arbitration. Planning ahead based on what treaties are in place in the targeted jurisdiction is key in protecting IP rights. In one case, a pharmaceutical company forced an Eastern European state to settle a dispute relating to generic versions of its star-drug by bringing arbitration under the relevant Bilateral Investment Treaty (BIT). Another pharmaceutical company was able to bring an arbitration under a BIT with a Latin American state in order to protect its patent rights, which were not being adequately recognised by that state's domestic courts.

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Zoe Dong
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Patents, Litigation, and Beyond

Arbitrating life sciences supply chain disputes

Supply chain disputes in life sciences cover a wide range of issues such as reasonable endeavours to commercialize, disputes over quality and force majeure. Disputes over termination rights and limitations and exclusions of liability are also increasingly common. The complex regulatory environment often adds additional elements to these disputes, requiring evidence on both technical and regulatory matters.

However, there can also be a need, particularly from a buyer's perspective, to keep a supply contract alive despite the dispute in order to allow that party to continue to perform its own obligations to third parties. One approach to addressing such disputes is to seek rapid resolution through arbitration.

Arbitration can provide quicker resolution of disputes than many court systems. Arbitrations under many institutional rules, such as those of the International Chamber of Commerce (ICC), also provide for 'expedited arbitration' procedures, with a reduced fee scale and a condensed timetable for the streamlined resolution of disputes. The truncated timetable still provides a robust process and produces an enforceable award. In cases of particular urgency this can be further supported by claims for interim relief either from the Tribunal or from the courts. These procedures can be particularly effective for lower-value supply chain disputes where quick resolution is of utmost importance.

As regulatory agencies continue to increase scrutiny of manufacturing and supply chain issues in the wake of Covid-19, life sciences companies should pay keen attention to managing these potential risks. Arbitration provides a strong tool for resolution of lower-value but nevertheless potentially highly disruptive contractual disputes.

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Patents, Litigation, and Beyond

Unitary patent and Unified Patent Court – New opportunities and risks for your intellectual property rights in the EU

What is it about?

The unitary patent (UP) and the Unified Patent Court (UPC) together form a new, unified European patent system. In this new system, unitary patents will provide another way to obtain uniform patent protection in several participating EU member states, in addition to "classical" European patents (EPs, batch patents) and national patents. The unitary patent is a "European patent with unitary effect". It confers protection throughout the territory of the participating member states. The Unified Patent Court will be a common court of all participating member states and will in particular have jurisdiction for:

- Unitary patents, i.e., European patents with unitary effect,
- "classical" European patents, unless the patent owner decides to "opt out" for these patents, and
- supplementary protection certificates (SPCs).

In contrast, the UPC will not have jurisdiction over national patents.

The UPC will be a unified court whose judgments will have direct effect in all participating states. Before the UPC, both the infringement and the validity of the respective patent in suit will be decided in a single proceeding. The UPC is organized on a decentralized basis and will have court locations in several European countries, such as Paris, Germany (Dusseldorf, Hamburg, Mannheim and Munich), Brussels, Milan, and The Hague.

When will the new system go "live"?

It is expected that the UPC Agreement will enter into force in the second half of the year (2022). With the entry into force of the Agreement, patents with unitary effect can be filed. European patent applications that are already pending can be converted into unitary patents. European patents already granted will also fall under the jurisdiction of the UPC, unless an "opt-out" is declared.

Why are these changes already relevant for you?

- The new unitary patent system will affect all European patents and patent applications.
- Strategies for filing and enforcing patents need to be reconsidered and adapted. In particular, patent owners/applicants have to choose between the "classical" European patents (EPs), national patents and/or the European patent with unitary effect.
- In addition, patent owners/applicants need to be clear about whether an "opt-out" should be declared for granted patents and pending patent applications.

"Opt-out"

During a transitional period, patent owners and applicants will be given the option to exclude "classical" European patents (from the jurisdiction of the UPC (opt-out). This means that national courts will continue to have jurisdiction over national patents and those "classical" European patents (EPs) for which the owner/applicant has declared the "opt-out". However, such an "opt-out" is no longer possible as soon as an action is pending at the UPC. In addition, as long as national invalidity proceedings have not been initiated in any participating state, the owner/applicant can withdraw from the "opt-out". The patent in question then "returns" into the unitary patent system. In order to ensure that patent owners/applicants initially retain the possibility to "opt-out" (before, e.g., an invalidity action is filed before the UPC), the "opt-out" can be declared during a so-called "sunrise period", which will begin three months before the official start of the unitary patent court system (presumably in summer 2022).

What opportunities and risks does the unitary patent offer?

The new unitary patent system offers you an additional opportunity to protect and enforce your intellectual property. Whether you opt for the new form of protection or continue to choose “classic” European patents or national patents is a question of your patent strategy. Of course, you can pursue different strategies depending on the patent or patent family.

There are many arguments in favor of the unitary patent. If patent protection is sought in several participating member states, a significant advantage over the “classical” EP bundle patent will likely be the lower costs (depending on the scope of protection). The cost advantage over the bundle patent becomes greater the higher the number of countries in which it would have been validated. In addition, translation requirements will be largely eliminated.

Assignments of rights or licenses do not have to be registered individually for each country in the national patent registers, but are instead handled centrally by the EPO.

Concerning litigation, the main advantage of the new unitary patent is its cross-border enforceability. Cross-border patent infringements can be litigated more easily and quickly.

Conversely, however, this means that a unitary patent can be brought down by a single invalidity procedure for the territory of all participating member states. Therefore, there is also an increased risk for the patent proprietor compared to the previous system, in which the national parts of the batch patent are treated independently of each other.

