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2024 Horizons

Life Sciences and Health Care

Welcome

While economic factors, including the high cost of capital, continue to keep our clients up at night, we also see signs of optimism in 2024. Against this fiscal backdrop, significant recent regulatory changes and those on the horizon will impact supply chain planning, commercial launch preparation, and pricing and reimbursement, making a cross-border perspective even more critical for achieving long term business goals.

As our teams discuss, the global transition from soft law to hard law will keep Environmental, Social, and Governance (ESG) initiatives front and center in 2024 and beyond. The potential environmental impacts of supply chain planning now place companies at risk for regulatory and civil law penalties. While many of these regulations are industry agnostic, their impact will nevertheless be significant for clients across our sector. Life Sciences and Health Care (LS&HC) companies must also stay up to date on sector-specific developments. A new environmental risk assessment as part of a larger proposed European pharmaceutical law package, actions aimed at strengthening the pharmaceutical supply chain in the U.S. and elsewhere and global initiatives aimed to improve diversity in clinical trials are but a few examples. Manufacturing reliability – for pharmaceuticals, (traditional) medical devices, and now, increasingly, for radiopharmaceuticals, precision medicines, custom/customizable medical devices, and for AI-enabled products – are key areas requiring attention to agreements, export controls, appropriate corporate and tax structures, and an awareness of the risks from missteps that can result in an increasingly global economy.

Digitalization also continues to generate both opportunity and risk, driving innovations in AI, virtual health solutions, telehealth products, and related cybersecurity measures, while raising vexing questions on how to safely and appropriately access patient health data, protect patient privacy, and manage social media. The November 2023 signing of the Bletchley Declaration on AI signifies that jurisdictions globally are committed to safe and responsible AI. However, local approaches vary, with some jurisdictions placing higher scrutiny on "high-risk" uses, including many health and medical applications. Again, LS&HC companies are uniquely positioned and must grapple with both sector-specific and industry agnostic guidelines. Understanding the interplay between multiple regulatory and legislative efforts will be crucial to success for developers and end users alike.

In the transactional space, we also see increasing complexity, as partners consider alternative funding options to account for long development timelines and allocation of manufacturing risk for bespoke therapies. While investors continue to take a cautious approach towards all types of deal making, an uptick in activity as we enter 2024 hints at the possibility of a more robust life sciences capital markets, M&A and partnering market in the coming months. However, innovators with early stage pipelines (especially pre-clinical assets), may need to advance further into the development process with their own de-risking strategy before traditional players will partner or invest. Regional opportunities for government-backed research and other sources of non-dilutive funding may prove to be of strategic interest for companies with particularly innovative technologies.

LS&HC companies are also disproportionately affected by specific issues in each geographic area, where new legislation and regulation setting precedent locally, with regulators in other markets likely to follow. In the United States, impacts of the initial drug price "negotiations" under the Inflation Reduction Act of 2022 (IRA) will have broader implications for product lifecycle management and pipeline valuation. FDA also appears to be gearing up for changes across technologies as varied as psychedelic therapies, over-the-counter drugs, and skin substitutes, while drug patents and pricing are attracting scrutiny across agencies. The UK continues to promote a progressive regulatory environment supporting innovation and accelerated access to drugs and medical devices post-Brexit. In the EU, our LS&HC clients are also navigating changing legislation with proposals for new pharmaceutical regulations as well as local implementation of, among others, the AI Act and European Health Data Space. Companies are also tracking the early cases before the European Unitary Patent Court, which has already proven an attractive pathway for some life sciences litigants. These themes also carry over to Asia-Pacific markets, where we see fast-track routes for drug marketing authorization and incentives for research and development of cell and gene products, coupled with continued scrutiny on health care corruption. Companies with current – and future – interests in these regions would be well advised to factor these into their plans ahead. We are proud that our truly cross-border and cross-functional teams are here to help.

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. The 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.

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1 ESG and Supply Chain

Distributing products in the Middle East Gulf region

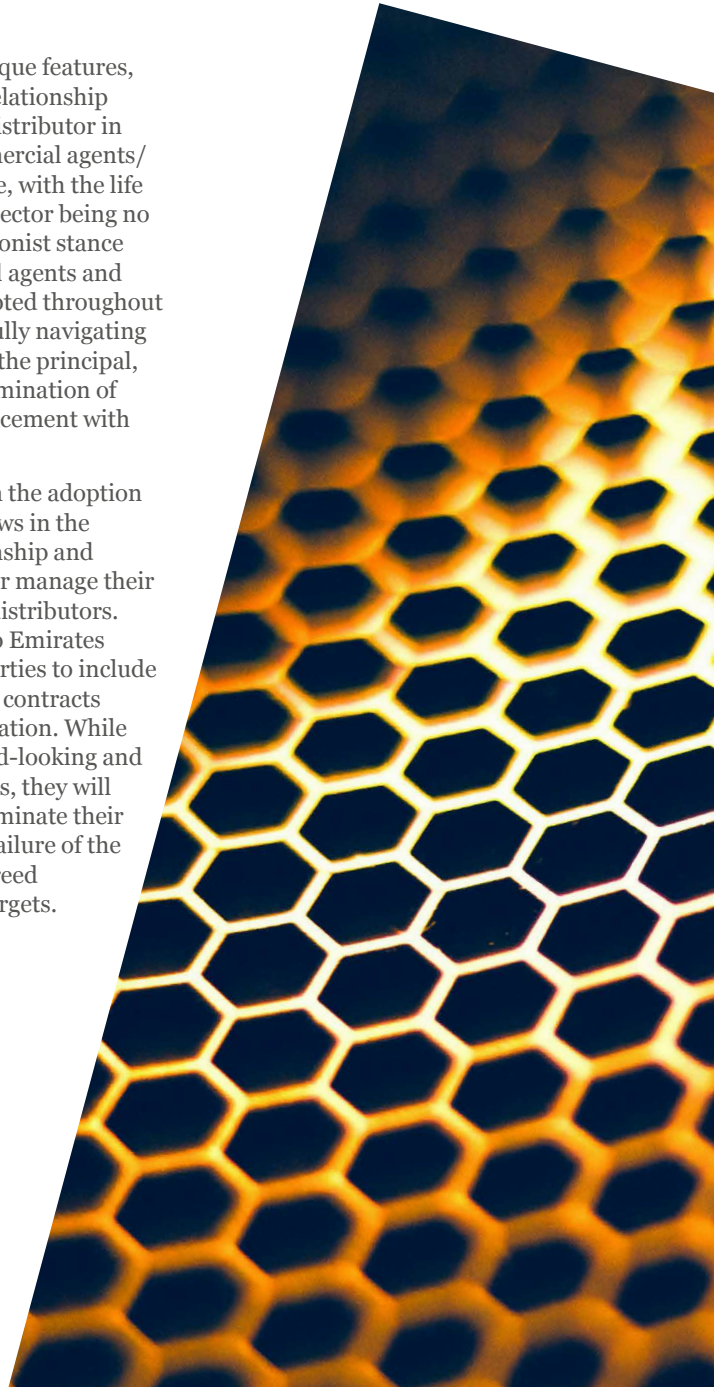
The growing populations and huge health care investment in the countries of the Arabian Gulf make it an increasingly attractive market for the sale of pharmaceutical products and medical devices. International companies will be considering appointing distributors in the region or changing distributors.

While each Gulf Co-operation Council (GCC) country has its own rules, there are a number of important and some unique features to these arrangements, which should be borne in mind:

- All GCC countries make a distinction between arrangements that are registered and those that are unregistered. Broadly, registered arrangements require consent from the agent/distributor before they can be terminated, which often requires negotiation and payment of compensation to the agent before a termination is agreed.
- Registered agencies are exclusive, and failure to agree can lead to exclusion from the market pending resolution. Court action will be required where there is a failure to agree, which can lead to exclusion from the market pending conclusion of such proceedings.
- In some circumstances, registration cannot be avoided, which is typically the case with medicinal products. Some customers, particularly Government (which tend to be the largest customers in the GCC countries) may insist upon registration before agreeing to contract, and in some GCC countries unregistered arrangements are unenforceable.
- As a general rule, registration should be avoided where it is possible to do so without compromising the business. If it cannot be avoided, then certain mitigations should be considered, including:
  - limiting the products/territory the subject of the arrangement to that necessary for the business in hand;
  - include clear and measurable key performance indicators (KPIs) so that underperformance can be easily proved to aid termination/limit compensation;
  - where possible, include pre-agreed amounts payable to reduce the risk of significant compensation claims;
  - consider carefully your regulatory strategy for the region. Having your local distributor hold product licenses/registrations can give rise to delays and costs when switching to a new distributor.

Possibly as a result of these unique features, and the general nature of the relationship between principal and agent/distributor in the region, disputes with commercial agents/distributors were commonplace, with the life sciences and pharmaceuticals sector being no exception. The general protectionist stance in favor of the local commercial agents and distributors that had been adopted throughout the region meant that successfully navigating these disputes was difficult for the principal, particularly with regards to termination of the agent/distributor and replacement with another.

This is, however, changing with the adoption of new commercial agencies' laws in the region, rebalancing the relationship and empowering principals to better manage their relationships with agents and distributors. The new law in the United Arab Emirates (UAE), for example, enables parties to include arbitration agreements in their contracts and refer any disputes to arbitration. While these developments are forward-looking and largely apply to new agreements, they will make it easier for parties to terminate their agreements, including for the failure of the agents/distributors to meet agreed milestones and performance targets.



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Embracing Diversity, Equity & Inclusion in the supply chain: An ESG imperative

The pivotal role of supply chains in the actual implementation of Environmental, Social, and Governance (ESG) principles is well-recognized in the contemporary business landscape. Indeed, it is not possible to achieve the goals that ESG principles pursue by working on a solo basis: it is crucial to create a chain in which all links play a role, ensuring consistency and effectiveness of ESG strategies.

As organizations strive to develop comprehensive ESG systems, the relevance of Diversity, Equity, and Inclusion (DE&I) must not be underestimated. Including DE&I in ESG strategies underscores the commitment to a holistic approach to ESG, where the value chain not only minimizes environmental impact and promotes good governance but also reflects a diverse and inclusive workforce and society.

We strongly believe in the importance of DE&I within the ESG systems. To this end, we work with our clients to establish and integrate ESG-compliant systems that encompass DE&I considerations. Additionally, we are among the founding members of an association - named "ForAll" - dedicated to promoting a culture of DE&I and social sustainability among its member companies, their suppliers, and the communities in which they operate.

More specifically, we deem that to implement ESG principles in the supply chain, with a focus on DE&I, these are the key elements:

1. **Supplier diversity programs.**

   Incorporating DE&I metrics into ESG supplier assessment and implementing procurement policies prioritizing sourcing from suppliers that share DE&I values, having implemented ESG-compliant systems and/or obtained ESG or DE&I certifications.

2. **ESG-specific clauses.**

   Including specific ESG clauses in contracts with suppliers that ensure adherence also to diversity and sustainability goals.

3. **Capacity building.**

   Providing training and resources to suppliers to help them also meet DE&I standards and rely on experienced subjects to conduct internal training activities.

It is also crucial not to overlook the power of leading through example by letting the DE&I culture penetrate all of the company's activities. This extends from more visible aspects, such as having an effective ESG system in place that encompasses DE&I requirements or having internal committees dedicated to DE&I initiatives, to less visible ones, such as - in the case of pharmaceutical companies - the implementation of DE&I requirements in research and clinical trials.

In conclusion, the journey of fully embracing ESG principles calls for a shift from a traditional approach. With the right support, the destination of this journey is the possibility not only to positively influence the business environment but also to contribute to building a better society.

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Environmental risk assessment in the new EU pharmaceutical law package

With its proposal for new pharmaceutical legislation, the European Commission aims to reduce the environmental impact of medicinal products. To achieve this objective, the new legislation will strengthen and extend the current requirements for environmental risk assessment (ERA) for marketing authorization holders.

Under the proposed EU legislation, the ERA shall include risk mitigation measures to limit or even avoid emissions to air, water and soil of pollutants. Non-compliance with the ERA requirements or not proposing (sufficient) precautionary and safety measures on the environmental risks that were identified in the ERA, should lead to *refusal* of the marketing authorization.

Although not yet adopted, the new set of legislation aims to impose a wider and stricter set of requirements on manufacturers of medicinal products with regard to their impact on the environment.

These new requirements that would apply specifically to marketing authorization holders of medicinal products, come in addition to extensive other new legislation in the area of environment, the European Commission's "Green Deal" as well as broader evolving ESG considerations.

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ESG compliance and supply chain due diligence

The regulatory landscape regarding Environmental, Social and Governance (ESG) topics has been evolving rapidly in the ESG compliance and supply chain due diligence the spearhead with the entry into force on 1 January 2023 of its Supply Chain Due Diligence Act (SCDDA). The SCDDA stipulates comprehensive due diligence obligations also affecting national and international players in the life sciences and health care sector. Due diligence obligations include risk management and risk analyses, but also preventive measures such as audits. As of 1 January 2024, the SCDDA applies to companies that are domiciled in Germany or have a German branch office and have normally at least 1,000 employees.

In Germany, the Federal Office for Economic Affairs and Export Control (BAFA, in German (Bundesamt für Wirtschaft und Ausfuhrkontrolle) as the competent authority has been actively enforcing the SCDDA from the very beginning, such as by issuing several waves of binding information requests and publishing various far-reaching official guidance. Notably, the Pharmaceutical Supply Chain Initiative (PSCI) provides a sound basis for SCDDA compliance. In particular, PSCI audits may serve as useful tools to create synergies for the risk analysis as well as for preventive or remedial measures. However, companies should diligently assess whether the evolving requirements are covered by PSCI standards.

This is equally true regarding the agreement in principle on the EU Directive on Corporate Sustainability Due Diligence (CS3D) (December 2023), which would finally lead to even stricter due diligence obligations as well as a public and civil liability regime for both EU and non-EU companies of a certain size in the medium-term.

Due to the ongoing transition from soft law to hard law environment cast in national and supranational laws and regulations, ESG will continue to remain a top regulatory driver for the life sciences and health care sector in 2024 with further legislative proposals in the pipeline, including the proposed EU import ban on forced labor goods.

Given this “regulatory patchwork rug” and the constantly evolving regulatory requirements around ESG, keeping pace is challenging. Since ESG issues no longer pose only reputational risks, but also regulatory and civil law risks, continuous regulatory monitoring and adaption of policies and procedures (*e.g.*, Compliance Management Systems) is key to cope with these challenges. Strong policies and procedures will also create synergies with other ESG related regulations such as the Corporate Sustainability Reporting Directive (CSRD) and European Sustainability Reporting Standards (ESRS) covering the full range of ESG.

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ESG litigation in the life sciences sector

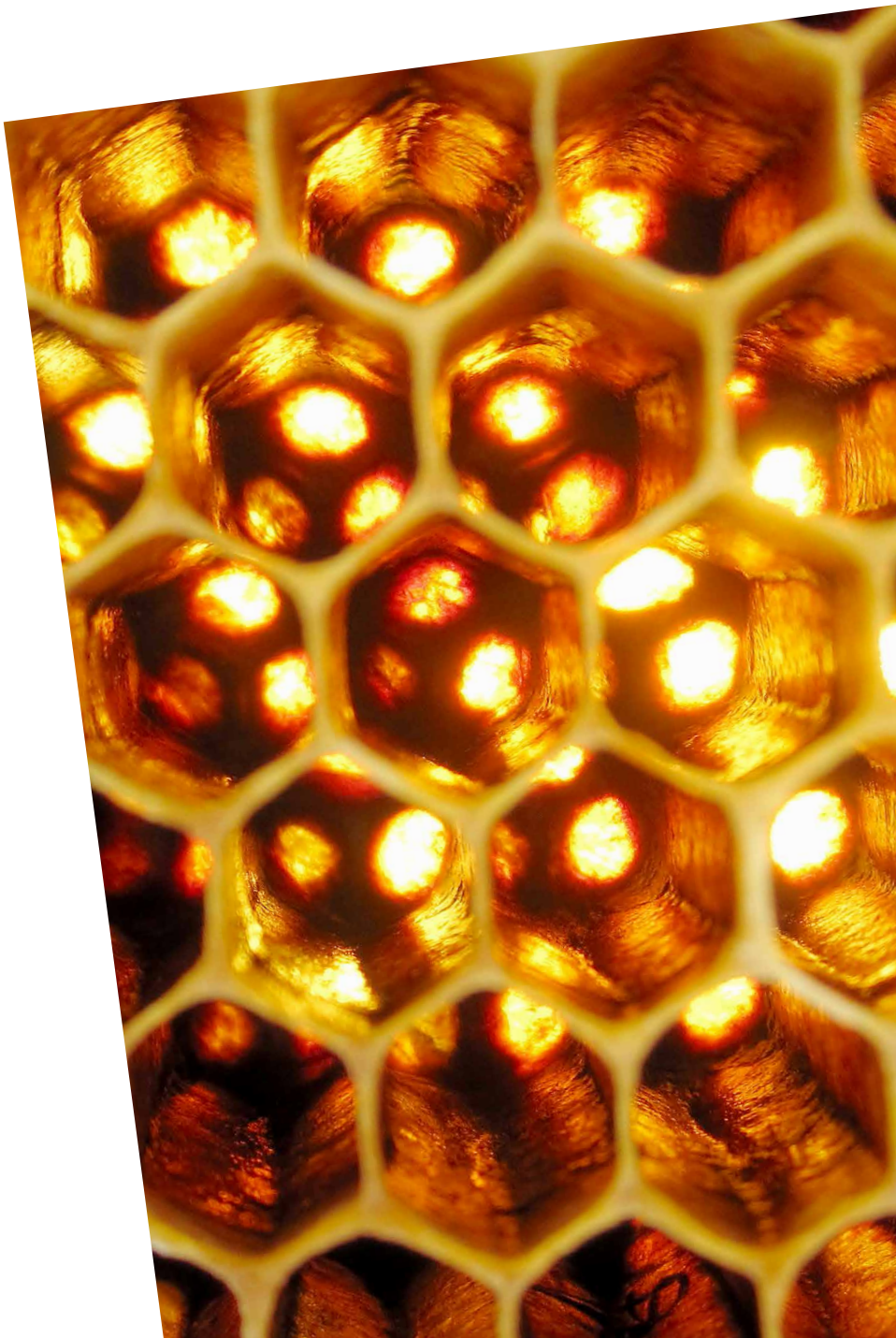
Lawsuits against state institutions for allegedly inadequate regulation of climate-damaging effects have become an established instrument for securing climate protection efforts. However, climate litigation is not limited to state actors. Recently, private companies, including those in the life sciences sector, have also been targeted.

Climate litigation against private sector emitters has increased rapidly in recent years, as the UN noted in its latest Climate Litigation Report. The specific subject matter of the lawsuits varies. For example, affected individuals or groups of people sue for actual or financial participation in measures to prevent or remedy against existing, emerging, or imminent future impacts of climate change (so-called climate liability lawsuits). Non-governmental organizations (NGOs) are also filing lawsuits against corporations that they believe are contributing significantly to the climate crisis. These lawsuits generally seek to force companies to adapt their business models to the needs of climate change or to reduce their emissions (so-called climate protection lawsuits). There are also cases brought by government agencies/authorities, *e.g.*, for violations of environmental laws or to expose misinformation by companies on sustainability issues.

Legal action can also be initiated by shareholders or investors who want to have a say in corporate strategy to ensure that companies meet or review their environmental, social, and ethical standards. General meetings represent nowadays a peak point where ESG legal risks materialize, in particular with the development of and increasing demand for 'say on climate' resolutions.