Finally, it must be taken into account that this is a new jurisdiction for which no case law has yet been established. Consequently, decisions can be predicted less reliably. Also, decisions - at least at the beginning - may still be influenced by the national background of the respective judges before a more uniform approach emerges. This may apply in particular to the extent to which the approach of separate decisions on validity and infringement (bifurcation”), which is particularly common in Germany and known as “patent owner-friendly”, will be applied before the UPC. Therefore, finding the right balance of unitary patents, “classical” European patents and national patents in your patent portfolio will be key for a successful patent enforcement strategy in Europe.

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Christian Stoll
Partner, Hamburg

Andreas von Falck
Partner, Dusseldorf

Patents, Litigation, and Beyond

Trends in life sciences patent litigation in Spain

The patent litigation landscape in life sciences in Spain promises to be exciting in 2022, with developments expected in both the court rooms and the legislative arena. The interplay between national infringement and validity litigation and opposition proceedings pending before the European Patent Office (EPO) has been hotly debated in the last few years, and will continue.

The Barcelona Court of Appeals, one of the most highly-regarded IP courts in Spain, has recently issued some landmark rulings allowing patentees to enforce their European patents as amended further to opposition proceedings in national litigation pending at second instance, and to give a second try to preliminary injunctions proceedings in view of the change of circumstances consisting of the amendment of the patent in opposition.

The triggering events allowing the patentee to take judicial action in case of imminent infringement of its patent rights by generics' and biosimilars' companies are currently under discussion in view of a controversial ruling recently issued by the Barcelona Court of Appeals, which included a dissenting opinion from one of the magistrates. Following a restrictive approach, the court considered that, absent an effective marketing declaration of the defendant's generic to the Spanish health authorities, there was no risk of infringement even if reimbursement price had been obtained. Relevant decisions dealing with supplementary protection certificates are also expected this year.

Reform of the Patents Act is also currently underway, which, amongst other amendments, would allow the protection of pharmaceutical substances and compositions by utility models and the possibility that the court may stay the national litigation while opposition proceedings are pending.

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Patents, Litigation, and Beyond

An update on patent term extension and patent linkage systems in China

With the amended Chinese Patent Law coming into effect on 1 June 2021 and the subsequent implementation regulations issued in early July, a number of patent linkage actions have now been filed with the Beijing Intellectual Property Court and the China National Intellectual Property Administration (CNIPA). These are the two venues with exclusive jurisdiction to deal with such cases and determine whether a generic drug covered by a marketing approval application falls under an eligible patent that has been registered with the Patent Registration Platform of Listed Drugs. The CNIPA proceedings are provided as an alternative to court proceedings, and provide administrative adjudication of patent linkage disputes. The early numbers of cases filed and some industry comments suggest the new administrative dispute resolution mechanism provided by the CNIPA may be preferred over the court, possibly because of an expectation of higher efficiency and obtaining a quicker decision. We are so far unaware of a decided patent linkage case or a generic drug marketing authorization being suspended in a patent linkage case. A number of cases are likely to be decided in 2022 and can be used as references for pharmaceutical companies when deciding on best strategies to protect their markets for their patented drugs.

On the equally important topic of patent term extension (PTE) in China, there are so far still no official implementation regulations on PTE, another new system brought in by the amended Chinese Patent Law. Key issues remain open, such as whether patent owners of originator drugs will need to ensure their new drug is “absolutely new”, in the sense that the same drug has not been approved for marketing authorization anywhere else in the world, in order to apply for Chinese PTE. The amended Patent Law used the wording “new drug” instead of “innovative drug”, leaving some room for interpretation by the implementation regulations. In its proposed clarification on PTE, CNIPA’s August 2021, Draft Revised Patent Examination Guidelines, requires an eligible chemical “new drug” to contain a novel active substance, or cover a new indication of a known active substance, or cover a substantively improved ester or salt form of a known chemical active ingredient, all of which need to have not been approved for marketing authorization anywhere in the world. While the draft regulations for implementation of PTE have not yet been finalized and may be subject to changes, international life science originators should bear in mind a potential dilemma they may face for some of their drugs if the current rules are enacted as suggested in the draft examination guidelines, of having to choose between an earlier global launch and possible loss of PTE in China, or a later global launch with the possibility of obtaining PTE in China.

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8 Asia-Pacific

Asia-Pacific

Chinese anti-monopoly issues when settling patent invalidation actions

In the life sciences industry, patent invalidation challenges brought by generic drug companies against originators' Chinese patents are fairly common. Settling invalidation cases can be difficult and it is not uncommon to have allegations of reverse-payment type arrangements, where the generic patent challenger agrees to discontinue the invalidation case and not challenge the patent again in return for obtaining a licence on favorable terms or some other benefit. The possible anti-competitive effect of such a settlement had not received detailed consideration by courts in China, until recently when the Supreme People's Court (SPC), on its own initiative, looked at this issue when deciding whether to allow AstraZeneca to withdraw an infringement action against a generic drug maker, Aosaikang.

The SPC's decision concerned an appeal in a patent infringement action brought by AstraZeneca against Aosaikang for infringing its Chinese patent covering Saxagliptin, a drug to treat diabetes. In April 2019, AstraZeneca sued in a lower court to stop Aosaikang supplying a generic drug until the patent expired in March 2021. The lower court dismissed AstraZeneca's claim based on a settlement agreement signed in 2012 between the previous patent owner, BMS and a third-party generic company, Vcare which provided that BMS would not pursue Vcare and its affiliates for patent infringement in exchange for Vcare withdrawing its patent invalidation action. The lower court decided that the alleged infringing acts of Aosaikang were allowed because it was an "affiliated entity" of Vcare under the settlement agreement. AstraZeneca appealed to the SPC, but subsequently applied to withdraw its appeal. Without either party bringing up the anti-monopoly issues, the SPC, in exercising its own discretion, looked at these issues in determining whether to allow AstraZeneca to withdraw the appeal.

The SPC decided that whether a "reverse payment" type of patent invalidation settlement may have the effect of restricting or preventing competition should be evaluated by comparing the situation where such an agreement exists, and a hypothetical scenario where no such agreement exists. The key point of this comparison is to evaluate the likelihood of the patent being invalidated, had the generic party not withdrawn its invalidation action. In particular, the SPC considered if the patent owner provides a substantial benefit to the generic company without a reasonable explanation, this may suggest that the patent is likely to be invalidated. If this is the case, a further analysis should be conducted on whether the settlement agreement substantially extends the market exclusivity of the patent owner, by delaying or preventing the market entry of actual or potential generic drug providers. In the present case, the SPC decided there was no need to evaluate any potential anti-competitive effect of the 2012 Vcare settlement agreement because the patent had expired, and there was insufficient evidence concerning whether BMS had a good reason to grant Vcare early entry into the market, or on the likelihood of the patent being invalidated had there been no settlement. Thus, the SPC allowed AstraZeneca to withdraw its appeal.

The SPC's decision provides important guidance to Chinese courts and administrative enforcement bodies on evaluating anti-monopoly issues concerning "reverse-payment" types of patent invalidation settlements. For originator companies considering the settlement of patent invalidation cases in China, they should keep in mind that if the invalidation action appears likely to succeed, having a settlement agreement where the invalidation claim is withdrawn may later be held to violate the Anti-Monopoly Law, resulting in administrative penalties and civil claims from competitors. In particular, providing significant benefits to the patent challenger when settling can increase the risk.

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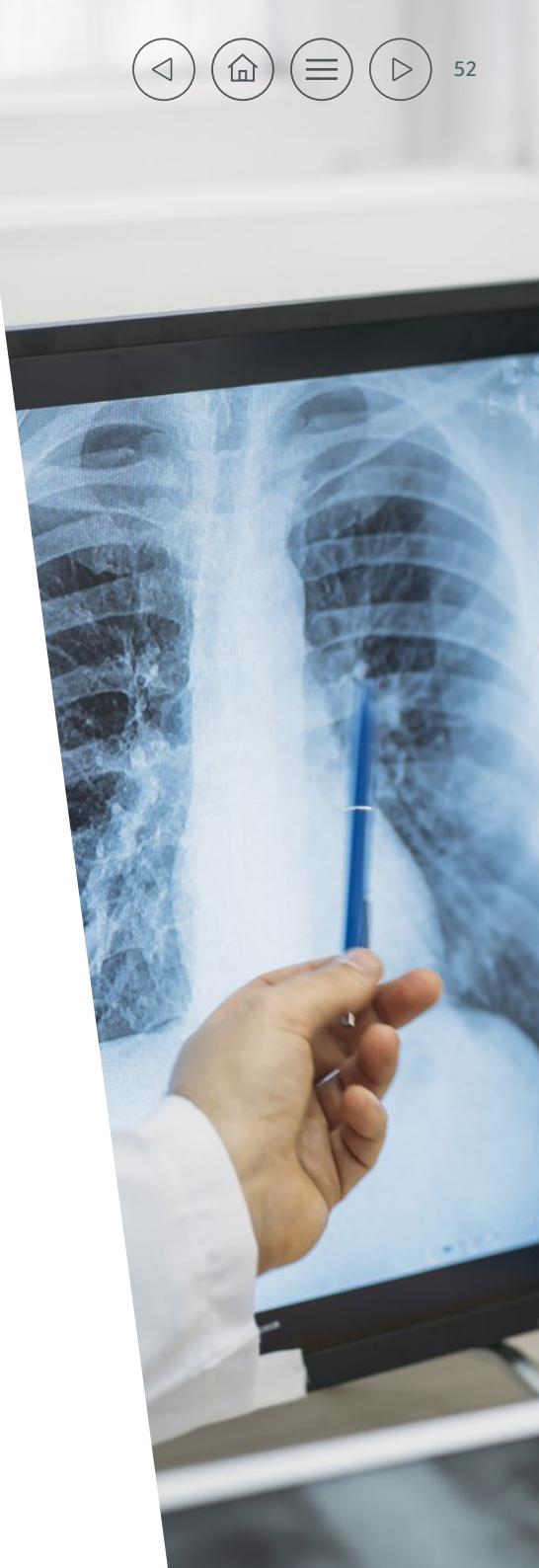

Asia-Pacific

Use of Real-World Evidence for the registration of medical devices and drugs in China

Real-World Evidence (RWE) has been allowed to be used as supplemental evidence of clinical evaluations in the registration for market authorization of medical devices (including in vitro diagnostics) and drugs with the National Medical Product Administration (NMPA) in China since 2019.

In particular, as a pilot project, the unregistered foreign medical devices and drugs (with home country approval having been obtained) in urgent clinical needs can be imported and used in designated medical institutions in Hainan Boao Lecheng International Medical Tourism Pilot Zone (Boao) through the special approval from the local authorities, in order to generate the real-world data which could then turn into RWE to the benefit of subsequent product registration with the NMPA. Typically, using RWE for market authorization application will shorten the registration approval time of products in China.

So far, the NMPA has approved the market authorizations of one ophthalmic medical device from each of Ireland and U.S., and one U.S. drug, all of which were applied by using the RWE generated in Boao pilot as the supplemental evidence for the registration.

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Asia-Pacific

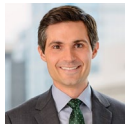
China's combat on medical insurance fraud

In keeping with the Chinese government's continuous focus on cracking down on corruption in the health care industry, the National Healthcare Security Administration (NHSA) launched a nationwide operation in 2018 to combat medical insurance fraud. According to the NHSA, from 2018 (the year when it was founded) to the end of October 2021, health care security regulators across China conducted approximately 2.34 million inspections related to insurance fraud in medical institutions. Through these inspections, approximately 50.6 billion RMB (7.94 billion USD) in medical insurance funds were recovered.