Emissions-intensive companies should take care to identify their own environmental risks and claims. This is not only because of potential litigation risks, but also because of EU sustainability legislation. The recently enacted Corporate Sustainability Reporting Directive (CSRD) and the forthcoming Corporate Sustainability Due Diligence Directive (CSDDD) mean that companies will face new obligations that need to be integrated into internal compliance processes.

In addition to that, environmental claims are also a gateway to potential litigation. National courts are increasingly called upon to determine whether or not certain environmental statements or corporate promises are misleading. In March 2023, the EU has taken legislative action to combat greenwashing and, in particular, to prevent companies from making misleading voluntary claims about the environmental benefits of their products and services with the so-called Green Claims Directive proposal. The Directive furthermore aims to set minimum criteria for environmental labelling schemes and could also be finalized in early 2024.



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EU supply chain issues for medicinal products: Important recent developments

Supply chain structures of import and distribution of medicinal products in the EU should be carefully set up, taking into account logistics, but also regulatory, customs requirements as well as tax considerations.

An important recent development is that, in a different context, the Court of Justice of the EU (CJEU, 47/22, 21 September 2023) made clear that a wholesaler in the EU may not obtain medicinal products from others than holders of an EU wholesale license. Further, the European Commission (Commission)'s proposal of reform to the EU's pharmaceutical legislation published in April 2023 (Pharmaceutical Law Package) explicitly included fiscal transactions in the definition of wholesale activities. This amendment seeks to make clear that entities which merely fiscally purchase products, even without touching them, are wholesalers. Thus, wholesalers engaged in (tax driven) fiscal transactions would be subject to good distribution practice (GDP) laws. As a consequence, they would need to obtain the products solely from entities which hold an EU wholesale or manufacturing license. Purchasing products from entities outside of the EU would no longer be possible. Fiscally importing products would arguably then require holding the manufacturing license under the proposed amendment. However, in several jurisdictions it is currently not even clear whether a manufacturing license could be granted by local authorities for such mere wholesale activity. We are seeing many countries now becoming less flexible in regards to tax-optimized supply chain planning.

In addition to structuring questions around import and distribution, supply chains of medicines are under scrutiny of the EU authorities. For example, the above-noted Pharmaceutical Law Package proposals include strengthened requirements for marketing authorization holders with respect to supply shortages, including an obligation to have in place a shortage prevention plan. These proposals followed the Commission's October 2022 publication of its main findings from a Structured Dialogue on the security of medicines supply, which addressed global supply chain vulnerabilities and risks of shortages. Topics raised included identifying critical medicines, increasing manufacturing capacity in the EU, optimizing regulatory environment, promoting green and digital innovation in manufacturing and global cooperation.

Medicines shortages are also on the radar of the authorities in several EU Member States as well as of the European Medicines Agency (EMA). The EMA published key principles and examples of good practices to support patients and health care professionals in preventing and managing shortages of medicines. Structuring supply chains and combatting medicines shortages will remain key areas for companies and regulators in the EU in 2024.

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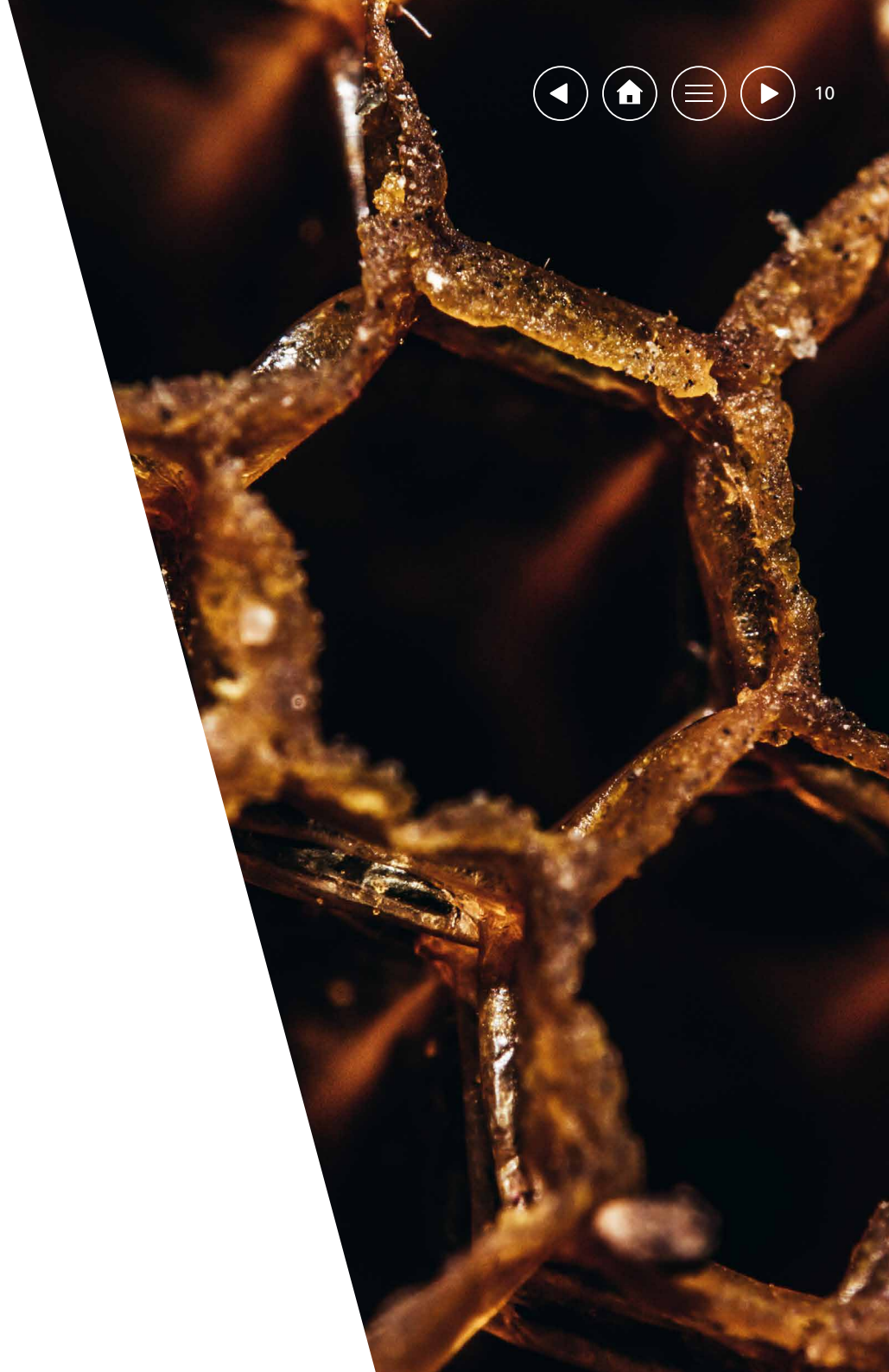

A business case for Quality Management Maturity

Quality Management Maturity (QMM) is achieved by implementing quality management practices that go above and beyond minimum current good manufacturing practice (CGMP) requirements to manage continuous improvement, resulting in sustainable compliance, reliable supply chains, and confidence for patients in the availability of their medicines. Investments by drug manufacturers in mature quality management practices mitigate the likelihood of issues associated with poor drug quality and can lead to higher operational performance, improved relationships with regulators and customers, and higher revenues.

FDA first proposed a QMM program in 2019, when an interagency task force called for a system to measure and rate the QMM of drug manufacturing facilities to address drug shortages. A major challenge has been convincing the pharmaceutical industry how the program would alleviate drug shortages, especially when there are no clear regulatory incentives. In the past 18 months, FDA appears to have ramped up efforts to develop a QMM program, including running pilot programs, publishing multiple white papers, convening an advisory committee workshop, and soliciting comments from industry. Although these efforts suggest that FDA is preparing more seriously to launch a formal QMM program, the exact timing and components of the program remain unclear.

What is more clear are key revisions to FDA's compliance programs for drug manufacturing inspections, which appear to align with underlying QMM principles requiring a holistic approach to quality and compliance.

For example, FDA investigators are instructed during pre-approval or pre-licensure inspections to gather data in support the firm's commitment to quality in pharmaceutical development. Additionally, the agency updated its drug manufacturing inspection program to include an assessment of quality management practices to gain insight into continual system improvements. FDA has increasingly cited firms during inspection for ineffective quality systems, specifically requiring a comprehensive assessment of the company's global manufacturing operations and support from executive leadership to proactively address emerging issues and to assure a continuing state of control.

While FDA's formal QMM program currently remains a moonshot idea, the agency's revised compliance policies may suggest a higher threshold standard for drug manufacturers' quality programs. An increasing focus on proactive and continuous improvement is critical for drug manufacturers to keep pace with or ahead of FDA's expectations, and manufacturers should continually assess the potential impact of both major changes (*e.g.*, organizational transformations, strategic acquisitions) and routine quality events (*e.g.*, investigations, FDA inspections) on their state of control. We routinely monitor for developments in this area as we continue to counsel clients on complex quality remediation efforts, strategic quality maturity assessments, and sustainable CGMP compliance.

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Real estate and life sciences: ESG through a trans-Atlantic lens

The pandemic catapulted Life Sciences into the spotlight. While the UK and US Real Estate Life Sciences markets continue to thrive, both do so in the face of an ever-tightening ESG agenda. Here we reflect on the respective challenges and opportunities to sustainable growth.

	UK	U.S.
E	Many of the sector's success stories involve repurposing existing, often obsolete stock, into lab/research-enabled/CAT A+ turnkey space. Leases must go darker green on alterations to lock in the benefit of repurposed use and allow recycling of ready-fitted space (and ensure contaminative risk in wet labs is mitigated by suitable audit and reporting mechanisms along the way).	Ground up construction can be less expensive on a per square foot basis than retrofit though harder to finance without a committed tenant(s). The recent shift in the wet to dry lab ratio from 70/30 to 40/60 has also resulted in a modification to construction and infrastructure requirements.
S	Government funding and commitment to Horizon Europe demonstrates commitment to making the UK a global Life Sciences superpower, but most impactful will be the UK government's "levelling up" agenda, which will connect academia and lower-cost facilities within the triangular boundary of London, Oxford, and Cambridge.	Government investments in building new workspaces, curating a diverse pipeline of talent to develop new cures and treatments and fostering access to health care. One example is New York City's LifeSci NYC, a $1B+ commitment launched to build new infrastructure, create thousands of new jobs and give every neighborhood access to the best health care available.
G	Investors and operators must implement robust corporate governance not only to satisfy shareholder requirements, but also their own legislative requirements and customer accountability. ESG has its place firmly at the corporate table and any market participants ignoring this will be left behind.	Organizations must incorporate ESG in their daily decision-making and implement comprehensive programs to identify, manage and mitigate issues and liabilities. As governments and shareholders demand greater transparency regarding progress toward ESG goals, investors, and operators need to insure their corporate governance complies with relevant regulations.

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Tapping into the Defense Production Act to strengthen the pharmaceutical supply chain

In response to the supply chain challenges that arose during the COVID-19 pandemic, in the past several years the Biden Administration has taken steps aimed at strengthening the U.S. industrial base. A key focus has been shoring up domestic manufacturing capabilities to help ensure a sufficient supply of drugs, countermeasures, and other critical items to support public health. Following on the significant activity in 2023, we expect additional focus in this area in the coming year.

In November 2023, the Biden Administration convened the first meeting of the White House Council on Supply Chain Resilience. Subsequently, in late December 2023, President Biden published a Memorandum for the Secretary of Health and Human Services that included a Presidential determination stating that essential medicines, medical countermeasures, and critical inputs are vital to the national defense and also included a waiver that in effect, expands the Department of Health and Human Services' (HHS) authority under Title III of the Defense Production Act (DPA) to further the goal of bolstering domestic production capabilities for these products. The DPA provides agencies with extraordinary contracting authority and the ability, through "rated orders", to prioritize supply to the government. President Biden's actions followed up on prior executive orders that were focused on building up long-term supply of essential medicines, in light of the vulnerability that was exposed during the pandemic.

HHS will start by investing $35 million in domestic production of key starting materials for sterile injectable medicines. To facilitate its work, HHS Biomedical Advanced Research and Development Authority (BARDA) created a consortium, the Biopharmaceutical Manufacturing Preparedness Consortium (BioMaP-Consortium), which boasts members from various segments of the drug and vaccine manufacturing supply chain. The Consortium recently issued its first Request for Project Proposals. The formation of the Consortium signals that there will be more activity, and likely more investment, as it is widely recognized that $35 million is just an initial investment. To make an impact much more significant, injection of additional funding will be needed.

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2 Digital Health and AI

Current regulatory landscape of Artificial Intelligence and Machine Learning-enabled devices

AI and Machine Learning (AI/ML) based technologies are transforming health care at a rapid pace. Software incorporating these cutting edge technologies has become a critical part of an increasing number of medical devices. The surge of Software as a Medical Device (SaMD) in recent years has enabled the speedy adaptation of AI/ML algorithms for a wide range of applications, such as earlier disease detection and diagnosis, development of personalized diagnostics and therapeutics, among many others.

A powerful feature of AI/ML-based technology is its ability to continuously learn from real-word use and then utilize that information to improve device performance. The ability to adapt over time presents a unique problem to FDA that requires both short and long term visions that challenge the conventional idea of a static device around which existing regulations and policies are established. This sentiment is echoed in a recent interview with FDA Commissioner Robert Califf, who discussed the exciting potential of such algorithms benefitting public health but also the need for oversight to prevent unintended harm.[1] While the regulatory framework for AI/ML-enabled devices is evolving, one thing is certain: the traditional paradigm of medical device regulation needs to be reconsidered, especially for adaptive and generative algorithms. To date, only locked algorithms - an algorithm that provides the same result each time the same input is applied and does not change with use - have been cleared or approved by FDA.

FDA recognizes, however, its need to adapt so as not to stifle innovation. Accordingly, in April 2023, FDA issued a draft guidance document that sets forth a proposed regulatory framework for modifications to locked algorithms following FDA clearance or approval through the use of a Predetermined Change Control Plan (PCCP). According to FDA, "a PCCP, as part of a marketing submission, is intended to provide a means to implement modifications" to AI/ML-enabled devices "that generally would otherwise require additional marketing submissions prior to implementation".[2]

We are continuously assessing the evolution of this regulatory framework to provide the latest insight on FDA's approach towards this rapidly burgeoning technology. As more device manufacturers innovate with AI/ML, there is both uncertainty and opportunity. Device manufacturers would be wise to engage with FDA early, as the agency has made it clear that it intends to lean on industry experts, professional organizations, other regulatory bodies, and also real-world data from its own database on how to best approach regulating AI/ML-enabled devices.

1 Dan McKay, *FDA 'Can't Do This Alone,' Wants Help Vetting AI In Healthcare,* LAW360 (Jan. 10, 2024, 4:48 PM EST), https://www.law360.com/articles/1782163/print?section=lifesciences.

2 Draft Guidance for Industry and FDA Staff, Apr. 3, 2023, *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions*, https://www.fda.gov/media/166704/download.

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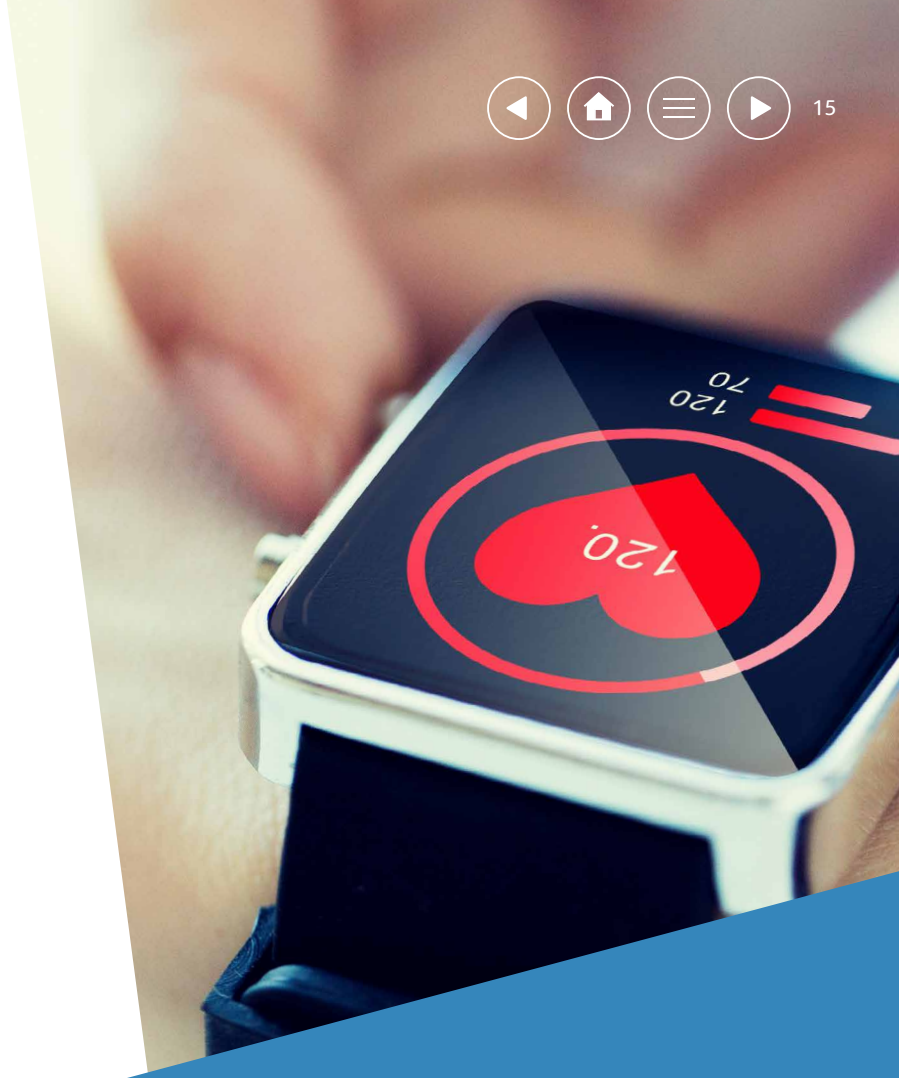

Read the Life Sciences and Health Chapter of our AI Hub

How the AI Act and the EHDS will influence research and development with AI in health care

Health care companies are facing and will continue to face challenges when developing AI systems that use health data. Such challenges can result from the interaction of the AI Act with other EU regulations like the Medical Device Regulation (MDR), the EU General Data Protection Regulation (GDPR) and the upcoming European Health Data Space (EHDS).

In the evolving landscape of health care and AI, the synergy between the AI Act and the EHDS plays a pivotal role. This interplay is especially significant for AI developers, who could benefit immensely from the vast reserves of health data available in Europe.

In the context of the EHDS, a key challenge lies in the potential limitations on the availability of electronic health data (eHD), particularly regarding their utilization as training datasets for AI systems. Should the input data be limited or not fully representative, it could lead to biased and imbalanced outcomes. Such skewed data can significantly impact the effectiveness and development trajectory of AI systems. This risk shows the importance of diverse and comprehensive datasets to ensure that AI algorithms in health care are well-informed and unbiased, ultimately contributing to robustness and reliability.

The concurrent application of the AI Act and the EHDS presents a complex regulatory landscape. AI systems that employ eHD for training are subject to both regulations (as per Art. 1 of the EHDS draft). The European Parliament's proposal for an opt-out mechanism for general eHD and consent-based access to particularly sensitive data, such as genetic information, introduces challenges in data accessibility. This could lead to a scarcity of certain types of health data or health data from a certain peer group with the risk of imbalanced and biased AI outcomes due to non-representative datasets. The AI Act's provision to correct bias by permitting, under specific conditions, the use of sensitive data as per Art. 9(1) GDPR, may not adequately address these imbalances in the health care sector. The success of the AI Act in promoting non-discriminatory AI systems in the EU hinges on the EHDS's ability to facilitate equitable access to health data.