In a statement issued in January 2022, the NHSA discussed the case of a pharmaceutical giant's employees suspected of tampering with the genetic testing results of cancer patients to defraud medical insurance funds. Following an investigation by the Chinese government, several employees involved were arrested, and the NHSA demanded that the company "close loopholes" in the supervision of marketing activities, as well as conduct internal training to ensure that employees comply with the local laws. The NHSA further stated that it will now work with other authorities to carry out a nationwide campaign against fraud involving genetic testing results.

To avoid reputational and financial damage amid increasing efforts to combat medical insurance fraud, health care companies in China, especially international pharmaceutical companies, are strongly recommended to carefully review their compliance and incentive programs to ensure that they have taken all reasonable steps to reduce the risk of medical insurance fraud.

Calvin Ding
Partner, Shanghai



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Yang Bai
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Asia-Pacific

Life sciences in Japan

We expect the on-going Covid-19 pandemic in Japan to continue to heighten public interest and awareness of the biopharma industry. The initial delays in the vaccine rollout may now lead to greater alignment of Japan with international standards for clinical trials, with the relevant regulator potentially accepting the benefits of harmonizing the Japanese rules and regulations more closely with those of other countries.

We expect sustained efforts to educate citizens and to enhance access to new and innovative vaccines and drugs (including those for Covid-19 now being developed by Japanese pharma companies). Advocacy for the maintenance of suitable pricing for innovative drugs may increase; if successful, this may lead to improved commercial predictability and thus some restoration of the Japanese market's attractiveness.

We anticipate that companies will still prioritize Japan, while monitoring closely how the world's third-largest market refines the regulatory process to strike an appropriate balance between encouraging innovation and managing associated costs.

Originator *versus* generics patent cases are expected to endure. The "patent linkage" system may evolve such that the extent to which the regulator typically refrains from granting a marketing authorization for a generic product falling within the scope of relevant patents may become less clear. A number of biologics and biosimilar patent cases remain the focus of dispute resolution in Japan, somewhat mirroring cases elsewhere, and we expect these to increase. We recommend analyzing and assessing the practical impact of Japan-specific developments in due course.

Dr Frederick Ch'en
Office Managing Partner, Tokyo

Band One for Life Sciences in Japan and Asia-Pacific in Chambers Asia-Pacific, *2022*

Asia-Pacific

Conducting life science investigations in India

Ambitious growth strategy or strategic divestment can foster corruption. But traditional misconduct (bribery, corruption or fraud) is not the only exposure for companies with an identity in India.

We highlight three factors to allow for the thorough investigation and accelerated conclusion to crises our life sciences clients may face in India throughout 2022 and beyond.

1. Handle forcefully and early.

Issues can rumble on, and become 'a hydra' if not handled forcefully, early, and with wide-lens to other exposure. Complaints not satisfactorily responded to can attract a captive audience in the Indian Police, politically-affiliated unions, Central Bureau of Investigation, Narcotics Control Bureau or Enforcement Directorate. The outcome: a well-written, even if tenuous or unfounded complaint can result in litigation or inspection. These issues are then difficult to withdraw from, often taking months or years. We recommend early handling of any whistleblower complaint.

2. Tricky third-parties.

India's vast geography can necessitate the reliance on third parties. And the life sciences sector (pharma, medical devices, biomedical tech and engineering) heavily involves third parties. Contractual clauses, regular monitoring, benchmarking fees charged and incurred and testing their justification are prescriptions for compliance.

3. Compliance++ - beyond bribery and corruption.

Reflect on money laundering exposure, your supply chain and the latest regulatory guidance. For example, not having a mandatory internal committee in place to investigate complaints of sexual harassment can result in a financial penalty, reputational harm and unwanted attention. In contrast, by working together with us and trusted local counsel, having an efficient compliance system can be a legislative defense to misconduct.

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Partner, Washington, D.C.

Stephanie Yonekura
Partner, Los Angeles

Khushaal Ved
Senior Associate, Singapore

9 Europe

Europe

Early access in early launch markets France and Germany

Pharma and biotech companies wanting to bring a new product to patients in the EU go first to France and Germany. The reason, besides the size of these markets, is local reimbursement schemes. Both countries allow companies to commercially launch a product and generate revenue – and only then negotiate the price – thus making France and Germany very attractive early launch markets.

In addition, many companies enter Europe by way of early access programs in France and Germany. These programs allow for pre-launch access to drugs in advance of marketing authorization (MA). The overarching European law only provides a rudimentary framework for early access such as by offering a product for compassionate reasons. Local laws differ widely and determine the early access pathway.

In France, a major reform of early access came into force on 1 July 2021. The basic principles of early access remain, such as delivery to health care providers (HCPs) under a free price subject to repayment in exchange for immediate financing by the health insurance. However, the decision-making system and criteria have been clarified. In particular, two health authorities will be involved to decide on the presumption of innovation and benefit / risk, depending on whether the request for early access is made before or after MA. The financial regulation system has also been made more complex. Also, to compensate for its deficit in terms of time to market for innovations compared to other European countries, the French government introduced a system of direct access to the market for innovative products that cannot benefit from early access, following the example of the German model, such as where the product is already authorized elsewhere.

Germany, likewise, is an early launch market. Germany allows companies to fully commercially launch a pharma product and to determine the price for the product. The commercially launched product can be sold to the entire German population at that price. Only one year after the first commercial sale a negotiated reimbursement price kicks in. However, even before such commercial launch, many companies bring their product to German HCPs and patients by way of early access, either by way of allowing importing product, which is authorized elsewhere, or under an official compassionate use program, like in France.