In conclusion, while the AI Act aims to ensure that AI systems used in the EU are fair and non-discriminatory, the success of this objective in the health care sector largely depends on the final formulation of the EHDS. We are optimistic that the EHDS, in its finalized version, will effectively support this goal by facilitating access to a diverse and balanced range of health data.

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Looking ahead to the U.S. regulation of Health AI

In the U.S., federal and state regulators are poised to expand the regulation of artificial intelligence for health-related purposes (Health AI). To date, many regulatory and legislative efforts targeting Health AI have taken the form of high-level guidelines, non-binding recommendations, voluntary commitments, and agency guidance, such as Executive Order 14110, the Health Sector AI Commitments, and Centers for Medicare & Medicaid Services' (CMS) AI Playbook. Binding legal and regulatory efforts are, however gaining momentum.

The lead agency on health care in the U.S., the Department of Health and Human Services (HHS), has taken a number of concrete steps toward the support and regulation of Health AI with a focus on research and discovery, drug and device safety, health care delivery, and public health. In just the past year:

- The Office of the National Coordinator for Health information Technology (ONC) finalized a rule requiring increased transparency in the use of AI in certified health IT.
- FDA published a draft guidance document outlining a framework for regulating AI and machine learning (AI/ML) enabled device modifications as well as guiding principles.
- The National Institute of Health (NIH) announced new initiatives to fund development of AI/ML tools and improve the usability of NIH-supported data for AI/ML analytics and started a program to support underrepresented communities in the development of AI/ML models.

Federal and state legislators are moving at a relatively fast pace in this area. Congress held multiple hearings on AI, including a health subcommittee hearing on Understanding How AI is Changing Health Care. States are introducing laws that protect privacy and prohibit discrimination that may result from implementing AI in the health sector focused largely in three areas: (1) preventing discrimination when health care providers use AI-powered automated decision systems; (2) increasing transparency by giving patients the right to know when an algorithm is used as part of their care; and (3) requiring consent and use of only pre-approved technologies that are monitored and shown to achieve accurate results.

In anticipation of new requirements, businesses can:

- evaluate their Health AI use cases with a focus on ensuring fair, appropriate, and safe use;
- document measures taken to support transparent and responsible development and use of Health AI; and
- implement safeguards to protect individuals' rights and minimize bias, discrimination, and other AI-specific risks.

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Striking the right balance between data protection and research and innovation in the EHDS

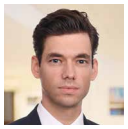
On 3 May 2022, the European Commission (Commission) published the first draft of the Proposal on the European Health Data Space (EHDS). The EHDS aims to expand the use of electronic health data (eHD) to deliver health care (primary use), and to enhance research, innovation and policy making by processing eHD initially collected in connection with the provision of health care (secondary use). With regard to the latter, 'data holders' are obliged, if certain requirements are met, to make requested eHD in anonymized or pseudonymized form available for 'data users' for secondary use purposes (*e.g.*, AI development).

One of the most contested questions is the level of control the EHDS should grant to the affected natural persons with regard to sharing of their personal data for secondary use. This question is immensely explosive since data subject rights (DSRs), such as object rights (opt-out), or even the condition of prior consent (opt-in), may impede the availability and utilization of eHD for secondary use which is a fundamental legitimate interest of industry stakeholders but also the public health.

Examining the Commission's proposal and the subsequent proposals of the Council of the European Union (7 December 2023) and the European Parliament (13 December 2023) from this standpoint, significant differences can be observed.

Pursuant to the latest version of the European Parliament, data subjects shall have an unconditional right to opt-out of the processing of any of their eHD for secondary use (and for human genetic and other sensitive data types secondary use requires mandatory consent), which would significantly strengthen their position compared to the DSRs under the EU's General Data Protection Regulation (GDPR). In contrast, the Council's proposal does not stipulate a specific opt-out, but leaves it up to the Member States, which "may" cater for a specific right to object to secondary use. Such right would complement the GDPR right to object of Art. 21(1) GDPR. At the other end of the spectrum is the first Proposal of the Commission, which provides neither a specific opt-out right nor a consent requirement for secondary use at all.

Striking the right balance between data protection and the promotion of scientific research, is a challenging and important task. However, considering that due to the pseudonymization or even anonymization requirement for secondary use provided in all proposals eHD of individuals are already significantly protected, it is questionable whether strengthening DSRs beyond the GDPR is a reasonable approach in light of the legislative goal of the EHDS of enhancing research and innovation.



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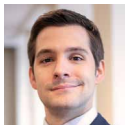

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The future of safe and responsible AI in Australia

Currently, there is no law that specifically deals with AI in Australia. Instead, depending on its use, AI may be captured under existing laws (such as, for example, privacy and consumer laws), and through sector-specific regulations in industries such as health and medical applications, therapeutic goods, food, financial services, motor vehicles, and airline safety. Additionally, there are a number of voluntary frameworks in place, including the national AI Ethics Framework, which was released in 2019 to help guide businesses to responsibly design, develop and implement AI.

In June 2023, the Government released the Safe and Responsible Use of Artificial Intelligence in Australia Discussion Paper which set out a number of potential mechanisms and regulatory approaches through which AI can be regulated in Australia and sought industry input into how best to implement appropriate governance mechanisms and regulatory responses to ensure AI is used safely and responsibly. It was announced that artificial intelligence will be a priority in 2024 with a commitment of AU$41.2 million to support the responsible deployment of AI in the national economy.

On 1 November 2023, Australia alongside the EU and 27 countries, including the U.S., UK and China, signed the Bletchley Declaration on AI. The Bletchley Declaration affirms that AI should be designed, developed, deployed, and used in a manner that is safe, human-centric, trustworthy and responsible.

On 17 January 2024, the Australian Government published its interim response to the consultation on safe and responsible AI in Australia which called for further guardrails on legitimate but high-risk uses of AI, as current regulatory risks do not fully address potential risks. High-risk settings would include many health and medical applications, including medical devices, AI-enabled robots for medical surgery, or those involving data analytics and privacy. The Government's proposed next steps include (among other things) consulting on the form of new mandatory guardrails for organizations developing and deploying AI systems in high-risk settings (such as in the life sciences sector).

Life sciences stakeholders should be on the lookout in the near term for ongoing guidance from the Government on:

- using testing, transparency and accountability measures to prevent harms from occurring in high-risk settings;
- clarifying and strengthening laws to safeguard citizens;
- working internationally to support the safe development and deployment of AI; and
- maximizing the benefits of AI.

Visit our website to read more on Digital Health and AI


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3 Cell, Tissue, and Gene Therapies

Collaborative strategies for ATMP development through Investigator-Initiated Trials

Advanced Therapy Medicinal Products (ATMPs) are revolutionizing the pharmaceutical industry, challenging the traditional regulatory landscape. Unlike conventional medicines, ATMPs demand a re-evaluation of clinical research practices, particularly within the EU where they adhere to specific regulatory frameworks.

For industrial sponsors, conducting ATMP research is complex. However, for individual investigators, initiating such research appears daunting. Investigator-Initiated Trials (IITs) offer a promising avenue for exploring new therapeutic areas. These trials, led by investigators, can address unmet medical needs and provide patients access to treatments outside of industry-sponsored trials. For pharmaceutical companies, IITs generate additional data, speeding up the discovery process and aiding in market access. IITs are also a way for smaller pharma companies who lack resources for conducting wide clinical trials to support the development of their research.

Typically, IITs allow investigators freedom in study design and methodology. Pharmaceutical companies' roles are generally confined to supplying the product and sometimes financial support. In return, they gain access to data and intellectual property rights. However, this dynamic shifts with ATMPs. Their complexity demands more involvement from pharmaceutical companies than mere product supply and financial backing.

ATMP development requires specialized skills and training, from samples collection to patient treatment. This includes:

- detailed protocols for cell or gene collection, often necessitating specific training from pharmaceutical companies;
- sophisticated manufacturing and logistics involving third-party providers adept in handling sensitive materials under stringent regulations (*e.g.*, human cells and genes, hazardous materials, genetically modified organisms, products that must be carried out at specific temperatures and storage conditions, products with very short lifetime);
- centralized manufacturing, often in the U.S., involving complex international transport arrangements;
- high manufacturing costs; and
- complex liability questions in case of patients' safety issue during the IIT.

These factors present practical challenges for IITs involving ATMPs. The classic model of limited pharmaceutical company involvement may be impractical. Instead, a more collaborative approach is needed where investigators retain research initiative and flexibility, but with substantial practical support from pharmaceutical companies and innovation in funding given the potential costs involved in setting up such trials. This collaboration is essential for the successful development and delivery of ATMPs, ensuring these innovative treatments reach patients efficiently and safely. The EU clinical trial regulation allows for such collaboration without the pharmaceutical company necessarily being classified as a sponsor or co-sponsor, and the new draft Soho Regulation which should be endorsed in 2024 should not impact this materially.

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FDA's efforts to support CTGT products

The U.S. Food and Drug Administration (FDA) has increased efforts to support the development and approval of cell, tissue, and gene therapy (CTGT) products. This is evidenced by the upswing in CTGT approvals in the last few years and the unprecedented approval, on the same day in 2023, of a novel gene editing product and another gene therapy product for sickle cell disease. Although FDA's approval rate is still far behind the one to two applications FDA receives each week, the agency continues to demonstrate commitment to the accelerated development of these therapies. The agency recently increased its repertoire of tools for accelerating the development of CTGT products by providing additional opportunities for early interactions with sponsors:

- **The START Program.** Under FDA's Support for clinical Trials Advancing Rare disease Therapeutics (START) program, sponsors with active INDs for certain CTGT products may be able to seek more frequent advice and have more communication with FDA on issues such as clinical study design, choice of control group, and choice of population, if they meet certain eligibility criteria. FDA is accepting applications for the program until 1 March 2024. FDA may repeat the program, depending on stakeholder feedback.
- **The Voluntary Consensus Standards (VCS) Recognition Program.** This program permits sponsors to recommend novel scientific standards applicable to their products if the standard meets certain criteria. Developed in response to a mandate under the 21st Century Cures Act and modeled after a similar program for medical devices, this program is especially helpful for regenerative therapies, including CTGT products, whose complex nature makes regulatory standards challenging and unpredictable. FDA has started accepting standard recognition requests and will maintain a public list of recognized standards.
- **Platform Technology Designation Program.** This designation is intended to accelerate review of products for sponsors who have multiple products that use a similar technology or platform, like adeno-associated viral vectors. Designation gives sponsors additional opportunities for early FDA interactions and may also permit a sponsor to reference data from the designated technology.

Other recent efforts include FDA's advocacy for greater use of the accelerated approval pathway under its Split Real Time Application Review (STAR) pilot program for new uses of approved therapies to address unmet medical need, as well as a Rare Disease Endpoint Advancement (RDEA) pilot program.

Collectively, these FDA initiatives should lead to more CTGT approvals in the next few years.

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Laboratory developed tests under FDA scrutiny

"Precision" or "personalized" medicine seeks to provide a bespoke therapy for the right patient – with the right treatment at the right time – by adjusting for the nuances within an individual's genetic profile, health records, and lifestyle. These drugs can produce unprecedented clinical effect with low toxicity compared to other therapies by relying on molecular structures that are not present in all patients. For example, patients may be screened by identification of novel biomarker(s) to guide clinical decisions. The recent clear trend is towards an increase in the number of precision therapeutic products that have received regulatory approval dependent upon the development and validation of a biomarker assay, such as a companion diagnostic (CDx) test.

In addition, FDA has recently announced a landmark proposed rule, which would make explicit that certain in vitro diagnostic products (IVDs) that are laboratory developed tests (LDTs) are medical devices as defined by the Federal Food, Drug, and Cosmetic Act (FDCA) and will be regulated by the Agency accordingly, including requiring premarket review. Historically, the FDA has not attempted to require compliance for LDTs, with the exception of certain test categories, such as direct-to-consumer tests, some pharmacogenomic (PGx) tests, and tests that respond to public health emergencies.

However, given that today's LDTs often rely on highly specialized components with complex functionalities involving bioinformatics, software development, and underlying specialties such as genetics for next generation sequencing (NGS) test systems, FDA has become increasingly concerned that such tests are being offered without assurance that they work.

The FDA has signaled its intention to finalize the proposed LDT rule by April 2024. Although the FDA faces numerous hurdles before final implementation, the interplay between drug and device approvals is clearly under scrutiny and only becoming more complex. Industry stakeholders must plan accordingly to future-proof their development strategies.

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

Medical device regulatory considerations for novel cell-based gene therapies, Casgevy and Lyfgenia, FDA approved as biologics

On 8 December 2023, FDA approved two groundbreaking cell-based gene therapies, Casgevy and Lyfgenia, for treating sickle cell disease (SCD) in patients 12 years and older. While Casgevy utilizes CRISPR/Cas9 gene editing technology to modify patients' hematopoietic stem cells (HSCs), Lyfgenia uses a lentiviral vector to treat SCD in patients with a history of vaso-occlusive events. Both therapies are approved for autologous use only, meaning healthy stem cells are collected from the patient's body, stored, and reinfused in a single dose to the donating patient. Casgevy and Lyfgenia are regulated as biological products (biologics) by the Food and Drug Administration (FDA); however, ancillary products and components used in preparing or processing the biologics are often regulated as standalone medical devices or combination products, depending on their intended use.

The process of collecting stem cells involves mobilizing stem cells from a patient's bone marrow into their bloodstream, separating them from other blood components using an "apheresis machine", and subsequently modifying them by gene editing and cryopreserving them to maintain viability until transplantation. Blood collection devices (*e.g.*, tubes, centrifuges, and filter systems) and blood administration sets used to prepare autologous substances, with no specific indications for use, have historically been regulated by FDA's Center for Devices and Radiological Health (CDRH) through the 510(k) premarket pathway.

In contrast, blood collection bags, automated blood cell separators, and centrifuges labeled specifically for use in processing substances, have mostly been regulated by FDA's Center for Biologics Evaluation and Research (CBER) as a standalone drug or biological product. Moreover, if the gene therapies were packaged or labeled for use with, for example, a catheter used to attain vascular access for apheresis (a device), FDA would likely regulate the product as a biologic-led combination product. Therefore, considering the type of ancillary product/component and its manner of use, a manufacturer may be required to comply with additional FDA regulations beyond those applicable to biologics.

Key Takeaways

FDA's approval of Casgevy and Lyfgenia provides important precedent and regulatory clarity for emerging cell-based gene therapies regulated as biological products. Nevertheless, it is essential that manufacturers stay apprised of potential regulatory hurdles involved in developing future products. Understanding the complexities of how ancillary products and components are regulated will help ensure manufacturers remain compliant with relevant pre- and postmarket FDA regulations, while also helping to ensure safe, seamless, and effective delivery of these innovative therapies.

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Negotiating cell, tissue, and gene therapy agreements with HCOs

Legal challenges for innovative cell, tissue, and gene therapies (CTGTs) are mainly seen in the still evolving regulatory environment. However, it is also crucial for the manufacture and supply of CTGTs to have agreements in place with all apheresis and treatment centers (ATCs) in the respective launch markets. CTGT companies should be aware that the negotiating and execution of such agreements with (often public) hospitals and other health care organizations (HCOs) can be both challenging and time-consuming. That process should thus be thoroughly planned and initiated long before obtaining marketing authorization for a CTGT product.

From our experience, in particular, the following key terms are often controversial:

- **ownership of patient cells** collected by the institution (which, depending on the local laws applicable may also need to be aligned with a respective consent by the patient waiving ownership rights in their cells);
- **loss of cells and/or product;**
- **intellectual property,** in particular with respect to ownership of product-related inventions made by institution's employees (although rather unlikely); and
- **liability, indemnification, and insurance,** specifically with regard to the demarcation of product liability (to be borne by the pharmaceutical company anyway) and medical malpractice. This is particularly challenging for CTGTs where the hospital is closely involved in the manufacturing of the product and its, often very specific, preparation and handling.

Public hospitals tend to not be very flexible in terms of accepting contractual clauses to their disadvantage; in addition, they often have rather long review cycles. Therefore, it is important to develop very clear and balanced template agreements in order to not delay negotiations. In European Union (EU) countries an EU-wide template agreement can be the starting point, but it needs to be localized for key jurisdictions in order to ensure a smooth negotiation process with local ATCs. Also, a negotiation handbook providing for fallback positions in respect to the above and further topics can facilitate swifter negotiating.

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Patient finding initiatives: Legal considerations

In the age of personalized medicine and as treatments for rare diseases increase, identifying potential patients and providing targeted product education to those patients and their treating health care professionals (HCPs) has become increasingly important to manufacturers. Beyond significant privacy concerns, however, initiatives to find patients and to engage with their HCPs may present risk under the fraud and abuse and other laws, and should be structured in light of available industry guidance and emerging enforcement trends. Three types of patient-finding initiatives warrant particular consideration.

- **Sponsored testing programs** provide manufacturer-sponsored testing for patients to determine whether the patient has the condition for or is an appropriate candidate for an approved treatment. These programs have recently come under scrutiny. In 2022, the Office of Inspector General (OIG) for the U.S. Department of Health & Human Services (HHS) issued a favorable Advisory Opinion 22-06 (AO 22-06) on one such program, and in December 2023, the Department of Justice (DOJ) announced a $6 million settlement related to a sponsored genetic testing program, with particular focus on the manufacturer's receipt and use of test data (including physician ordering information) for marketing and promotional purposes. In response, sponsored testing programs should be structured to align with the safeguards and principles enumerated in AO 22-06, wherever possible, and manufacturers should consider limiting their receipt and use of physician ordering information and other testing data.
- **Telehealth platforms:** Manufacturers have implemented or explored offering direct-to-consumer access by connecting patients from the manufacturer product websites to telehealth vendors for assessment and potential prescription of the manufacturer's product. These programs, particularly for certain lifestyle drugs, or when limited to cash-pay, have grown in popularity since the COVID-19 pandemic transformed patient acceptance of telemedicine. However, programs that bill insurance, and particularly federal health care programs, raise risks under the Anti-Kickback Statute (AKS), both through the referral to the telehealth provider and through potential payments to the telehealth vendor that could be viewed induce prescriptions for the manufacturer's product, and should be carefully structured.
- **EMR tip sheets** that offer guidance on how to identify potential patients through the electronic medical records (EMR) may be particularly important for identifying patients of rare diseases. Providing information about how HCPs can query their EMRs consistent with the product's indication likely presents low risks, but there are execution risks in how the tip sheets are used, particularly if personnel assist HCPs through accessing patient protected health information or overstep into the HCP's sole responsibility to determine whether a particular product is appropriate for a specific patient.

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Product sameness considerations for cell, tissue, and gene therapy products

Whether a product is considered the same as a previously approved product has a broad impact on a number of important regulatory decisions, including exclusivity awards, priority review vouchers, patent term extension, and approval actions. Cell, tissue, and gene therapy products challenge FDA's existing regulatory framework and its traditional notions of product sameness.

FDA has issued a guidance that broadly outlines the analytical framework for determining when two gene therapy products are considered the same drug for purposes of orphan drug exclusivity. Among other things, this general framework proposes a separate analysis of the transgene and vector elements of the product. However, the inherent complexity of cell and gene therapy products means that this general standard must be tailored on a case-by-case basis, with a focus on components that contribute to the overall therapeutic effect.

This analytical framework was implemented with the licensure of the CAR-T product, Breyanzi® (lisocabtagene maraleucel) in 2021. FDA determined that Breyanzi® did not contain the same drug as a previously licensed CAR-T product for orphan drug exclusivity purposes because the products use different transgene hinge and transmembrane sequences. FDA also noted that the final cell compositions of the products are different because Breyanzi® is administered at a defined ratio of T cell subsets.

This cellular composition rationale will likely become more important as FDA analyzes more complex cell-based gene therapy products with differing cellular compositions. FDA has a long history of determining sameness for products comprised of complex mixtures in other contexts, where it is often difficult or impossible to determine which components are "active" and contribute to the function of the product.

In a December 2023 draft guidance, FDA recognized that many cell and gene therapy products consist of a complex mixture of different cell types where the contribution of each to the activity of the product is difficult to determine. In those cases, FDA considers the activity of the product to be based on the totality of the cellular mixture. Importantly, the mixture itself is considered the single active ingredient, not the individual cell types, and sameness determinations based on the active ingredient generally would involve a comparison of the mixtures.

New developments in this area are expected in 2024. We are ever watchful of this evolving regulatory framework and advise our clients on when and how to engage with FDA to achieve favorable outcomes.

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The convergence of high-tech emerging technologies in precision medicine: Human organ chip systems

Organ-on-a-chip technology (OoC) emerged as a powerful tool to model human physiology and disease by merging microfluidic and *in vitro* cell culture techniques to create microscale models that mimic the structure and function of human organs. OoC shows promise in drug discovery, nonclinical testing, and disease modeling. Traditional development approaches rely on animal testing before human testing; however, differences in human physiology and animal welfare considerations have advanced approaches in modeling human biology and diseases *in vitro* to accelerate drug development and personalized medicine.

Animal models are not fully reflective of human physiology, which means drugs shown to be safe and effective in animals may be harmful or ineffective in humans. Advanced therapies including monoclonal antibodies, vaccines and cell and gene therapies, account for nearly half of all drugs in development. There is a critical need for human-relevant preclinical models because some advanced therapies are specific to human target molecular sequences such that non-human models do not translate to humans.

OoC shows potential as an ethical and feasible alternative to the traditional approach. While OoC technology is not new, technological advances and recent legislation could transform OoC's use in nonclinical testing. Through the FDA Modernization Act 2.0, Congress expanded the requirement that new drugs undergo preclinical animal testing to a requirement that new drugs undergo "nonclinical tests", including OoC. This represents a significant step forward for OoC development, which could reduce the risk of drug development failure, accelerate the drug development timeline, and lead to faster access to more effective and safer drugs for patients.

Advances in artificial intelligence (AI) provide improvements for the design (higher-throughput) and data processing of OoC. As described in FDA's discussion paper on AI in drug development as technology that could be leveraged for evaluating toxicity or exploring mechanistic models in nonclinical research, OoC platforms require standardization and validation to ensure reproducibility and reliability of the data, and developers should understand FDA's expectations with respect to safety studies that are intended to support applications for research or marketing of regulated products, including applicable Part 11 and Good Laboratory Practice (GLP) requirements.

In addition, OoC is a focus area for the Administration, stated in the March 2023 goals for implementing Executive Order 14081. Although questions remain over the quality and reliability of OoC biological data, FDA provides numerous engagement opportunities, including discussion forums and grant programs, including its Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program.

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The hospital exemption scheme for advanced therapy medicinal products in reform of the EU pharmaceutical legislation

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of diseases. Like any other medicinal product (with a few exceptions), ATMPs must obtain the relevant marketing authorization before they can be placed on the market in European Union (EU) Member States (MSs). As an exception to the general rule, MSs may authorize the provision of an ATMP without marketing authorization under the so-called hospital exemption scheme. Hospital exemption (HE) products must be "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".

Within the context of the reform of the EU pharmaceutical legislation, and having expressly admitted that there are great differences in the application of HE among MSs, Article 2 of the European Commission's (Commission) Proposal for the new Directive on medicinal products for human use (Proposed Directive) introduces measures to improve the application of ATMPs prepared under hospital exemption (ATMPs under HE):

- By way of derogation from Article 1(1) (rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of medicinal products), only Article 2 shall apply to ATMPs under HE.
- The manufacturing of ATMPs under HE shall require approval by the MS and MSs shall (1) notify any such approval, as well as subsequent changes, to the European Medicines Agency (EMA) and (2) inform the EMA and other MSs if an approval is revoked due to safety or efficacy concerns.
- ATMPs under HE shall comply with the requirements equivalent to the good manufacturing practices (GMP) and traceability for ATMPs, as well as with pharmacovigilance requirements equivalent to those provided at EU level.
- Approval holder shall collect and report data on the use, safety, and efficacy of ATMPs under HE at least annually and the MS shall review such data, verify compliance with GMP, traceability, and pharmacovigilance requirements and transmit it to the EMA, who shall set up and maintain a repository of that data.
- The Commission shall adopt implementing acts to specify (1) the details of the application for the approval; (2) the format for collection and reporting of data; (3) the modalities for the exchange of knowledge; and (iv) the modalities for preparation and use of ATMPs under HE on a non-routine basis.

These measures have aroused the interest of many stakeholders, who have already expressed their position on the matter, including a joint position paper from the Alliance for Regenerative Medicine (ARM), European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio, European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) and International Society for Cell & Gene Therapy (ISCT).

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4 Clinical Trials

Decentralization and digitalization trends in European clinical trials: A focus on data aspects

Decentralized clinical trials (DCTs) are reshaping the landscape of medical research in Europe, integrating digital technologies to enhance participant involvement beyond traditional clinical settings. This innovative model offers significant benefits such as increased accessibility, cost reductions, and the potential for more diverse patient groups. It, however, introduces unique legal and regulatory challenges, particularly in terms of data protection and participant privacy.

The integration of digital tools in DCTs, like eConsent and tele-visits, significantly improves participant access and engagement. Yet, these advancements also raise substantial concerns pertaining to the General Data Protection Regulation (GDPR), data transfers outside Europe, and the safeguarding of participant privacy. Ensuring GDPR compliance is essential, particularly when handling sensitive health data, vital for validating trial outcomes, and supporting marketing authorization processes.

A major aspect of GDPR compliance in the context of DCTs involves the careful management of health data and its separation from direct identifiers, a principle well-established in clinical research for years. Traditionally, trial sponsors must not collect the names of the patients. This practice is key for protecting participant confidentiality while adhering to GDPR provisions. Thus, the implementation of eConsent in DCTs requires meticulous attention to ensure privacy, and informed, voluntary, transparent participant consents.

These developments signify a historical shift in clinical trial practices.

Taking this into account, the European Commission released its recommendations on DCTs in December 2022 to underscore the importance of digital tools and decentralized procedures in health research. Many countries and authorities, following the European Commission's recommendations, are actively working to adapt and implement these new practices. An innovative EU pilot project has been launched to align innovation with GDPR compliance. In France, like in several European nations, there has been a request for involvement in the pilot phase (until June 2024) and it is expected that guidelines will be released between 2024 and 2025, which will reflect these developing practices.

In conclusion, the EU's initiatives in decentralized clinical trials are poised to significantly advance medical research, while simultaneously addressing the complexities of GDPR compliance. It is hoped and believed that the upcoming guidelines will introduce flexibility in this area, enhancing the efficiency of clinical trials while rigorously safeguarding patient privacy rights. This delicate balance between technological innovation and legal-ethical considerations is crucial in shaping the future of clinical trials in the EU, promising a more dynamic, effective, and ethically robust research environment.

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Decentralized clinical trials in the U.S. and EU

Decentralization of clinical trials is a hot topic across jurisdictions, both in the pharmaceutical and in the medical device space. Parts of a clinical trial may take place outside the setting of a traditional clinical trial site, ranging from remote monitoring using digital tools to delivery of the investigational product to the patient's home.

In May 2023, the U.S. FDA released highly-anticipated draft guidance on the implementation of DCTs for drugs, biologics, and medical devices. In the draft guidance, FDA promotes DCTs as a way to advance medical product development and to increase diversity in clinical trial recruitment. There is a tremendous amount of interest in the life sciences industry in this policy, as it may offer substantial benefits to study sponsors. It, however, also carries potentially significant regulatory and operational risks, including how to ensure appropriate oversight of individuals performing remote trial-related activities. In finalizing the guidance, FDA will need to consider the almost 100 comments to the docket including, for example, the recommendation that there be a single physical location where trial records and personnel reside for inspectional purposes, which seems in contrast to the definition of DCTs where all activities take place at sites other than a traditional clinical trial site. Further, fully DCTs may not be practical for medical devices that are not intended for self-use or that pose significant risks to trial participants, but these may be more appropriately studied in "hybrid clinical trials" where some activities take place at a traditional trial site while others take place at non-traditional sites.

In the EU, both regulators and industry have expressed interest in decentralized clinical trials. The European Medicines Agency (EMA), European Commission, and member state authorities issued a recommendation paper on decentralized clinical trials in December 2022. Since then, questions have continued to arise around, for example, data integrity, compliance with the General Data Protection Regulation (GDPR), and the use of data generated in decentralized clinical trials for marketing authorization applications. Despite an EU-wide approach taken by regulators, legal and practical differences remain on a country-by-country basis. For example, the distribution of investigational medicinal products direct to patients' homes is subject to different requirements in different countries. When setting up a cross-border distribution model for investigational products within the EU, both EU-level and country-specific regulatory requirements should be considered.

We expect to see further debate and potential further harmonization of regulatory guidance for decentralized clinical trials in the EU.

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Evolving human subject protection rules for clinical trials

At the end of last year, FDA published a final rule on "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations," which permits an exception from the requirement to obtain informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. Notably, FDA added a criterion permitting an additional exception from the general informed consent requirements for certain FDA-regulated trials involving the use of identifiable private information or identifiable biospecimens. In those situations, an exception from informed consent may be warranted if the study could not practicably be carried out without using such identifiable private information or biospecimens in an identifiable format. An IRB waiver of authorization under the Health Insurance Portability and Accountability Act (HIPAA) may also be necessary to the extent HIPAA applies.

Also, last year FDA finalized nine-year-old draft guidance on informed consent for sponsors, institutions, IRBs, and investigators. FDA's changes to the draft guidance reflect innovations like platforms supporting DCTs, about which FDA issued milestone draft guidance in May 2023. The changes in the final version of the informed consent guidance also respond to the evolving ability to target therapies based on genetic variations using machine learning and artificial intelligence, coming on the heels of FDA's March 2023 revised draft guidance on regulation of the use of electronic systems, records, and signatures in clinical investigations to account for advances in digital health technologies.

These moves follow FDA's proposed rules to clarify inconsistencies between FDA's human subject protection regulations and the Common Rule, and to promulgate a single IRB requirement. Taken together, this spate of agency efforts show increasing regulatory focus on human subject protection issues, and greater coordination between HHS and FDA.

Visit our website to learn more about our Clinical Trials experience

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FDA inspections of drug manufacturing and bioresearch monitoring facilities: Expect heightened vigilance in 2024

FDA inspections play a pivotal role in identifying and rectifying potential issues that could compromise the safety of drugs, the reliability of research findings, and the rights and welfare of clinical trial participants. In 2024, FDA is likely to intensify its focus on whether drug manufacturing and bioresearch facilities are adhering to Current Good Manufacturing Practices (CGMP) and Good Clinical Practices (GCP), respectively.

FDA takes a risk-based approach that involves the weighing of several factors in determining whether to inspect a given facility. For example, facilities involved in an application for a new molecular entity or those involved in a sponsor's first marketing application are top candidates for inspections. During the COVID-19 pandemic, FDA relied heavily on remote interactive evaluation tools to evaluate drug and device manufacturing facilities and has stated that it will continue to do. Although a remote evaluation does not constitute an inspection under the federal Food, Drug, and Cosmetic Act (FDCA), it gives FDA greater insight into a facility's operations and issues that may warrant an on-site inspection.

Relatedly, the number of foreign and domestic inspections conducted has steadily increased since 2020. Additionally, in 2023, the U.S. Congress granted FDA greater authority to inspect a wider range of parties involved in clinical research and development activities, such as consultants and vendors, and records related to studies and FDA submissions. FDA also submitted a legislative proposal for the 2024 fiscal year requesting that Congress expand FDA's capabilities under the FDCA to conduct inspections of establishments manufacturing non-application finished dosage forms, active pharmaceutical ingredients and sterile drug substances.

For drug manufacturing and bioresearch facilities, these trends serve as a reminder to prioritize CGMP and GCP compliance, invest in robust quality management systems, and foster a culture of continuous improvement. Manufacturing establishments should pay particular attention to process validation procedures and records, the adequacy of written production procedures, and records evidencing the investigation and review of batch discrepancies. Key GCP areas, including study monitoring, informed consent practices, and maintenance of adequate case history and study records, should also be addressed.

Establishing a proactive approach to identifying and addressing potential compliance gaps is essential. If you have any questions about this article, please contact one of the authors or the Hogan Lovells attorney with whom you work.

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Forecasting FDA activities to foster diversity in clinical research

The U.S. Congress, FDA, and industry have taken several bold steps to increase the enrollment of historically underrepresented populations in clinical research in recent years. Looking ahead, we anticipate how FDA will continue to emphasize and set expectations regarding diversity in clinical trials and explore the potential directions that industry may take in fostering diversity in clinical research.

In the Food & Drug Omnibus Reform Act of 2022 (FDORA), Congress directed FDA to require that sponsors submit diversity action plans describing the sponsor's (1) enrollment goals disaggregated by race, ethnicity, sex, and age, (2) rationale for the goals, and (3) an explanation of how the sponsor intends to meet the goals. This requirement will apply to all Phase 3 clinical trials conducted for drugs and biologics, as well as for all devices and diagnostics that use the 510(k), premarket approval, de novo, and investigational device exemption pathways, with some exceptions. FDORA also mandates that FDA publish draft guidance documents on how FDA plans to implement the diversity action plan requirement. Such guidance is likely to feature recommendations on the content of a diversity action plan, including circumstances under which a diversity plan waiver may be granted. Although the statutory deadline for issuing the diversity action plan guidance was December 2023, FDA has yet to publish the guidance. We anticipate that the agency will likely issue it early this year.

FDA is likely to continue encouraging greater collaboration between sponsors and the communities where clinical trials are conducted and emphasize transparency in reporting and analyzing demographic data. In early phase discussions with the agency, sponsors should be prepared to field questions on their relationships to diverse patient communities, including education and recruitment strategies aimed at underrepresented patient groups. This year may also see FDA provide detailed recommendations on how sponsors should collect, analyze, and report demographic information, and conduct sound subgroup analyses.

Embracing diversity in clinical trials is a crucial step towards ensuring that scientific findings are applicable and beneficial to all members for the relevant patient population. As FDA continues to evolve its approach to clinical trial oversight, sponsors should proactively incorporate diversity into their trial designs and recruitment strategies, working collaboratively with communities and health care providers to achieve more inclusive and representative clinical research outcomes.

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Single-trial approvals: Key trial design considerations

Between the lines of the September 2023 draft guidance discussed in our "Spotlight on Single-trial approvals" is a critical message to any sponsor intending to rely on a single trial for product approval. Although the draft guidance provides greater detail regarding the quantity, quality, and appropriate sources of confirmatory evidence, it is critical to recognize and address the challenges associated with relying on one clinical trial when seeking approval. To that end, the draft guidance includes recommendations for early engagement with the FDA for sponsors who intend to seek approval using this approach.

Sponsors must be mindful of the inherent challenges associated with pursuing an approval based on one pivotal study. Multiple adequate, well-controlled clinicals trials will typically yield the most robust evidence of effectiveness, especially when using a randomized double-blinded, concurrently controlled superiority design. Even so, other types of study designs can also convincingly establish effectiveness – such as non-inferiority studies or designs utilizing external controls.

In situations where a sponsor will rely on a single pivotal trial for product approval – regardless of whether the trial measures standard clinical endpoints or surrogate endpoints – the trial should show a clinically meaningful effect and the strength of evidence should be evaluated by appropriate, pre-determined statistical methods. Expanding upon the statistical framework, criteria for determining the reliability of the confirmatory evidence, including meaningful effect sizes and uncertainty surrounding estimates, should be considered. Additionally, sponsors should address how these metrics relate to the primary endpoints of the clinical investigation. Sponsors should also consider potential sources of bias or confounding that may affect the interpretation of the confirmatory evidence, including selection and performance bias. This will prove particularly useful for sponsors who may need to employ external validation techniques, such as replication studies, to validate the confirmatory evidence.

Applications supported by a single adequate and well-controlled clinical investigation and confirmatory evidence can raise unique challenges on the path to approval. Hogan Lovells will continue to work closely with sponsors as they engage with FDA on this approval pathway.

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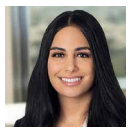

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Update on FDA enforcement of ClinicalTrials.gov requirements

U.S. federal law requires sponsors of certain clinical trials to register and post results of their studies on ClinicalTrials.gov. If a sponsor fails to submit the required registration or results information for a study to ClinicalTrials.gov, FDA may issue a Preliminary Notice of Non-Compliance, which allows sponsors 30 days to bring their study record into compliance. If a sponsor does not address the violations identified by FDA, then the agency can take further enforcement action, which can include issuing a Notice of Non-Compliance, civil monetary penalties, injunction, and criminal prosecution.

Although penalties for ClinicalTrials.gov non-compliance can be significant, FDA's enforcement of ClinicalTrials.gov requirements has to-date been quite light. Since 2021, FDA has only issued five Notices of Non-Compliance to clinical trial sponsors for failing to submit clinical trial results. FDA's lack of enforcement has been noted by the U.S. Congress, with the Energy and Commerce Committee sending a letter to FDA in January 2023 expressing concern with FDA's "limited enforcement activities for failure to comply with ClinicalTrials.gov requirements." The letter pointed to a study that found widespread non-compliance with ClinicalTrials.gov results submission requirements, with 31 percent of trials failing to report required results, and another 30 percent of trials failing to report required results on time. The letter noted that FDA had not yet imposed any civil monetary penalties for non-compliance with ClinicalTrials.gov requirements, even though such penalties "would provide a stronger incentive for trial sponsors to comply."

There are some recent signs, however, that FDA may be taking a closer look at ClinicalTrials.gov compliance. In December 2023, FDA commissioner Dr. Robert Califf issued a statement describing FDA's oversight of ClinicalTrials.gov and the actions FDA has taken to address non-compliance. Dr. Califf stated that FDA was "committed to promoting clinical trial transparency and will continue to advance our compliance activities related to the ClinicalTrials.gov database." In addition to Dr. Califf's statement, FDA released a report in January 2024, in collaboration with the Clinical Trials Transformation Initiative, investigating factors and barriers to registration and results reporting on ClinicalTrials.gov and offering suggestions for improvement. We at Hogan Lovells will continue to monitor the agency's actions to see if FDA is indeed preparing to take a stronger stance on ClinicalTrials.gov enforcement.

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5 Privacy and Cybersecurity

Good hygiene: Navigating federal oversight of sensitive health data

Federal regulators, and in particular the Federal Trade Commission (FTC) and U.S. Department of Health and Human Services (HHS), are working together and stepping up efforts – through agency guidance and enforcement actions – to ensure that organizations processing sensitive health data provide robust privacy and security protections.