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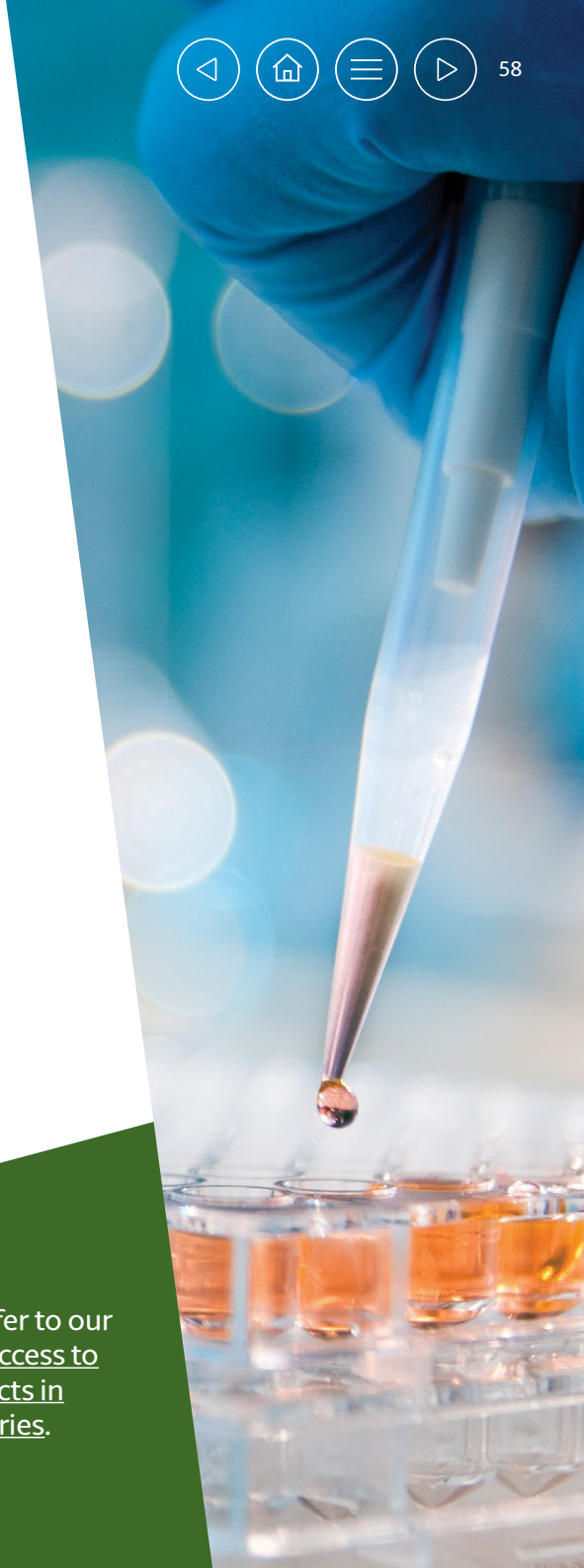
For more details we refer to our client brochure Early Access to pharmaceutical products in major European countries.



Europe

The European Commission's revision of EU pharmaceutical law, in particular relating to regulatory data protection and market exclusivity

The European Commission is revising the EU pharmaceutical legislation. In addition to assessing supplementary protection certificates (which extend patent protection) and the orphan drug regulation including orphan market exclusivity, regulatory data protection is one of the main topics for the review.

Regulatory data protection aims to reward innovation and development of new medicinal products. It is an incentive in return for the mandatory pre-clinical and clinical data that must be submitted in order to obtain a marketing authorization. Currently, innovator medicinal products enjoy eight years of data exclusivity during which no generic or biosimilar marketing authorization application may be filed. During another two years of market exclusivity, no generic or biosimilar medicinal product maybe placed on the market.

In its review of the current legislation, the European Commission notes the importance of supporting innovation, especially to address unmet medical need. At the same time, it strives to ensure access to affordable medicines, by supporting competitiveness and availability of generics and biosimilars.

Several alternatives to the current system are being considered. These include (i) differentiating protection periods depending on the type of product; (ii) reducing the current protection periods allowing for earlier generic and biosimilar market entry; and (iii) introducing new types of incentives such as a transferable exclusivity voucher or a priority review voucher; and (iv) allowing early generic entry in the event of delayed innovator market launch across the EU.

The European Commission is expected to present proposals for revised EU pharmaceutical legislation by the end of 2022.

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Europe

Hospital exemption for academic gene and cell therapies in the EU

The hospital exemption rule (Sec. 3(7) Directive 2001/83/EC and Recital 6 Regulation No 1394/2007) allows for the use of Advanced Therapy Medicinal Products (ATMPs) (the so-called academic or non-industrial ATMPs) without a marketing authorization (MA). At an EU level, academic ATMPs are defined as ATMPs prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient. Although academic ATMPs are exempted from applying for and obtaining an 'ordinary' MA, their use/manufacturing still need to be approved by the competent authorities of the Member States.

Hospital exemption in **Spain** shares with the Directive 2001/83/EC that leaves many aspects open to interpretation ('non-routine', 'custom-made', etc.). The position in Spain seems to be as follows: academic ATMPs serve to enable patients to receive therapies in cases where no authorized medicinal products are available and should not become the normal route to market ATMPs; rather, the goal should be to obtain a centralized MA. These interpretations all suggest that co-existence between 'ordinary' ATMPs and academic ATMPs sharing the same indication will likely not take place.

In the **Netherlands**, prior approval of academic ATMPs must be obtained from the Healthcare Inspectorate (Inspectie Gezondheidszorg en Jeugd or IGJ). The request can be made by completing a detailed application form as published by IGJ. The form requires the applicant to provide information on, inter alia, the qualified person for batch release, rationale for the need for the hospital exemption, clinical experience with the product and pharmacovigilance.

In **Germany,** the use of hospital exemption mainly requires that the procedure is done in a 'non-routine manufacturing'. However, the law defines this very broadly, mainly as treatment procedures done in an amount of cases for which likely comprehensive data/evidence cannot be expected. Thus, the demarcation to authorized ATMP is not really made and co-existence of authorized ATMP and procedures in hospitals remains, to the detriment of the authorized ATMP therapy.