The two agencies issued joint guidance in 2023 as well as a warning letter to 130 health care providers about the risks involved with using tracking technologies such as pixels and cookies where sensitive health information is involved. The guidance highlights requirements under the Health Insurance Portability and Accountability Act (HIPAA), the FTC Act, and the FTC Health Breach Notification Rule. HHS on its own issued guidance on privacy and security risks when using remote communications for telehealth and entered settlements targeting unauthorized disclosures of sensitive health information and violations of patient privacy rights. The FTC issued guidance setting out expectations for use of consumer health data and clarifying – under FTC authorities – what constitutes deceptive practices with regard to sensitive health information.

The FTC health sector actions have targeted businesses dealing in many types of sensitive data including biometric, geolocation, reproductive health, diagnostic, mental health, and genetic information and made clear that their reach includes and extends far beyond the clinical and prescription data that is often under the purview of HHS and HIPAA. In the FTC settlement agreements with GoodRx (prescription information), Vitagene (genetic data), and others, the agency cited the lack of user transparency, misleading statements about data privacy and security, and its concerns about downstream uses of data and the lack of express and affirmative consent.

As the consumer health experience is transformed by the use of new technologies, including generative AI, businesses in the U.S. processing sensitive health information will need to be prepared for federal scrutiny of their privacy and data security practices. Looking at recent HHS and FTC actions, several themes emerge including: (1) the need to determine whether sensitive health data is covered by HIPAA and/or the FTC authorities; (2) the requirement for express, affirmative consent (opt-in) in order to disclose sensitive health information, especially for tracking technologies (like pixels and cookies) and marketing activities; and (3) the expectation that privacy and security will be addressed through a formal compliance program that includes risk assessments, written policies, and employee training.

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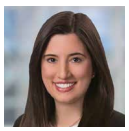

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Navigating the AI horizon: Safeguarding against cybersecurity challenges

The use of artificial intelligence (AI) in the life sciences industry has opened doors to a realm of possibilities. By harnessing the capabilities of big data and machine learning, companies can expedite the drug discovery process, identify treatment patterns, and even personalize health care solutions. For instance, AI tools can analyze vast datasets to predict drug interactions, potential side effects, and efficacy, significantly cutting down the time required for research and development. This efficiency translates into quicker access to life-changing treatments for patients. In addition, personalized treatments, tailored to the patient, are becoming a reality, ushering in a new era of precision medicine and medical devices.

Cybersecurity risks

While AI brings unprecedented benefits, it also introduces significant cybersecurity risks. AI systems and tools can be hacked, or can be fed with inaccurate, misrepresentative or maliciously designed data to manipulate the AI tool. Cybersecurity vulnerabilities in the supply chain can also be used to hack or manipulate systems. The consequences of cyber incidents can have a significant impact: not only can they compromise data and systems, but they can also undermine the integrity of research findings and treatment outcomes, erode public trust, and impede the progress of life-saving innovations.

Evolving legal landscape

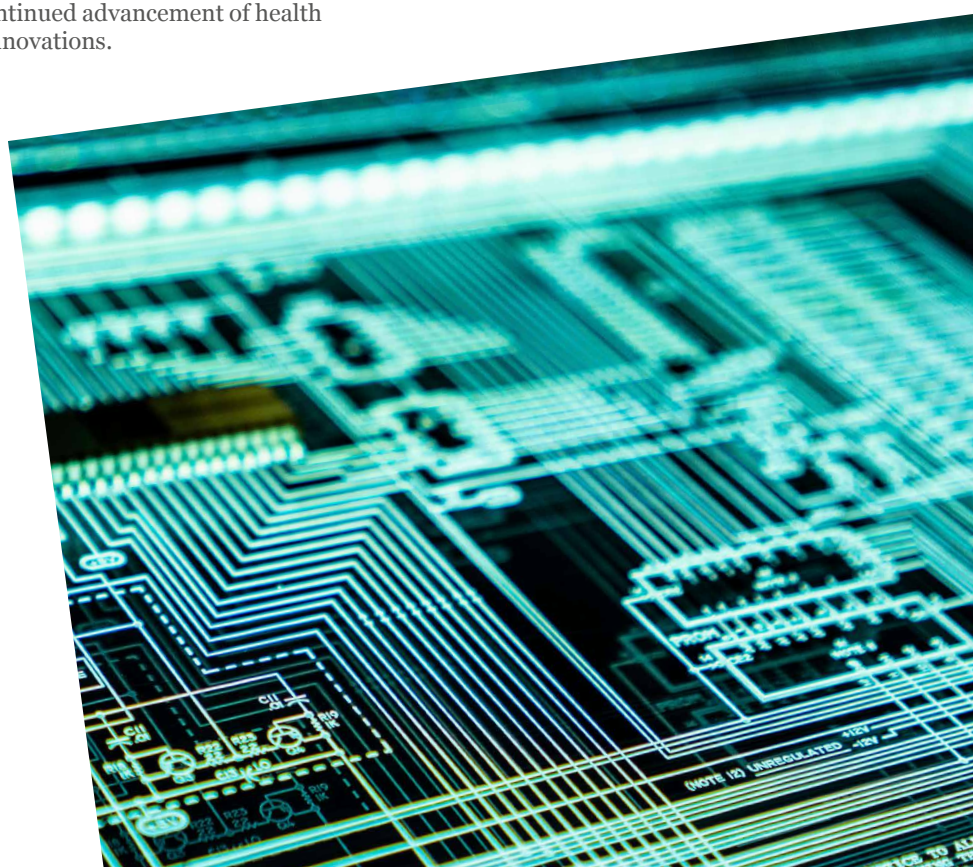
As part of its digital strategy, the EU has a strong focus on enhancing cyber resilience and regulating AI. The Network and Information Systems Directive 2 (NIS2), the EU AI Act, and the EU Cyber Resilience Act are crucial frameworks shaping the regulatory landscape. From a cybersecurity perspective, the focus is on requiring companies to take appropriate and proportionate technical, operational, and organizational cybersecurity measures to manage the risks posed to the security of network and systems, and protect them against cyber incidents.

Building a resilient AI and cybersecurity governance program

Prioritizing cybersecurity is key for harnessing the benefits of AI in a secure and compliant way. Despite the ongoing activity on AI and cyber regulations, companies are advised to take a proactive approach in future proofing their AI and cybersecurity governance program, including by considering core elements such as:

- conducting regular cybersecurity risk assessments and AI impact assessments to determine potential risks and vulnerabilities of AI systems;
- adopting and monitoring appropriate technical and organizational measures and controls for the safety, accuracy, and reliability of AI systems;
- adopting and monitoring cybersecurity policies and procedures for preventing, handling, and notifying cybersecurity incidents;
- creating a multi-functional AI governance team with a strong focus on cybersecurity.

The synergy of AI and life sciences holds immense promise, but it demands a strategic and vigilant approach to cybersecurity. By embracing comprehensive security measures and adopting an adaptable yet sustainable approach to AI and cybersecurity governance, companies can confidently navigate the AI horizon while ensuring the integrity of their research, protecting data, and contributing to the continued advancement of health care innovations.



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Secondary use of research data in the U.S.

We have all this data—can we use it? This is a common question given the potential value of data. Several factors affect whether data from a research study may be used for secondary research in the United States.

Consent: One key consideration is whether the secondary use falls within the informed consent form (ICF) obtained for the initial study. Sometimes a secondary use is part of the main study or the ICF includes specific consent for the intended secondary research use.

IRB waiver: If consent for the secondary use of data was not obtained, an Institutional Review Board (IRB) may be able to waive the ICF and Health Insurance Portability and Accountability Act (HIPAA) authorization, subject to certain requirements. If consent was requested, however, and a subject refused, the IRB may not waive the subject's consent.

State law: State health information privacy and sensitive condition laws could impose additional requirements, particularly for genetic data or genetic testing. Some state laws even provide individuals with property rights in their genetic information. Applicable state laws should be carefully assessed.

De-identification: If the data will be fully de-identified in accordance with HIPAA and relevant research regulations, this helps mitigate risk, including under state law. Thus, consideration should be given for whether de-identified data can be used. Note, however, that coded data may not be considered fully de-identified under HIPAA.

Other restrictions: Applicable clinical trial or other agreements may limit use of research data. In addition, if the data was collected from outside the U.S., it may be subject to restrictions under the laws of the country of origin.

Each of these considerations should be assessed to determine the permissibility of a secondary use of data. Including permission for secondary uses in ICFs from the start helps maximize the ability to use research data for such purposes. While the language can be broad, some description is necessary under the Common Rule and HIPAA, which require sufficient information that a reasonable person would expect their information to be used. Secondary research consent can be part of the main study ICF—an opt-in is not required. This could cause some individuals not to participate in the main study but eases the operational burdens of tracking who opted-in to the secondary research uses.

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States are reining in the use of consumer health data

State legislators have a newfound enthusiasm for restricting the use of consumer health data that is not protected by Health Insurance Portability and Accountability Act (HIPAA). Last year three states – Connecticut, Nevada, and Washington – enacted new laws restricting the use of consumer health data. These laws require notice and opt-in consent before consumer health data can be used and prohibit data sales unless a longer written authorization is obtained. Geofencing is also prohibited within a specified range of mental health, reproductive health, and other care providers.

Compliance requirements

Covered businesses will have new obligations to obtain opt-in consent for many uses and disclosures of consumer health data that are not necessary to provide a product or service that the consumer requested. Consent obtained via acceptance of a company's Terms of Use will not be sufficient. Nevada and Washington require companies to obtain "written authorization" – similar to an authorization under HIPAA – from consumers prior to selling or offering to sell their consumer health data (including some cases where health data is made available through third-party web trackers). Notably, Connecticut requires only opt-in consent for such practices. Businesses will also have additional, unique notice obligations under these laws. The privacy policy requirements in Nevada and Washington's laws differ significantly from the notice requirements in general state privacy laws, such as the California Consumer Privacy Act (CCPA), and Washington's law will require a separate privacy policy for consumer health data collected from Washington residents.

Under these new laws, businesses are also prohibited from implementing a "geofence" of less than 1,750 to 2,000 feet around certain health care facilities to identify, track, collect data from, or send any notification to a consumer regarding the consumer's health data. Geofences include technology that uses GPS coordinates, cellular data, or even Wi-Fi to establish a virtual boundary and the laws will prohibit companies from using certain location-based check-in features or targeting advertisements to consumers based on a visit to certain health care facilities.

Next steps

Businesses subject to the new Connecticut, Nevada, or Washington laws should determine whether they process consumer health data and if so, operationalize the requirements taking account of the broad definition of consumer health data. Specifically, as needed: (1) update consumer privacy notices; (2) implement a process for collecting additional opt-in consents or authorizations; and (3) prevent the use of impermissible geofencing. We are counseling clients on how to comply with these new laws efficiently and in alignment with their existing compliance programs.

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6 Transactions

Healthspan funding opportunities

Investment in the development of new drugs and biologics is well calibrated for products that treat a specific disease or condition – emerging drug development companies routinely talk of "targeting" a specific indication. Innovative technologies for disease prevention likewise are focused on a "one disease at a time" approach. However, the emerging category of healthspan products is geared to reducing the risk of onset of major chronic diseases, such as cancer, heart disease, diabetes, dementia, and frailty, by addressing the underlying factors that make aging the strongest dominant factor for most major chronic diseases.

An already challenging life sciences financing market can seem especially daunting for companies pursuing innovative healthspan technologies. Astute stakeholders can take strategic steps now to better position their healthspan development programs for success.

Particularly in today's challenging fundraising market, emerging companies should consider available non-dilutive funding opportunities to avoid impacting their cap table. In the United States (U.S.), these include government grants, such as from National Institutes of Health (NIH), National Cancer Institute (NCI), National Science Foundation (NSF), Biomedical Advanced Research and Development Authority (BARDA), U.S. Department of Defense (DOD) as well as state-sponsored options with significant global reach including the Cancer Prevention and Research Institute of Texas (CPRIT) and California Institute for Regenerative Medicine (CIRM).

Significantly, the newly announced and constituted Advanced Research Projects Agency for Health (ARPA-H) research funding agency may provide a unique opportunity for healthspan innovators to seek this type of non-dilutive funding from the federal government and the timing couldn't be better for life sciences entrepreneurs launching such efforts. ARPA-H aims to support fundamental research that cannot readily be accomplished through traditional research or commercial activity. In particular, ARPA-H's Proactive Health initiative supports preventative programs that will promote treatments and behaviors that will reduce the likelihood that people will become patients. ARPA-H also provides opportunities to work directly with the FDA to accelerate innovation and accelerate better health outcomes, *i.e.*, companies seeking to introduce new healthspan technologies into the market. As with any government funding program, there are considerations regarding governmental rights and other restrictions on the use of funds that grantees will need to navigate and account for in their other fundraising efforts.

Public-private partnerships will likely play an outsized role in the healthspan area not least because of the less clear regulatory pathways for approval of these therapies. Many chronic diseases have national nonprofit foundations that can provide funding opportunities for companies involved in research and commercialization within specific focus areas. Strategic development partnerships with similar foundations are another funding source to consider in the path to developing and commercializing products without impacting the cap table.

Finally, more traditional venture and institutional equity financings will continue to (must) play a role, but to successfully attract such investment, emerging healthspan companies will need to demonstrate a clear and manageable regulatory path leading to a significant market supported by a variety of payors. Piecing these elements together into a concise financing plan remains a mission critical undertaking for any life sciences company.

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Horizon Europe: Research and innovation funding in Europe for life sciences and health care companies

The Horizon Europe program of the European Union (EU) provides a substantial budget of 95.5 billion EUR to fund research and innovation until 2027. Horizon Europe offers a range of funding opportunities and support for the life sciences sector, especially in the areas of health, food, bioeconomy, natural resources, agriculture, and environment.

The Horizon Europe Program

Horizon Europe is the EU's key framework program for funding research and innovation in areas that the EU considers essential for the EU's competitiveness, growth and implementation of its strategic priorities. The overall budget of the program, which runs from 2021 to 2027, is 95.5 billion EUR. Health is identified as one of the key technology areas to be supported by the program. The budget reserved for research and development in the field of health technologies is approx. 8.2 billion EUR.

Who is eligible for funding? Entities from the EU and Associated Countries

Legal entities, which are established in an EU Member State or in one of the currently 18 Associated Countries, including Israel, Norway, Turkey, and the United Kingdom, are eligible for funding.

Affiliates and subsidiaries of non-eligible parent companies are also eligible for funding if the affiliate/subsidiary is established in an EU Member State or an Associated Country and if the applying entity is capable of performing the research and innovative action.

In exceptional cases, the EU may even decide that entities from non-associated countries, such as the United States, are directly eligible for funding.

Which actions are funded in the health area and how much funding can be awarded?

The EU publishes calls for proposals describing the topic and objectives of the research, the activities which should be included in the proposal and the funding available for the call. Within the framework of such calls for proposals, applicants may submit their proposals for research and innovation projects. The funded projects are selected on the basis of their excellence, impact, quality, and efficiency of the implementation. If funding is awarded, it may cover 70% or even up to 100% of the eligible costs.

In the field of Health, the calls cover topics like treatment of cancer, performance evaluation of medical devices and in vitro diagnostics, new approach methodologies for regulatory safety and efficacy testing, antimicrobial resistance, and new tools, technologies, and digital health solutions.

Summary

The Horizon Europe program provides an attractive framework for obtaining funding for research and innovation projects in the field of health care and life sciences.

When planning new research projects, innovative pharmaceutical, medtech and biotech companies from both inside and outside the EU should check whether Horizon Europe funding may be available.

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Manufacturing relationships underlying transformative technologies

Cell, tissue, and gene therapies (CTGT) have for years offered the potential for truly personalized medicine for many near-incurable disease indications. In addition, radiopharmaceuticals and custom and customizable medical device deliverables have recently shown to have great promise for individualized patient care. All of these new technologies leave little margin for error due to the time-sensitive nature of their manufacture and delivery. Manufacturers face tough choices on how much of the delivery process can be centralized or brought in-house, often at a very high cost, versus partnering with a specialist, which may increase logistical hurdles. Additionally, the potential geographical location of manufacturing/distribution facilities requires careful analysis; for example, with respect to radiopharmaceuticals and autologous cell therapies, close access to high population regions and hospital and treatment centers, in addition to robust transportation/distribution/logistics systems is essential.

Increasingly, many of these steps are carried out by one or more specialty contract manufacturing or contract development and manufacturing organizations (CMO/CDMO) creating or utilizing distribution and treatment centers in close proximity to large patient populations (*e.g.*, near major hospital systems), raising important considerations and logistical challenges with respect to the relationships between the "legal" product manufacturer and these partners, as well as the contractual challenge of ensuring safety in unique point of service supply chains, which require an integrated approach to distribution and manufacturing.

Additionally, these processes and relationships can raise tricky contractual issues, resulting in greater complexity in core license terms and potentially greater challenges in diligencing investment opportunities. The end result is greater scrutiny and intense negotiations around:

- what is being licensed;
- what are the potential costs associated with manufacturing, distribution, and possible commercial scaleup;
- what is the available manufacturing and distribution capacity and geographical footprint and what impact will this have on the relationship with the contracted partner;
- how comfortable are the regulators with new methods for manufacturing and distribution in all applicable jurisdictions;
- what impact possible regulatory delays (including product approvals and/or facilities inspections) may have on manufacturing and distribution planning;
- how to balance centralized versus decentralized delivery models; and
- how best to partner with administering health care providers (HCPs) who ultimately have access to patients.

Capacity, materials shortfalls, and delivery logistics continue to impact the bottom line for partners across the supply chain. Ultimately, planning for every eventuality and building controls and contingencies for every step are the key to successfully being able to deliver transformative therapies to patients. Early consideration of nuanced contract terms and planning at the development/clinical stage of an agile and efficient framework for commercial manufacturing/logistics arrangements is advisable as is careful construction of a trigger to negotiate an early exit on satisfactory terms if a suitable outcome ceases to be achievable.

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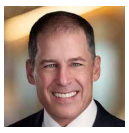

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Strategic considerations in view of a (proposed) broader Bolar exemption in EU

Recent European Commission (Commission) proposals, including a broadening of the so-called 'Bolar exemption', would substantially change various incentive schemes related to medicinal product approvals in some jurisdictions, with the stated goal of increasing competition from earlier market entry of generic/biosimilars. The proposal raises a number of considerations for stakeholders thinking strategically about where to invest in manufacturing, clinical trials sites, and/or contractor relationships in European Union (EU) Member States and neighboring markets, including the United Kingdom, and the impact these may have on their agreements and the prospect of future litigations. Companies engaged in early development programs should consider the impact the proposals could have (if implemented) on their R&D and future launch.

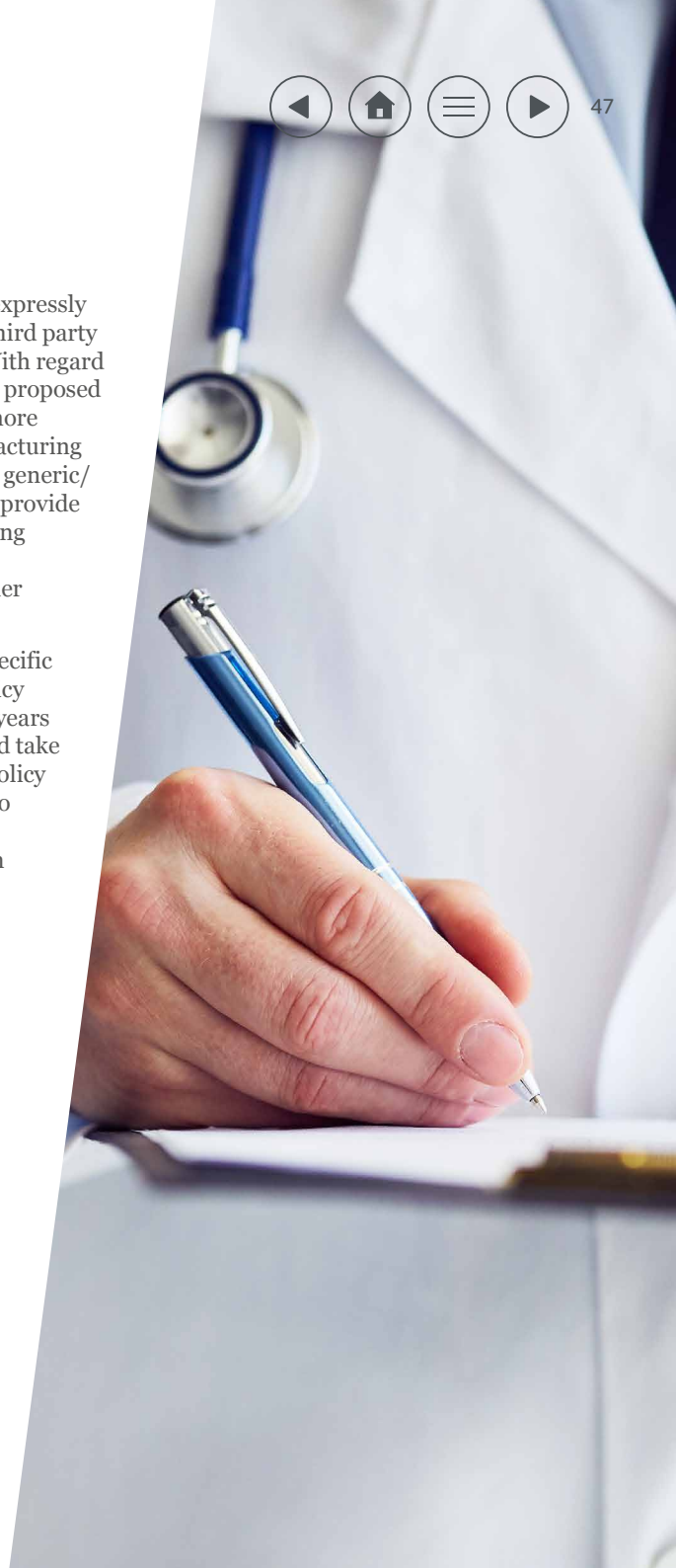
The proposed exemption provides that covered activities (studies, trial and other activities conducted to generate data that might otherwise infringe a patent or supplementary protection certificate (SPC)) must be conducted exclusively for the listed purposes (to generate data for an application for (1) an MA of generic, biosimilar, hybrid or bio-hybrid medicinal products, (2) health technology assessment (HTA), or (3) pricing and reimbursement), as well as the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes.

The exemption expressly excludes placing the resulting medicinal products on the market, but the proposal that test product generated during the regulatory approval process may be used for commercial purposes after the patent/SPC expiry. An expanded exemption could thus make the impacted jurisdictions more attractive as manufacturing locations for generic/biosimilars.

The proposed exemption makes clear that activities conducted to generate data for HTA and pricing and reimbursement are expressly permitted. Under current national laws in certain Member States, the submission of pricing and reimbursement data is sufficient to trigger the granting of a preliminary injunction (PI). A change in the Bolar exemption could impact the PI landscape, as well as making these jurisdictions more attractive for administering clinical trials and generating other types of data. Another consideration, depending on how the proposals are implemented, is to what extent activities performed within a jurisdiction could be used for the purpose of seeking regulatory approval in jurisdictions outside of the EU, which again, could encourage investment in local manufacturing and clinical trials sites.

Finally, the proposed exemption expressly includes activities performed by third party suppliers and service suppliers. With regard to these covered beneficiaries, the proposed framework would likely provide more legal certainty for contract manufacturing organizations (CMOs) involved in generic/biosimilar production. This could provide welcome relief to parties negotiating contracts related to their active pharmaceutical ingredients or other essential product components.

While implementation of these specific proposals is subject to further policy advocacy and may still be several years away, prudent stakeholders should take note because the underlying EU policy goal of facilitating patient access to innovative medicines through pharmaceutical and patent reform will likely remain.



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Valuation: Bridging gaps with earnouts

Earnouts remain a common device to bridge valuation gaps in private M&A transactions, particularly in the life sciences and health care sector where there are inherent challenges in assessing the viability of the long development cycles required to bring therapies, devices, and other technologies to market. An earnout in a purchase agreement contractually requires a buyer to make additional – sometimes substantial – contingent payment(s) if certain specified events or performance targets are met post-closing (such as patient enrollment or data milestones, regulatory submissions or approvals, or drug indication milestones).

With high stakes, earnouts often lead to post-closing disputes and litigation. While disputes may arise on the basis of any number of reasons (*e.g.*, earnout metrics, drafting ambiguity, accounting principles, etc.), the buyer's obligations with respect to the operation of the acquired business during the earnout period, including the level of efforts required to achieve the earnout targets, is a prime cause for dispute and therefore a critical point of negotiation.

While the applicable law governing the purchase agreement will influence the earnout provisions and their interpretation and enforceability, there are a number of universal practice points that buyers and sellers should consider when negotiating earnouts, including:

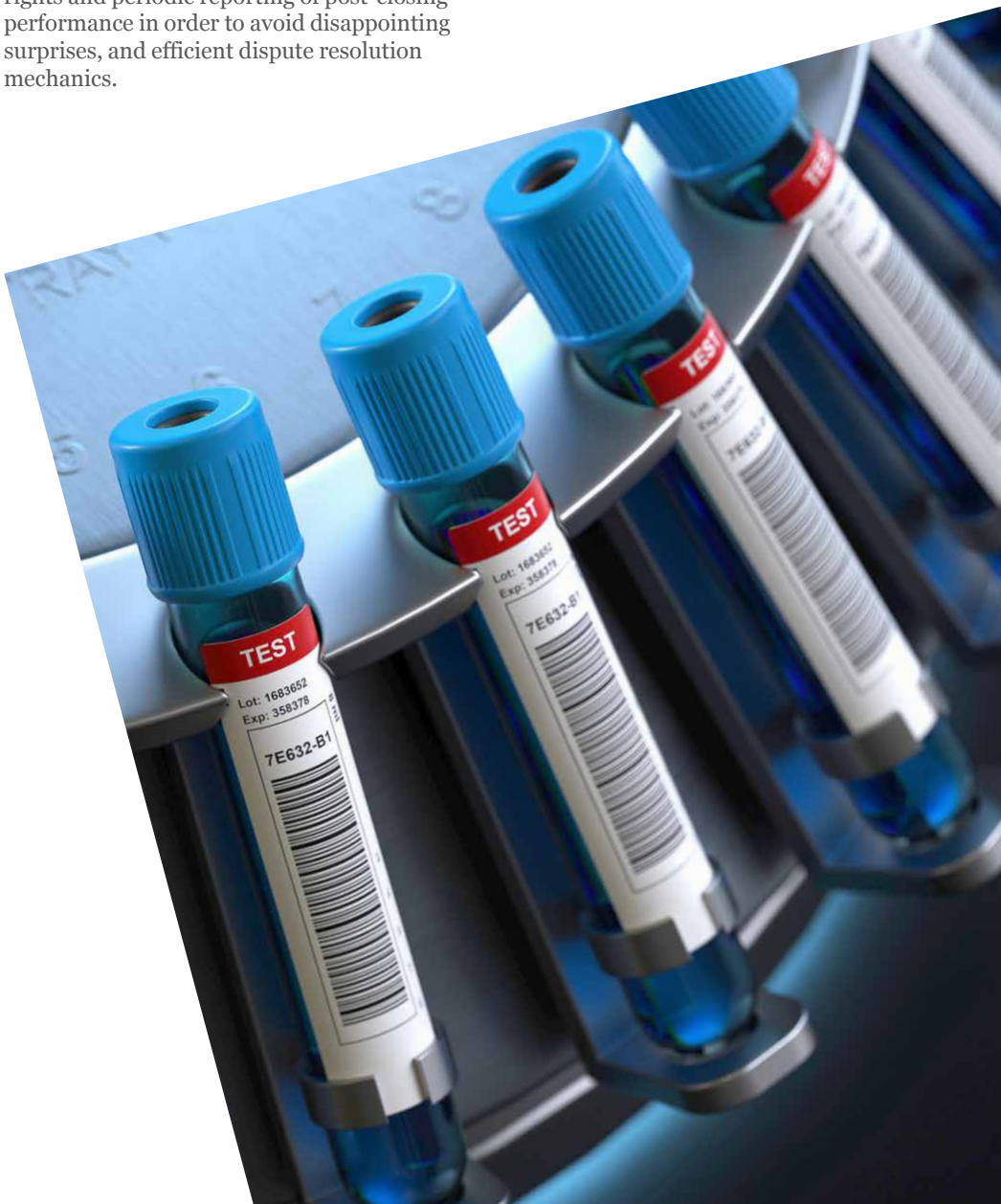
Clear, detailed drafting. Whether the buyer may operate the acquired business in its sole and absolute discretion or has agreed to a general level of efforts or specific actions that it must take during the earnout period, both buyers and sellers can benefit from explicit, unambiguous contract language. Parties are ill-advised to rely on implied covenants and imprecise drafting.

Target specific metrics. Milestone language should be drafted in concert by lawyers and business people with deep knowledge and expertise about the target company and its operations and industry in order to fashion meaningful, specific milestones that are less prone to manipulation or subjective interpretation after the fact.

Anticipate disputes. By their nature, earnout provisions get reviewed and tested after the closing – sometimes by parties who were not involved in or familiar with the negotiation of the acquisition – so contract provisions can often benefit by a final, pre-signing review by litigators to ensure clarity.

Consider contingencies. The buyer's business is not static and fixed in time at the point of closing, so the parties should consider and provide for the possibility of post-closing changes in control (both with respect to the buyer as a whole and the target company assets individually), the buyer's acquisition of competitive assets (which could divert resources and attention away from the target's business), and changes in applicable law, among other events.

Compliance and reporting. Thoughtful acquisition agreements include information rights and periodic reporting of post-closing performance in order to avoid disappointing surprises, and efficient dispute resolution mechanics.



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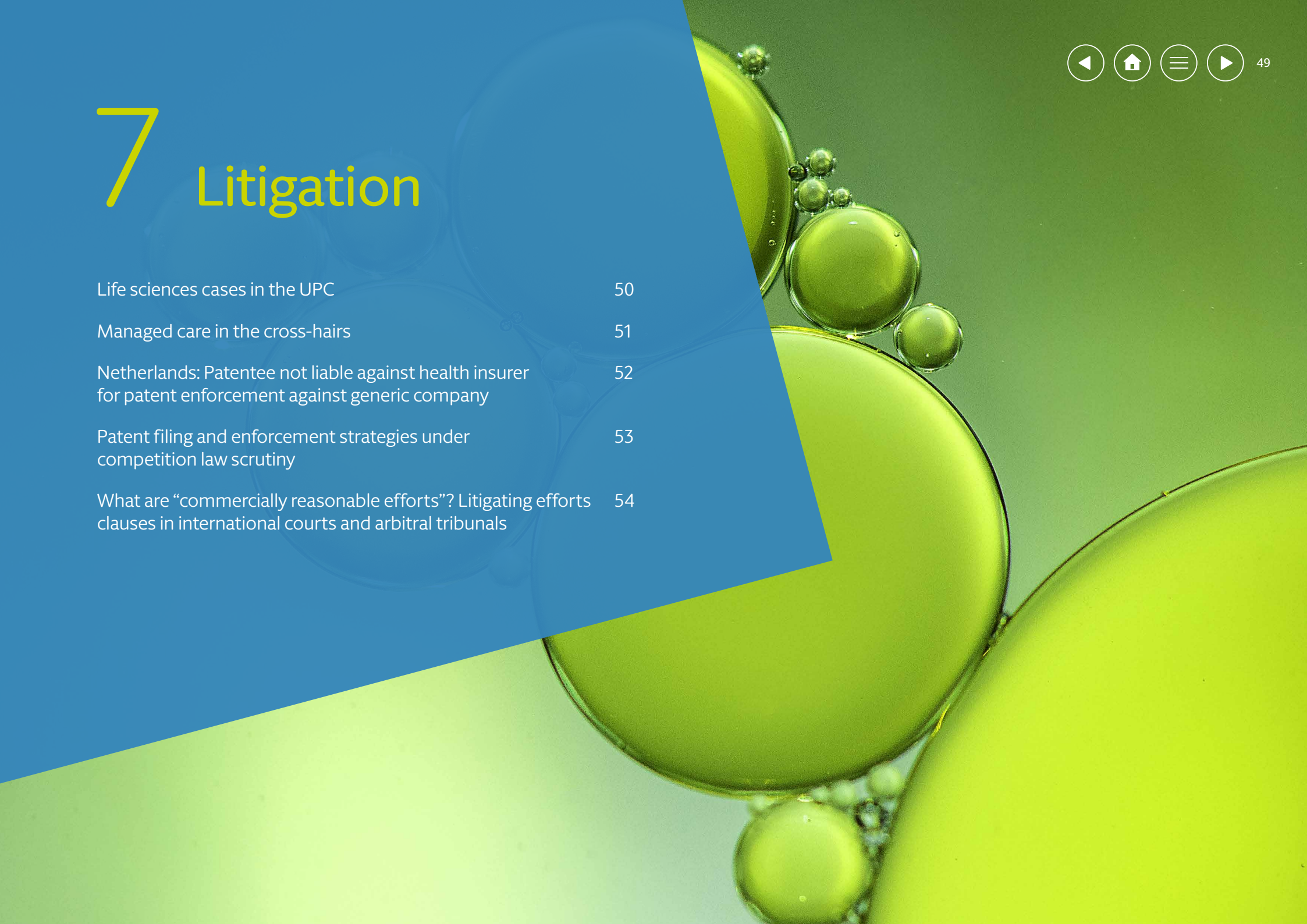
7 Litigation



Life sciences cases in the UPC

On 1 June 2023, the first truly European Unified Patent Court (UPC) opened its doors. Contrary to most expectations, life sciences cases – primarily covering technical classes (CPCs) of Human necessities (A) and Chemistry and Metallurgy (C) – have featured prominently during the first eight months of the UPC, and account for almost half of all UPC cases. However, with the exception of a small number of pharmaceutical innovator companies, the majority of cases come from the device and diagnostics side of life sciences. This is likely because the vast majority of the global blockbuster drug related patents were "opted out" during the so-called "sunrise" period before the court system became operational, meaning that these patents can only be enforced and attacked in the "traditional" way through the national court systems of the participating Member States.

An attractive venue for revocation actions

As anticipated, it appears that the UPC is particularly attractive to life sciences companies trying to revoke competitor patents. Unless opted out of the jurisdiction of the UPC, European Patents can now be attacked with a single central revocation action for all participating Member States without the need for parallel "country by country" litigation and has already proven an attractive pathway for litigants.

The patentee's perspective

Leaving aside the threat of central revocation, the UPC is an attractive venue for patentees. With life sciences companies usually validating their patents across all participating Member States there is substantial potential for broad injunctions including preliminary injunctions (such as in the proceedings No. UPC CFI 2/2023). The patentee can obtain broad protection across all participating Member States even when there has only been a single act of infringement in one UPC-member state. Additionally, the UPC allows broad seizure and inspection rights for patentees, *e.g.*, with a view towards inspecting generic/biosimilar manufacturing processes, or seizing documents regarding regulatory approval or supply chains throughout Europe by the combined use of different tools, such as the order for inspection of premises (similar to the *saisie-contrefaçon* in France).

In return for such broad remedies, the patentee has to weigh the risk of central revocation and the uncertainty of being subject to a new system without, currently, a sufficient body of case law and developed precedents. In this regard it is very interesting to note that 17 of 25 isolated revocation actions are in the field of life sciences. In other fields, revocation actions are mostly brought by way of a counterclaim. Thus, not only patentees are making use of the new court system.

Looking forward

It seems likely that some companies are purposefully using the court at this early stage, while a harmonized body of UPC case law has not yet been established. Different UPC judicial panels may still rule issues differently. For example, there is evidence of plaintiffs choosing different venues within the same enforcement campaigns, *e.g.*, the Nordic-Baltic regional division in Stockholm and the Munich local division in a life sciences case, or different local divisions within Germany, in a recent telecoms case.

Currently, the preferred local division for life sciences cases is Munich, followed by Paris, the Nordic Baltic regional division, and Düsseldorf.

While the number of cases in the UPC is rising, it is clear from the cases filed to date that in many important cases, patentees have continued to file infringement proceedings in Member State courts in parallel. In the long run, we expect that the UPC will not replace national courts in the enforcement of patents but that it will be an (albeit essential) element in enforcement strategies, always accompanied by national actions in most important local markets. Unlike in pharmaceuticals, where key products are often protected by only a small number of key substance, process or indication patents, in other areas such as diagnostics or devices the portfolios are often larger and the individual patents less valuable. Therefore, we expect to see these parallel enforcement strategies more often in these areas.

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Managed care in the cross-hairs

As enrollment in Medicare Advantage and Medicaid Managed Care programs has grown over the past decade, so too has the flow of federal health care dollars. This transition away from traditional, fee-for-service (FFS) reimbursement models to more complex, risk-based payment systems is giving rise to intricate legal issues, including in the realm of government enforcement. One challenge facing regulators and companies alike is that traditional badges of fraud associated with FFS reimbursement frequently do not apply in managed care, where systems are constructed to shift economic risk away from the government.

The increased enrollment and associated cost of Medicare Advantage and Medicaid Managed Care plans has heightened the government's interest in these programs. Most overt Department of Justice (DOJ) enforcement in the space has focused on the submission of false diagnosis codes, in cases against both plans and providers. But managed care payment systems pose unique issues under the False Claims Act (FCA), including because: (1) a private insurer sits between the government and health care services providers; and (2) the amount the insurer is paid is decoupled from the amount or type of health care services provided to federal health care program beneficiaries. Thus, although the government undoubtedly is putting money into the system, it is more difficult to trace the flow of funds in relation to individual items or services.

These factors can make it more difficult for the government—as well as private relators litigating FCA cases—to carry the burden of proving all elements necessary to prevail under the FCA. Among other challenges, capitated payment systems obscure the nexus between the government's payment decision and any alleged false statement or claim linked to individual items, services, or diagnoses. As a result, in such cases the government may face obstacles to establishing the submission of a materially false claim. In addition, capitated payment systems can make it inherently difficult to prove damages, including in cases when a provider is paid by a capitated plan on a FFS basis. Importantly, this has not prevented the government from securing multiple settlements in the Medicare Advantage context, particularly in the risk-adjustment space.

In 2024 and moving forward, we anticipate that the government will continue efforts to use the False Claims Act as an enforcement tool to target alleged fraud involving Medicare Advantage and Managed Medicaid programs. Companies and providers operating in this space would be well-advised to monitor developments in this evolving area of government regulation and enforcement.

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Netherlands: Patentee not liable against health insurer for patent enforcement against generic company

The Dutch Supreme Court upheld a decision of the appellate court in which an innovative life sciences company was held not to be liable towards a health insurer for the enforcement of a preliminary injunction against a generic company, while the patent was later found invalid.

The appellate court considered that there is no strict liability vis-à-vis third parties, such as a health insurer. The appellate court found that the life sciences company did not know nor should have known in the circumstances of the case that there was a serious chance that the patent would be revoked in opposition or court proceedings. The appellate court also rejected a claim based on unjustified enrichment, as it considered that the enrichment did not have an unjustified nature.