France has implemented the exemption for academic ATMPs, and their manufacturing is subject to detailed requirements and Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) approval. Highlights of new rules being adopted in 2022 include: (i) hospital preparations are no longer limited to specific cases covered by European law or cases of rupture; (ii) automatic reimbursement by the health insurance when the pharmaceutical product benefiting from a MA 'is not available'; (iii) no clear restrictions on manufacturing to limited purposes. The French government aimed to allow alternatives to some of the gene therapies that recently received an unfavorable clinical assessment that did not allow their access to the market, which is a direct competition to pharma companies that have implemented a clinical development.

Moving to **Italy**, the main requirement for the exemption is the "preparation on a non-repetitive basis", which is defined as the non-routine preparation (even for a cycle of doses) following specific quality requirements, to be used exclusively in a public hospital, under the exclusive professional responsibility of a physician, in the execution of an individual prescription for a specific product intended for a concrete patient. Similar to Germany, the definition is very broad. Demarcation to authorized ATMP is not really made and co-existence between the two types of ATMPs remains.

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Europe

Reimbursement of digital health applications in Europe

It is still a new development that digital health applications are becoming part of regular health care services in some European countries. Not long ago medical apps were not reimbursed by public – or private – health care insurance funds or other payors. Expedited by the Covid-19 pandemic, reimbursement of digital health applications is slowly taking off in European health care systems.

- In Germany, certain digital health applications – so-called DiGAs – were added as standard health care service of the German public health care system (SHI) in 2019/2020. Once evaluated and approved by the German authority BfArM in a Fast Track Process, physicians are able to prescribe accredited DiGAs to patients which detect, monitor, treat or alleviate diseases, injuries or disabilities. As of now, over 30 digital apps have been accredited for reimbursement.
- In UK, there is no specific national reimbursement pathway for digital health applications and such applications do not fit easily within the existing public health system reimbursement pathways. There are a number of initiatives to help address this, such as the MedTech Funding Mandate policy which supports NHS uptake of selected health technology assessed digital technologies, and on-going industry discussions to develop a clearer reimbursement approach to digital health technologies.
- In Spain, the Ministry of Health has recently launched a digital health strategy for the National Healthcare System (SNS) which aims to help lay the necessary foundations for reimbursement of digital health applications. The so-called 'public procurement of innovation' (compra pública de innovación) is one of the first instruments for integrating digital health solutions into the SNS. However, there is still a long way to go to develop a regulatory framework for reimbursement.
- In Italy, to date, the following digital applications exist: telemedicine and teleconsultation, e-prescription, health digital card, electronic health records and digitalised reports. There is still much to do like medical app, cloud, AI, etc., but especially in terms of reimbursability. As for now, in fact, there is no specific national reimbursement pathway for digital health applications and such applications do not fit easily within the existing public health system reimbursement pathways. Nevertheless, the digitalization process has begun and is progressing rapidly as demonstrated by the Government's development of the first National Telemedicine Platform, which could give rise to rapid development of the sector.
- In France, the French government is planning to promote market access for medical device innovations, particularly digital devices for therapeutic purposes (DTx). A €32 billion market in 2024 driven by chronic diseases (diabetes and obesity) has been identified. The French Health Authorities (HTA) have adapted their methods to digital devices and clarified the criteria for taking into account their therapeutic value as well as the AI features. A derogatory reimbursement system has been created from 2022 for digital innovations "presumed to be innovative" with precise requirements, particularly in terms of data collection. The pricing authorities will also have to adapt their methods, but this is underway.

Apart from Germany, reimbursement for digital health applications does not currently exist in the major EU countries. Only France is about to introduce such a reimbursement pathway. However, in the other EU countries similar developments are expected in the coming years.

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Europe

New pitfalls in EU pharma supply chain

The starting point of any supply chain is the manufacture of a product. If manufacture of a finished medicinal product happens outside of the EU, an import into the EU must be performed. For pharmaceutical companies, this importation, as well as the further distribution across EU markets, has to meet all the regulatory and customs requirements while also considering internal tax optimization. This is particularly important, for example, for ex-EU companies subject to favorable tax, such as by a Swiss affiliate. For this reason, the physical product flow and the legal product flow are often not in sync and regulatory requirements may jeopardize tax optimization without careful planning.

Important new aspects for life sciences companies to consider in supply chain planning include:

- The European Commission no longer considers the act of selling by an ex-EU entity to customers/affiliates within the EU as an act of 'legal importing'. However, some local authorities may still do so, which would require the purchaser to hold a manufacturing and import license (MIA).
- Some countries interpret gross domestic product rules in a way that a wholesale distributor which procures and receives a product can only do so from an entity holding an EU-granted MIA/wholesale distribution license. This means, for example, that a local EU affiliate could not easily buy product from a Swiss or a U.S. affiliate.
- The use of logistics service providers across Europe requires great care to ensure that sufficient levels of control and involvement of all companies in the supply chain are met.
- Local reimbursement laws may require that the entity selling a product to local reimbursement authorities have a local presence.

However, while these new pitfalls arise, there are still ways to compliantly structure a company's EU distribution system while balancing taxes and other considerations. Using a branch office of a non-EU company may help, as can structuring via a low risk and favorable-tax entity in the Netherlands.

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Band One for Life Sciences in Chambers Europe-wide, *2022*

Europe

Proposed reform of UK medical devices regulation

The UK Government is proposing to reform existing UK medical devices legislation with effect from 1 July 2023. Currently, UK medical devices legislation continues to be based on previous EU legislation. At a high level, the reform is intended to further protect patients and to support the UK as an attractive market to develop, produce and supply medical devices.