The Supreme Court considered that the mere ruling that the patentee did not act unlawfully does not mean per se that the enrichment was justified. The Supreme Court however held that the appellate court did not reject the unjustified enrichment claim solely on this ground but on the basis of various circumstances.

The Supreme Court also considered that the appellate court did not set too high a threshold for culpability in the context of unlawful act. The Supreme Court considered that the appellate court took various circumstances into account when concluding that the life sciences company did not know nor should have known that there was a serious chance that the enforced patent would be revoked:

- the Dutch first instance court had previously held the patent to be valid;
- the patentee's position with respect to inventive step was not clearly incorrect;
- a patentee may in principle rely on a decision on the merits of a Dutch court confirming the validity of a patent. A revocation decision of a foreign court does not per se mean that the patentee knew or should have known that there was a serious chance that the Dutch part of the patent would be revoked.

The decision of the Supreme Court shows that liability of a patentee towards a third party, such as a health insurer, for enforcement of a preliminary injunction decision against another party, such as a generic company, is not easily accepted.

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Patent filing and enforcement strategies under competition law scrutiny

The European Commission (Commission) and many European competition authorities regularly pursue investigations in the life sciences sector. In recent years, their focus seems to have shifted and new practices have come under scrutiny. We summarize these developments and provide take-aways for the compliance practice.

After the Commission's 2009 inquiry in the pharmaceutical sector, the Commission and national competition authorities sanctioned several companies for agreements to extend the exclusivity of an otherwise ending patent protection "pay for delay" under the cartel prohibition (Article 101 Treaty on the Functioning of the European Union (TFEU)). Hefty fines were imposed and there is a risk of potential civil damages claims.

More recent cases focus on different practices and rely on the abuse of dominance prohibition (Article 102 TFEU), which does not focus on anti-competitive agreements but rather prohibits unilateral conduct. Infringements can equally trigger fines and civil damages claims.

The Commission's recent *Teva (Copaxone)* case illustrates this enforcement trend. After raiding several Teva subsidiaries, the Commission opened an investigation against Teva in March 2021. It accused Teva of delaying the market entry of generic drugs competing with its blockbuster drug Copaxone. The Commission alleges a misuse of patent procedures by applying for multiple divisional patents and selectively withdrawing them in appeal proceedings to avoid negative precedents.

In addition, the allegations concern Teva's communication on rival products towards health care professionals. Teva rejected the allegations and a decision by the Commission is pending.

The Commission and national competition authorities in Europe pursue several further practices of pharmaceutical companies related to the filing and enforcement of patents or other exclusive rights and communication campaigns. We indicate some of these practices that the authorities are investigating below (without covering all individual circumstances).

For the practice, this enforcement trend means that companies should ensure compliance with competition law if considering practices such as (taking all circumstances into account):

- patent, brand or product strategies to maintain – de jure or de facto – exclusivity after patent expiry;
- applications for (multiple) divisional patents or supplementary protection certificates (SPCs) in particular combined with specific enforcement strategies;
- acquisition of patents that are not used for own product innovation (but could potentially be enforced against competitors);
- communication campaigns that are critical towards rival products.

Finally, since competition authorities often rely on internal documents to prove anti-competitive intent, companies should be careful when drafting internal documents "watch your language".

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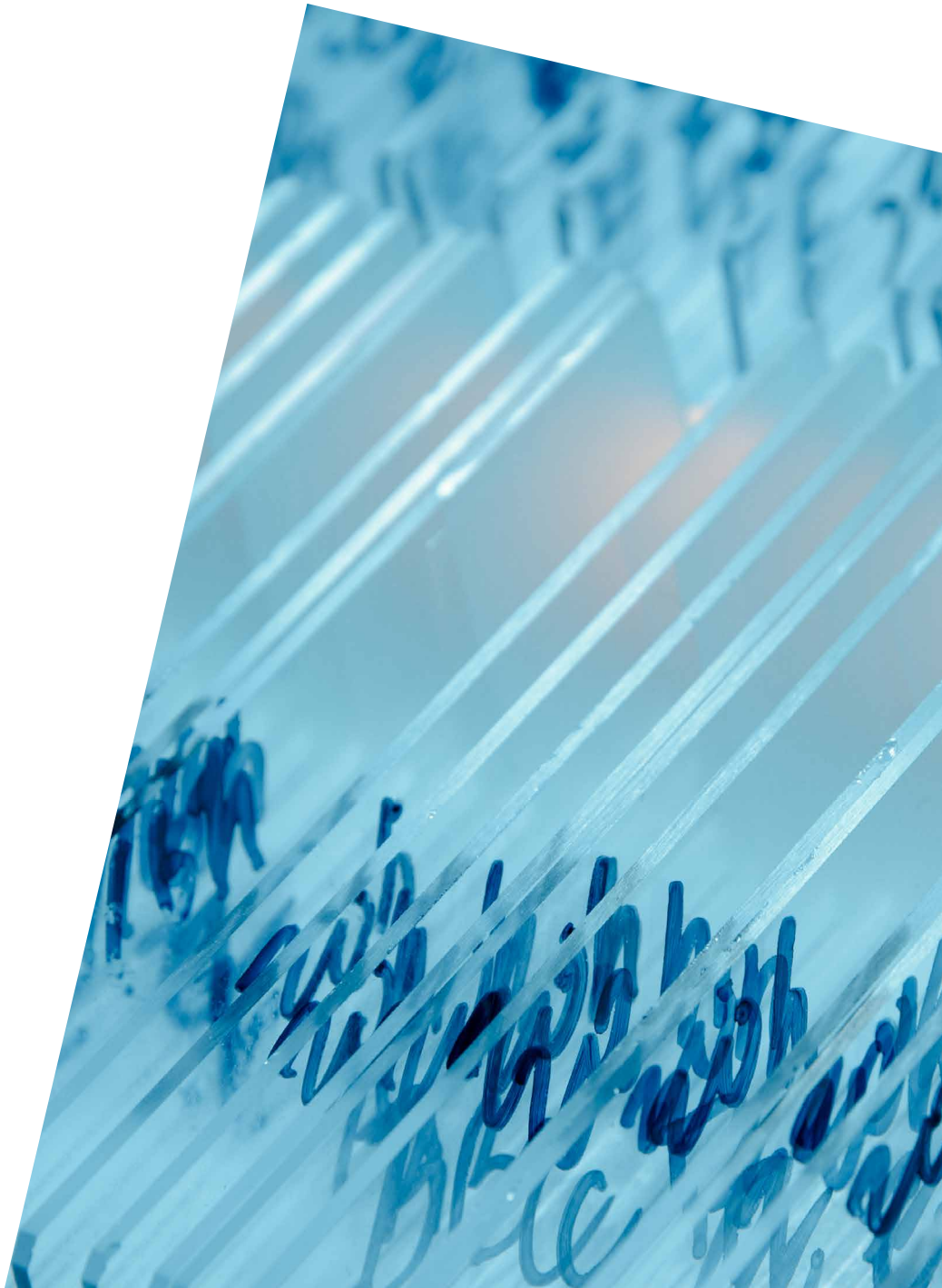

What are "commercially reasonable efforts"? Litigating efforts clauses in international courts and arbitral tribunals

Many agreements in the life sciences sector, notably development and/or commercialization contracts, include so-called efforts (endeavors) clauses, obligating the parties, or one party, to use a certain level of effort in respect of all, or some, of their obligations in support of a project.

The concept is vague, but international courts and arbitral tribunals have provided some guidance as to what efforts/endeavors obligations entail. For example, "best efforts" typically requires all steps a prudent and reasonable person would take, even if against their own commercial interests. "Reasonable efforts" normally only requires a party to take reasonable steps to achieve an outcome; they are not required to act against their own interests.

Commercially reasonable efforts (CRE) are usually understood to be less onerous than best efforts. But what are *commercially reasonable efforts?* Given the uncertainty, contract makers are well-advised to define CRE in their contract. Do they wish to include: a fixed minimum expenditure or minimum hours requirement? A longstop date, by which development must be completed?

Most importantly, what is the relevant standard for CRE: is it "internal", benchmarking to the efforts/resources the party usually expends to develop similar products at a similar stage; or "external", referencing to efforts/resources that a similarly-situated company may use to develop a similar product at a similar stage of development? Whatever the parties select, it's important to consider potential procedural implications if a dispute arises, specifically:

- A party defending an alleged failure to meet an "internal" CRE standard may benefit from not being required to demonstrate that its efforts reached "industry standards"; however, the flipside could be the requirement to disclose significant quantities of highly confidential documentation relating to other products it has in development (to evidence its internal standards), thereby driving up costs of document production.
- By contrast, a party subject to an "external" CRE obligation may have stronger grounds to resist production of internal documentation, but will be heavily dependent on expert evidence on the likely efforts expended by a theoretical similarly-situated third-party pharmaceutical company developing a similar product to establish the standard it was required to meet; and, on fact evidence from its personnel to demonstrate that it met that standard. In such cases, early identification and instruction of appropriate expert(s) is key to a successful outcome.

Contested issues in CRE disputes typically include: whether adequate resources (financial and personnel) were allocated to development, whether development was conducted in accordance with the development plan and whether sufficient attention was devoted to the project. Risks associated with these areas can be mitigated, to an extent, by good record-keeping, communication with the counterparty and ensuring that budgets, staffing, and attention are in accord with usual practices for the relevant stage of development.

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8 Hospitals and Health Care Providers

2023 Health care reforms in France: Stricter regulations for health centers

Concerns about health care center oversight and economic models have grown, following several sanitary scandals. While the French Public Health Code already placed limits on governance and profit distribution, aiming to prevent lucrative arrangements with private companies, a new law adopted on 19 May 2023 has sought to address these concerns. The law, limited to health centers with dental, ophthalmological or orthoptic activities:

- provides for restrictions on health center directors with direct or indirect interests in private companies providing paid services to the management structure, in order to prevent conflicts of interests;
- implements a mandatory prior approval by the Regional Health Agency (Agence régionale de santé - ARS) for health centers or their branches engaging in dental, ophthalmological and orthoptic activities. Existing centers must obtain approval within six months. However, the scope of the law is limited to these specific activities, exempting others from approval requirements. An inspection visit can then be carried out by the ARS to verify compliance with applicable regulations within the year of the grant of the approval;
- includes the submission of employment contracts of dental surgeons, dental assistants, ophthalmologists and orthoptists to the ARS and the competent professional boards. The professional boards must give an opinion on these documents;
- establishes a medical or dental committee composed of health care professionals practicing activities in the center, with the aim of ensuring the quality, safety and relevance of the care provided in the center;
- provides for new prerogatives for the general director of the ARS, including the ability to refuse approvals for structures and the receipt of certified accounts from health center managers;
- inserts a prohibition on demanding full payment for care before it has been provided for all health centers, regardless of their specialties;
- an increase in the penalties applicable to health care centers by the ARS when they detect breaches of their regulatory and legislative obligations.

Several implementing decrees are still awaited to be published to complete some of the new applicable requirements. The complete applicable framework should be in force during 2024 and will require several organizational adaptations for existing health centers to comply with these new requirements. This regulation also makes it mandatory for investors interested in structures involving health centers to conduct thorough due diligences on how these structures are organized and the agreements in place among different stakeholders. This regulation also reflects a trend in the sector regarding private investments, indicating a more cautious stance by authorities on the structuring of such projects and the entry of private investors into the health care sector. While the sector presents attractive return on investments, these can only be realized in strict compliance with applicable regulations.

Visit our website to find out how we work with hospitals and health care providers

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Reform of companies formed by self-employed practitioners: Practical adjustments to be aware of

The regulatory landscape applicable to companies formed by health professionals is going through an important overhaul. Recent changes of self-employed professional activity in France reformed a wide range of companies, including the sociétés d'exercice libéral (SELs) of health professions (doctors, medical biology laboratories, etc.). Intended to streamline the rules governing these companies resulting from "the legislative sedimentation of successive reforms", **three series of amendments** deserve particular attention:

Right of withdrawal

SEL's shareholders are allowed to withdraw in accordance with the procedures set out in the articles of association. This reform is intended to correct a previous case law that denied the right to withdraw unilaterally from the company or to obtain a court order authorizing such withdrawal, regardless of the content of the articles of association.

Annual right of information of the professional bodies

The requirements introduced in respect of the professional bodies' annual right of information have increased considerably. Whereas previously only a statement of the composition of the company's share capital had to be provided, a statement of the associated voting rights and an updated version of the SEL's articles of association will now have to be disclosed.

The shareholders of such companies will also be required to disclose "any agreements containing clauses relating to the organization and powers of the management, administrative or supervisory bodies that have been amended during the past financial year".

These practical requirements will come into force on 1 September 2024; therefore stakeholders need to effectively anticipate upcoming notification and consultation deadlines.

Rules governing capital ownership and governance

The text adds a welcome clarification regarding the mandatory direct or indirect presence, among the partners, of at least one professional practicing within the company.

Next steps

The text must be ratified by a law, followed by a series of implementing decrees, which will complete the changes. As a whole these modifications emphasize the need of a practical approach when drafting the articles of association and the extra-statutory provisions governing the relationships between the members of these companies, whether they are doctors or financial investors, in order to guarantee the operational independence of health care professionals required to comply with the applicable ethical provisions, while ensuring effective protection of the legitimate interests of investors. Although they are not incompatible, it can be tricky to reconcile the various interests at stake and the applicable legal requirements, which often requires a more sophisticated legal structure. Recent court decisions have also demonstrated that the current approach of the supervisory bodies in the health sector is to ensure a strict application of all deontological rules when financial investors enter into the capital of these companies.

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The growth of state health care transaction reporting laws

A growing number of states have enacted health care transaction reporting laws that may delay or even unwind hospital and physician group mergers and acquisitions. California, Connecticut, Illinois, Massachusetts, Minnesota, Nevada, New York, Oregon, and Washington have already enacted such laws, and other states (*e.g.*, Florida) have considered joining. Multi-state transactions may need to navigate multiple different regulatory schemes at once, the scope of which can be fairly broad – reaching beyond health care providers (HCPs) to management services organizations (MSOs) and entities (such as insurers, universities, or private equity firms) that own or control a health care provider. We expect to see continued movement in this space in 2024.

New Minnesota legislation empowers regulators to block a transaction. Health care entities with average revenue of $80 million or more must provide 60-150 days' pre-closing notice to the Attorney General and the Department of Health.[3] The Attorney General may then "bring an action in district court to enjoin or unwind a transaction" if a transaction is "contrary to public interest" or lessens competition.[4] Minnesota joins Oregon in giving regulators extensive authority.[5]

New laws in New York, Illinois, and California may delay transactions anywhere from 30 to 175 days or more. New York requires written notice 30 days before closing any "material transaction".[6] Regulators will make a summary publicly available, solicit comment, and forward all information to the Attorney General.[7] Health care facilities and provider organizations in Illinois must give 30 days' pre-closing notice to the Attorney General of a "covered transaction", and the Attorney General may further delay closing while the parties respond to requests for additional information.[8] After receiving notice of a "material change transaction", California's Office of Health Care Affordability (OHCA) has 60 days to decide whether to conduct a "cost and market impact review" or "CMIR", a minimum 115 day process to analyze the transaction's effect on health care costs and competition.[9] These statutes join Washington State's 60-day notice requirement.[10] Even where such a reporting law may not delay or unwind a transaction, they often require reporting of sensitive information to the state regulators.

The flurry of new statutes shows three major trends: increased public disclosure of proposed transactions; regulator authority to delay closing while scrutinizing transactions; and increased antitrust enforcement risk in the health care space. Hospitals and physician groups should build transaction notices into their timelines and anticipate state pushback where transactions result in problematic consolidation, layoffs, or service cuts.

3 Minn. Stat. §§ 145D.01(Subd. 2)(b), (e).

4 *Id.* § 145D.01(Subd. 3), (Subd. 5).

5 Ore. Rev. Stat § 415.501; Or. Admin. R. 409-070-0060.

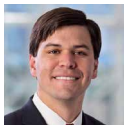
6 N.Y. Pub. Health Law § 4552(1).

7 *Id.* § 4552(2).

8 740 ILCS 10/7.2a(b), (d); Notifying the Attorney General of Covered Health Care Transactions, Ill. Att'y Gen. (Accessed Jan. 31, 2024), https://www.illinoisattorneygeneral.gov/Consumer-Protection/Health-Care/Antitrust-Health-Care/.

9 22 Cal. Code Regs. §§ 97435(a), 97440(a), 97442.

10 Rev. Code Wash. § 19.390.030; Healthcare Transactions Notification Requirement, Wash. Att'y Gen. (Accessed Jan. 31, 2024), https://www.atg.wa.gov/healthcare-transactions-notification-requirement.



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The hospital as a global institution

Hospitals are global enterprises. Like most industries in the 21st century, hospitals view "internationalization" as a fundamental business strategy.

At one time, hospital "internationalization" meant successful foreign patient recruitment, and even that was something of a luxury. Today, foreign patients are only one facet of a hospital's global aspiration.

Global advisory and consulting projects: As foreign governments and companies make deep investments in health systems infrastructure, hospitals are tapped to provide advisory services and technical support to arrayed projects abroad. Scopes of work range from how to design an emergency room to assessment of care models and clinical workflows. Some such projects also involve branding of foreign facilities and medical centers.

Global telemedicine: Modern technology has forever changed the delivery model. Remote second opinions, virtual services, and hospital-to-hospital telemedicine collaborations are flourishing across sovereign borders.

Global patient services: Revenue is mounting from foreign patients, particularly wealthy individuals who seek to travel for specialist "western" clinical services. Hospitals increasingly engage foreign employees, independent contractors, and marketing firms to socialize their in-patient specialties and liaise with current and prospective patients abroad.