As one of the first reforms of industry-sector level legislation post-Brexit, the UK Government is seeking both to minimise the regulatory burden on business by aligning with EU and international requirements, while also using its increased legislative flexibility to navigate some of the challenges of those requirements, create a flexible and proportionate regulatory system, and focus on innovation.

The proposed changes include:

- Bringing UK legislation into closer alignment with the new EU Medical Devices Regulation (EU MDR) and In-Vitro Diagnostic Medical Devices Regulation (IVDR), as well as with international standards;
- Increased collaboration with international regulators, including a fast-track access pathway that would enable medical devices to be approved in the UK based on approval in other trusted markets such as the US and Canada;
- A specific framework for regulating software and artificial intelligence solutions as medical devices;
- Introducing new measures such as impact assessments to support sustainable manufacturing and improve supply chain resilience.

The Medicines and Healthcare products Regulatory Agency (MHRA) consulted on the initial proposals at the end of 2021 and draft amending legislation is in development.

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ESG on the horizon - What do supply chain regulations and litigation trends mean for the sector?

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Environmental, social, and governance (ESG) and supply chain due diligence are becoming increasingly important for companies in the life sciences and health care sector. While countries like Germany and France have already enacted respective local legislation, the European Commission has just issued a proposed EU Supply Chain Directive (Directive), which provides for mandatory due diligence obligations.

The proposed Directive would apply to all companies established under the laws of a Member State having more than 500 employees and a worldwide annual net turnover of more than EUR 150 million. Companies established under the laws of non-EU member states generating an annual net turnover of more than EUR 150 million in the European Union would also be subject to the Directive.

Once the Directive is enacted and implemented into local laws, companies within the scope will have to actively assess and manage their supply chains. This includes integrating supply chain due diligence into company policies, identifying actual or potential adverse impacts on human rights or the environment, preventing and mitigating potential adverse impacts, and bringing actual adverse impacts to an end.

Furthermore, all Member States will also have to retrofit a civil liability basis in the medium term, so that we expect more civil lawsuits from eventually affected parties in the future.

Under current legislation we already see an increasing need for ESG advice on disputes and preventive assistance, for example, in the context of transactions, contracting, or working with suppliers and subcontractors throughout life sciences supply chains.

Visit our website to learn how we can help with your ESG needs.

10 United States

United States

Buy American: Efforts to strengthen the U.S. industrial base

Sparked largely by the Covid-19 pandemic, efforts continue this year to strengthen the U.S. health system supply chain. Indeed, the pandemic brought to light the extensive dependencies that U.S. pharmaceuticals, biologics, and medical device manufacturers have on material and component suppliers located ex-U.S.

Key government agencies, including the Department of Health and Human Services, were instructed by the White House in early 2021 to conduct in-depth research - together with industry partners - to identify the specific dependencies that pose risk to the public health system.

To spur use of U.S. supplies in the short term, the U.S. government has applied stricter domestic preferences in the context of Federal procurement. Specifically, the administration took steps in early 2022 to increase the domestic content thresholds in Federal procurements.

However, in cases where components are simply not available from domestic suppliers, domestic preferences in procurement are of limited utility. This is particularly relevant in the health and medical industry, where the majority of certain critical components, such as active pharmaceutical ingredients, are manufactured overseas in countries such as China and India, where production costs are substantially lower.

In an effort to address this imbalance, within the last year, a flurry of legislation has been proposed to create incentives to maintain and expand manufacture of drugs, devices, and critical inputs in the U.S. Proposals include tax incentives and other "carrots" for U.S. industry. We can expect these initiatives to continue to be front and center over the course of 2022.

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FDA formal dispute resolution and administrative hearing procedures

FDA has reported a significant uptick in the use of dispute resolution and other appeals procedures by sponsors in recent years. In the past two years, sponsors have even pursued a less commonly used formal administrative hearing process before FDA, in order to challenge agency proposals to deny or withdraw approval of their new drug applications. These trends highlight the importance of leveraging the appropriate mechanisms to resolve disputes with FDA, ranging from informal "pushback" in meetings or during the review process to formal hearings and even litigation.

There are a number of considerations in determining the appropriate dispute approach, including:

- **Subject Matter:** Is the dispute scientific, procedural, or legal/regulatory in nature?
- **Purpose:** What is the desired outcome? Additional agency interaction or a new audience?
- **Process:** Is a public forum desired? What information can be included in the dispute record?
- **Timing:** Where is the product in the review process? Has the sponsor exhausted all administrative remedies?

For example, a formal administrative hearing is a public process, with sponsor and FDA submissions and comments in a public docket, which may be necessary in order to take the dispute to court. Non-public interactions to resolve scientific/medical disputes between the sponsor and a review division include informal correspondence before approval as well as Formal Dispute Resolution after a Complete Response Letter.

Regardless of the mechanism selected, the likelihood of success can depend on several factors, such as identifying red flags early, creating a thorough record, knowing the procedure and audience, and understanding different successful outcomes. When issues arise, sponsors need to methodically evaluate all options in light of their specific goals and sensitivities.

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United States

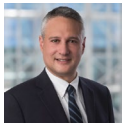
More FDA inspections are coming soon

FDA is facing pressure to reduce the backlog of pharmaceutical manufacturing inspections, especially foreign inspections, caused by the suspension of routine inspections during the Covid-19 emergency. Although FDA still has persistent vacancies among those who specialize in foreign inspections, FDA is expected to resume foreign surveillance inspections as soon as this spring for establishments in locations identified as Level 1 or 2 Covid-19 travel risk. In addition, FDA plans to implement pilot programs for foreign drug inspections in India and China, including using unannounced inspections and independent translation services. On 2 February 2022, FDA announced that domestic surveillance inspections are now also expected to resume.

During the period when FDA was not conducting routine inspections, the agency relied more on certain alternative inspection tools, including the following:

- Information from foreign regulators obtained through Mutual Recognition Agreements;
- Information from foreign regulatory counterparts obtained through confidentiality agreements;
- Information requested from the facility in lieu or in advance of an inspection; and
- Remote Interactive Evaluations (RIEs), which use livestreamed video of operations, as well as remote, live interactions with operators.

In a recently released report from FDA's Office of Pharmaceutical Quality (OPQ), FDA reported that such tools were applied in support of site evaluations for 269 product applications in 2021, which reduced the need for preapproval inspections by 52%. We anticipate that FDA will continue to use these alternative tools, to some degree, even after the on-site preapproval inspection frequency increases. However, so far, FDA has not been willing to use these tools as an alternative to an on-site inspection for firms that have never been inspected before or are potentially subject to compliance action based on a prior inspection, including sites that are the subject of Warning Letters or Import Alerts.



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United States

Real-World Evidence regulatory considerations in the United States

Advances in the availability and sophistication of real-world data (RWD) and real-world evidence (RWE) have led to an increased interest in a role for RWE in medical product development and FDA regulatory decisions. FDA has placed increasing emphasis in recent years on the use of RWE in regulatory decision-making, but questions remain as to whether the policies set out in FDA's recent guidances are a significant step forward.

RWD/RWE can enable more efficient and timely development of evidence that support regulatory decision-making, including where traditional randomized clinical trials (RCTs) are impractical (e.g., rare diseases) and where there are evidentiary gaps not easily addressed with traditional RCTs (e.g., patients with multiple comorbidities, patient experience, long-term outcomes). FDA's guidances reflect a formal willingness to evaluate RWE that meet regulatory standards. However, the Agency has not yet fully addressed complex considerations around the quality and reliability of the data and statistical methods that are critical to permit inferences regarding the safety and effectiveness of a medical product for a particular disease or condition. Until more meaningful guidance is developed, early and detailed discussions with FDA can help determine the extent RWD/RWE could be utilized for a particular purpose.

We expect FDA to prioritize additional RWD/RWE regulatory policies and systems to provide sponsors with greater confidence around the use of RWD/RWE that meet scientific and regulatory standards. We leverage our deep understanding of product development, clinical trial design, and data standards to guide our life sciences and digital technology clients through challenging regulatory issues and will continue to closely track FDA's evolving RWD/RWE paradigm.

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Reclassification of certain drugs as devices and combination products after *Genus v. FDA*

Sponsors are facing uncertainty regarding some products' regulatory classification after the April 2021 decision *Genus Medical Technologies LLC v. FDA*. In *Genus*, the DC Circuit held that FDA does not have discretion to classify as a "drug" products that meet the statutory definitions of both "drug" and "device."

The case arose out of a dispute over Genus's diagnostic contrast agents, which FDA classified as drugs, notwithstanding FDA's acknowledgment that the products also satisfied the overlapping statutory definition for devices. The court determined that, excepting combination products, drugs (that do not also meet the "device" definition) must be regulated as drugs, and devices as devices.

In an August 2021 Federal Register notice, FDA announced that it would comply with *Genus* and establish a process to determine which drug products should transition to device status. Notwithstanding its offer to establish a transition process, sponsors of certain drug products are already receiving deficiency notices, complete response letters, and information requests indicating that products are being transitioned to "device" or "combination product" status.

Genus is now critical to determining the regulatory status of certain single-entity products and products that appear to combine in one product a drug with a device, such as pre-filled syringes. Based on the statutory definitions of "drug" and "device," the analysis turns on whether an "article" achieves "its primary intended purposes through chemical action within or on the body," such that it is excluded from being regulated as a device. Deep analysis of FDA's statements in this regard will be required to determine regulatory status. We are assisting clients with analyzing the likelihood and impact of reclassification and optimal outcomes for regulation moving forward.

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Band One for Life Sciences: Regulatory/Compliance by *Chambers USA*, 2021

United States

Combination products and Part 4 compliance

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We expect pharmaceutical and medical device companies to continue and find new ways for developing products that combine their current products with another drug, medical device, or biological product, to identify eligible patients sooner and improve health outcomes. Continued advancements in the life science and medical device industries, specifically combination products, have propelled FDA to establish a comprehensive regulatory framework for the design and regulation of these products to ensure their safety and quality. Firms who have historically occupied one area (drugs, biologics or medical device) and have limited experience in the other areas should consider necessary programmatic changes to their quality system at early stages of product development to ensure compliance with the requirements set forth under 21 CFR Part 4 (Part 4) with regard to good combination manufacturing practice and postmarket safety reporting requirements.

Early planning and careful consideration of the unique regulatory and compliance challenges that combination products raise are essential. There are key differences to GMP approaches for specific types of combination products (e.g., prefilled syringe, drug-coated gauze/sponge), and different requirements for postmarket safety reporting for combination products and constituent parts. Earlier this year, FDA published a final guidance on principles of premarket pathways for combination products, and we anticipate additional guidance related to GMP compliance, performance requirements, and postmarket changes, among others, which may require additional updates to quality systems. FDA set compliance dates for certain postmarket safety reporting requirements though enforcement was impacted by the ongoing Covid-19 pandemic. That said, the requirements have been in place and compliance expected for long enough that the Agency is likely to expect that manufacturers have had sufficient time and opportunity to achieve compliance. As public health concerns and travel restrictions ease, we expect to see an increasing number of site inspections and assessments to evaluate combination product manufacturers' compliance with Part 4 requirements.

We know Part 4 compliance well, and we leverage our keen understanding of drug and device GMP requirements, trends and proposed regulatory changes, to provide practical approaches to achieve and sustain compliance. We will work closely with our clients to navigate the evolving regulatory landscape for combination products.

Get in Touch

Life Sciences and Health Care Horizons provides only a snapshot of some issues the industry will face in the coming months. 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 any of theauthors in this publication, or one of the partners with whom you regularly work.

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