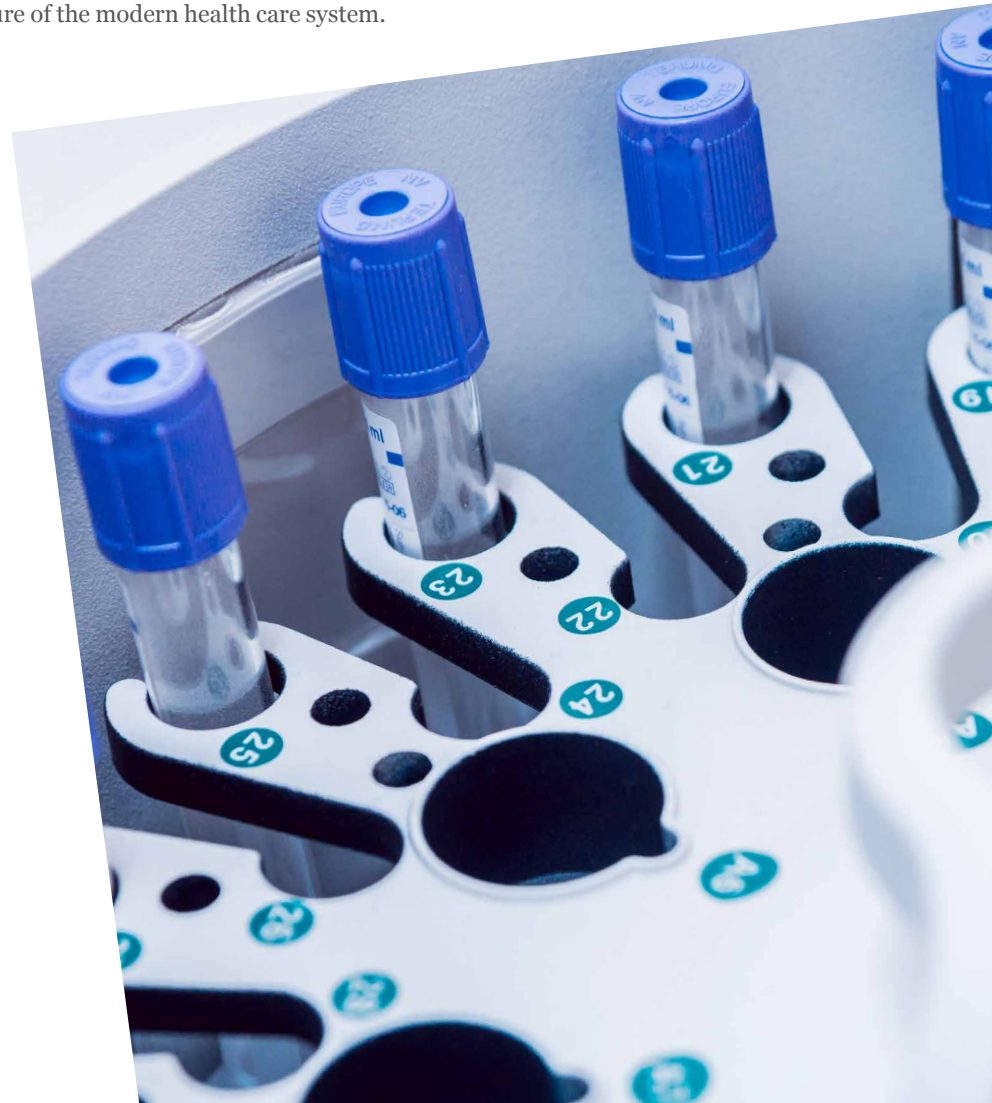
Global data initiatives: Multi-country transactions are underway to consolidate and monetize the rich repositories of patient data across academia, industry, and governments, holding great promise for the future of digital health.

Global capacity building and humanitarian projects: Hospitals are embedded in the United Nations' sustainable development goal to improve health outcomes in low and middle income countries. With U.S. government and related funding, providers are planting a flag in the Global South to drive health system strengthening.

Global research: Tracking foreign regulatory regimes – across privacy, tax, pharmaceuticals, devices, and more – is a full time affair for clinical trial professionals. On the flip side, concerns about inappropriate foreign influence, especially at U.S. hospitals, has ignited investigations into research compliance structures and national security.

Global clinical services: Physicians are traveling abroad daily for stints as "visiting physicians" at foreign institutions, or to backfill staffing at foreign locations. Often these programs stem from revenue-generating cooperations between hospitals and foreign Ministries of Health.

At a time when many hospital budgets are under pressure, the zeal for international activity has not abated. The diversity and variety of transnational initiatives give rise to numerous and complex legal issues. And laws of multiple jurisdictions factor in the analysis. Though the issues are many and outcomes are not perfect, a global footprint is a defining feature of the modern health care system.



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9 APAC

A spotlight on life sciences in Japan

With COVID-19 restrictions having been finally lifted in H1 2023, Japan and Japan's biopharma industry continue to generate renewed interest. From the perspective of Japanese Life Sciences companies, many appear re-energized and are now seeking cross-border opportunities, especially in the form of licensing transactions (especially in cell and gene therapy, regenerative medicine, oncology, and related fields) and other forms of collaboration.

We anticipate that international companies will still prioritize and invest in 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. Advocacy has continued for the maintenance of suitable pricing (price maintenance premium system) for innovative drugs, refinement of the system of repeated price cuts to patented medicines, and improvement of the Health Technology Assessment (HTA) processes; if successful, this may lead to improved commercial predictability and transparency, and thus some restoration of the Japanese market's attractiveness. There is continued desire to eliminate "drug lag," encourage simultaneous global development of drugs (with the relevant regulator seemingly recognizing the benefits of harmonizing Japanese rules and regulations more closely with those of other countries), and provide practical support for developing bioventures.

We expect continued focus on data privacy/protection, cybersecurity, digitization and digital health (especially wearable tech and personalized data-driven care), automation and artificial intelligence; there may also be a measured approach to addressing issues relating to access to medicines as well as unmet medical needs.

Originator versus generics patent cases are expected to endure. The "patent linkage" system has been under recent scrutiny following at least two on-going cases in which the relevant regulator apparently changed its policy and unexpectedly approved generic versions of originator products even though certain patent claims arguably covered the originator product. This has created some uncertainty for both originator companies (which may now query the precise scope of protection conferred by certain patent claims and potentially also the strategic investment in Japan more broadly) and generic companies (which may be forced to launch "at risk" and face heightened costs of patent litigation). We expect that the Japanese courts will help resolve this issue in the coming 12-24 months. In addition, 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. As in previous years, we recommend analyzing and assessing the practical impact of Japan-specific developments in due course.

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Band One for Life Sciences in Japan and Asia-Pacific in *Chambers Asia-Pacific*, 2024

Cell, tissue, and gene therapy opportunities in India

With the rising burden of chronic diseases, there is an increasing demand for innovative therapeutic approaches. India is emerging as a key player in the field of advanced medical treatments, given the available skilled scientific workforce and infrastructure resources. This is particularly true in the realm of cell and gene therapies.

Government support and private sector investment have helped advance developments in cell and gene therapies in India. For example, the Government of India is increasingly pushing towards conducting increased numbers of clinical trials in India. The Indian Council of Medical Research in 2019 issued the National Guidelines for Gene Therapy Product Development and Clinical Trials, which specifies the ethical, scientific, regulatory procedures, and requirements to be followed for developing and conducting clinical trial on gene therapy products in India. These guidelines were framed with reference to the U.S. FDA and EU guidelines on gene therapy.

Several clinical trials are currently being conducted in gene therapy for diseases such as hemophilia A, B-cell acute lymphoblastic leukemia, type-2 spinal muscular atrophy, and B-cell lymphoma, among others. Recently, in October 2023, India's first indigenously developed Chimeric Antigen Receptor T-cell (CAR-T cell) therapy earned approval from the Central Drugs Standard Control Organization, India's regulatory body for pharmaceuticals and medical devices. In the last few years, several products and procedures for oncology, immunocompromised diseases, and osteoarthritis have also been launched by Indian biopharmaceutical companies.

Considering that cell and gene therapies are still relatively nascent in India compared with the evolved approach in the United States and European Union, in particular, ongoing dialogue with regulators and industry participants at each stage of the product development process will facilitate advances in these technologies. Further, regulators and biopharmaceutical manufacturers in India can also take guidance from the already well-established FDA and European Medicines Agency guidance for compliance of such products.

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China's continuous efforts in improving the fast-track routes for drug marketing authorization

Recently, China's National Medical Products Administration (NMPA) and Center for Drug Evaluation (CDE) have issued several policies on the optimization of review and approval of drug marketing authorization, including, for example, the *Opinions on Reforming Review and Approval Process for Drugs and Medical Devices and the Announcement for Adjusting the Review and Approval of Drug Clinical Trials*. The release of these optimization policies aims to further improve the procedures of four fast-track routes available in China, namely, (1) Breakthrough Therapy Designation (BTD), (2) the conditional approval procedure, (3) the priority review procedure, and (4) the special review procedure for the drug marketing authorization established by the *PRC Drug Administration Law and the Measures for the Administration of Drug Registration* since 2020.

On 31 March 2023, the CDE issued the *Work Specification for Accelerating the Review of Innovative Drug Marketing Authorization Applications (Trial)* with immediate effect on the same day. This work specification is designed to expedite the review workflow of innovative drug marketing applications through early involvement, research and review coupling, rolling submission, and prior inspection. On 25 August 2023, the NMPA released the revised draft of *Review and Approval Procedures for Conditional Approval of Drug Marketing Applications (for Trial Implementation)* for public comments. This draft revised version provides certain definite responses to the opening issues regarding the drug conditional approval, which have not been addressed in the existing version issued by the NMPA in 2020.

The release of these new rules implies a significant acceleration in the progress toward the approval of drugs for pediatrics, rare diseases, and those granted BTD.

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China's regulatory pathways for cell therapy products

The development of cell therapy products has been a recent hot topic in China's life sciences industry. Generally, clinical research on cell therapies that do not aim for marketing authorization is regulated by the National Health Commission (NHC), while clinical trials of cell therapy products for the purpose of obtaining marketing authorization are regulated by the National Medical Products Administration (NMPA), following the application procedures for drugs.

In terms of clinical research, Chinese authorities released the *Administration Measures for Stem Cell Clinical Research (Trial)* in 2015, stipulating requirements on the clinical research institutions qualified for conducting clinical research, the application, review, and filing procedures for such projects, and certain other requirements during the clinical research process. Although this regulation is not applicable to stem cell clinical trials, it allows the submission of the clinical research results for supporting materials in applying for drug clinical trials aiming for product marketing authorization. In May 2023, the NHC released a draft *Working Guidelines for Somatic Cell Clinical Research (Trial)* (Working Guidelines) for public comments and later authorized the China Medicinal Biotech Association to issue the final and official version. Similarly, the Working Guidelines specify detailed requirements as to the constitutional and technical requirements to conduct somatic cell clinical research, and documentation materials required for pre-filing. In the application scope, the Working Guidelines mentioned that "the somatic cell clinical research administration cannot replace drug clinical trial administration," but it does not seem to clearly exclude the possibility that clinical research results can be used for supporting product clinical trials for product marketing authorization applications.

Certain cities, including Beijing, Shanghai, and Shenzhen, have also released municipal policies to incentivize the research and development of cell and gene products, for example, facilitating such products' application for marketing authorization.


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Drug and medical device advertising in China

Multinational life sciences companies considering commercializing products in China should familiarize themselves with the key rules governing the marketing activities of drugs and medical devices.

As a starting point, China requires the contents of advertisements for drugs or medical devices to be reviewed by the relevant authorities before publication. Specifically, any drug advertisement must receive prior approval by the competent provincial-level government and can only be based on the package insert pre-approved by the industry regulator, the National Medical Products Administration (NMPA). For medical devices, advertisers must obtain an "approval serial number" for the advertisement of a medical device. Such "approval serial number" is issued only after the contents of the advertisement have been examined by the local NMPA, and any subsequent alteration of the content will require reapplication for approval.

Given the lack of a comprehensive law coupled with rapid shifts in advertising channels and formats, it is challenging to keep track of all the regulatory requirements applicable to the advertising of drugs or medical devices in China. We have summarized the key requirements here.

Additionally, pharmaceutical companies operating in China usually engage in "academic promotion," which is a type of institution-to-institution, quasi-advertising activity that involves the exchange of scientific information. There are special rules governing the conduct of academic promotion. In general, academic promotional activities can only be undertaken by registered medical representatives who are professionals acting on behalf of a marketing authorization holder (MAH) by conveying, communicating, or collecting feedback information about drugs. It is important to note that academic promotion is not a sales activity. Therefore, medical representatives cannot perform drug sales, such as collecting payments or dealing with purchase/sales invoices.

China has ramped up the enforcement of pharmaceutical and medical device advertising regulations in the past few years and has gradually increased the penalties imposed on non-compliant advertisers, advertising agents, and publishers. However, challenges can bring opportunities. A well-rounded team of internal and external marketing experts, regulatory specialists, and legal advisors can help formulate promotional strategies that maximize the products' brand exposure while ensuring compliance with the evolving regulatory requirements.

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Life sciences beware as China tackles health care corruption

The Chinese government began a crackdown on corruption in the health care sector in 2023. Government authorities, including criminal and civil enforcement agencies in charge of overseeing health care, released joint statements on tackling corruption risks. Investigations and penalties followed. Hundreds of hospital heads were probed – many were stripped of public positions and imprisoned. Both multinational and domestic life science companies were implicated, for example, receiving dawn raids or inquiries from government authorities. Besides uprooting corruptive misconduct, the campaign also aims to reduce medical costs and stimulate consumption in light of a slowing post-COVID economic recovery because corruption, such as unnecessary tests and prescriptions, can drive up medical bills and inflate prices for consumers.

According to the National Health Commission, the campaign covers the entire industrial chain, including production, distribution, sales, and usage. Targets of this anti-corruption campaign include (1) industrial or academic associations' transfers of improper benefits, disguised as academic conferences and donations, to health care professionals, and (2) health care companies, distributors, and medical representatives giving kickbacks to health care professionals and tampering with the bidding and procurement process.

Under People's Republic of China (PRC) laws, bribery can trigger administrative liabilities and expose individuals and companies to criminal penalties, if certain thresholds are met. The newly passed 12th amendment to Criminal Law, which will take effect from 1 March 2024, increases penalties for bribery givers, especially for bribes that involve sectors such as social security and health care.

Beyond PRC law, life sciences companies, given their high number of touchpoints with government officials worldwide, face potential liability under various countries' laws, including but not limited to the U.S. Foreign Corrupt Practices Act (FCPA) and the UK Bribery Act. Cross-border collaboration among governments worldwide further poses serious challenges for life sciences companies. It's critical for multinationals to view anti-bribery and corruption issues as more than solely an FCPA concern.

The government's crackdown on corruption together with the wider world's increasing anti-bribery and corruption efforts create an uncertain outlook. Multinationals should be alert to the administration's efforts when issues are identified and brace themselves for potentially major international investigations. Anti-bribery and corruption enforcement regimes in many jurisdictions emphasize self-disclosure in exchange for leniency. While the benefits of voluntary self-disclosure are somewhat clear, for example, the decision whether to self-disclose is often less so. This further underlines the need to develop and maintain a rigorous, multidimensional compliance program.

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U.S. Foreign Extortion Prevention Act and its likely impact on life sciences companies, particularly in Asia

Late in 2023, President Biden signed into law the bipartisan Foreign Extortion Prevention Act (FEPA, or the Act). Within the Act, provisions seek to criminalize the demand-side of foreign bribery by making it illegal for any foreign public official to corruptly demand or accept a bribe from a United States (U.S.) person or company in exchange for influencing an official act, favors, or an improper advantage. The penalty is $250,000, or three times the item of value, or up to 15 years in prison.

The 1977 Foreign Corrupt Practices Act (FCPA), seen as a benchmark law with extra-territorial international impact in anti-bribery and corruption, prohibits the payments to foreign officials as one of its headline provisions. The FCPA had not provided for the demand element by a foreign official (something that is present in one of the other primary international benchmark laws: the UK Bribery Act). Like the FCPA, the conduct considered under the Act need not take place in the U.S.

Coupled with other enforcement tools - consider the deployment of sanctions on oligarchs and state officials in the wake of Russia's invasion of Ukraine - the Act is another weapon in the arsenal against foreign officials. Money laundering offenses and fraud have been the traditional route for enforcement against foreign officials. Those offenses, though, are often limited to proving transactions occurred through the U.S. financial system. The Act does not have that requirement and can therefore be a supplement to existing enforcement strategies.

Now, in theory, this Act is significant in extending the possible targets of U.S. enforcement, but it does raise questions on how enforcement will actually take place, and is set in a complicating diplomatic angle. Even if a foreign public official is alleged to have requested an improper payment, would the U.S. Department of Justice (DOJ) succeed beyond charging foreign officials? Imagine the geopolitical consequences of naming an ally or enemy's public official in an indictment. We will need to see how this element of the Act plays out, but we suspect it is likely to lead to international cooperation between government agencies on bribery allegations (which itself may lead to domestic enforcement in local nations).

This will impact life sciences companies in that (1) there may be confusion in local markets as to what is the impact of the Act on future business; (2) many Asian life sciences and health care organizations or personnel are State-connected, and therefore would classify as public officials; and (3) this may result in more proactive disclosure of improper conduct as this builds cooperation with the regulator, though may impact peers. Suppose a public official physician in Vietnam or in China has demanded a bribe or extravagant beyond-business norms hospitality, the company experiencing that conduct may report it. We expect the DOJ to ask soon thereafter if the company knows which other U.S. persons or companies do frequent business with that doctor.

In recent years, we have witnessed and are advising various life sciences companies in Asia – in India, Southeast Asia, and China – who are in the crosshairs of FCPA enforcement. Life sciences companies with a nexus to public officials are an enforcement hotspot, and FEPA fans those flames.

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10 Cross-jurisdictional

Life sciences exports in an era of geopolitical risk

Exporting clinical products is increasingly fraught with trade-related risks.

With Russia's invasion of Ukraine, western countries have imposed broad and deep sanctions on exports to Russia, certain regions of Ukraine, and Belarus, which make certain clinical exports practically difficult, or even outright illegal. For example, trading with these territories often involves payments to Russian banks, many of which are subject to UK, U.S. and/or EU asset freezes. More broadly, it is often the case that while a medical product is not sanctioned (as is generally the case for medicine to Russia), associated items such as packaging or temperature monitors required to accompany such items are.

Relatedly, life sciences companies often have to contend with a myriad of similar, but different, sanctions regimes in exporting their products; by way of illustration, while EU sanctions generally exempt exports where they are for medical or pharmaceutical purposes (provided certain requirements are met), UK sanctions do not.

Life sciences companies exporting to these high-risk locations have often adopted policies and procedures to ensure they comply with the ever-evolving sanctions landscape. However, such companies should not forget the ongoing need to comply with export controls.

Export controls, which can be of global application, are intended to regulate the export of certain products, software, or technology which could have military applications; however, they do not have to be designed, or in fact used, for such applications. Health care-related products, be it complex machines or certain vaccines, can be subject to requirements to obtain authorization prior to export. While export controls are often conceived of in the context of the physical export of products, technology (broadly, know-how) can also be "exported", including via a simple e-mail or phone call.

Whether because of the difficulty in determining which, if any, state license is required, or simply a lack of awareness as to the requirement generally, many companies have left state licensing unaddressed and many states are paying an increasing level of attention and are increasingly pursuing enforcement action instead of being satisfied with companies remediating the situation.

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Band One for Life Sciences: Multi-Jurisdictional in *Chambers Global*, 2024

Navigating the digital age: A comparative approach to pharmaceutical advertising on social media

The promotion of non-prescription medicines via online social media networks has been an increasing reality in recent years.

The primary advantage of utilizing social media networks lies in the opportunity to connect with a vast number of potential users. Conversely, the drawbacks of engaging in social networks (which includes posting, sharing, liking, tagging, etc.) are that they enable users to freely express their opinions and the rapid generation of new content, which may not adhere to applicable laws. This has led to the need for new guidance on how such promotions are regulated.

In Italy, with effect from July 2023, the Ministry of Health updated the Guidelines on the promotion of medicines not subject to prescription to include rules on promotions published on social media networks. The Guidelines ruled that: i) advertising of non-prescription medicines is only allowed on the social media networks cited by the Guidelines; ii) comments and reaction functions (such as likes, emoticons) should be turned off; iii) the sharing function should be deactivated; and, when this is not technically possible (*e.g.*, on Facebook), the advertising message must contain a proper disclaimer. Restrictions on non-prescription medicine advertising related to testimonials and influencers also apply to advertising on social media networks.

In France, rules on advertising of medicines on social media have recently been strengthened. Advertising of medicinal products is subject to strict regulations provided by the French Public Health Code, which applies to all types of advertising of medicines without regard to the means or platform on which the advertising is displayed.

In addition to this existing regime, a recent law dated 9 June 2023 has been adopted in order to regulate commercial influence on social media. Among the general rules edited in order to create a specific regime applicable to commercial influence practices on social media, this law provides for specific rules applicable to some sectors. With regards to medicines, this new law has extended the application of the current regulations on the advertising of medicines, as provided in the French Public Health Code, to social media influencers in their activities when they promote medicines. Social media influencers have, therefore, been included in the scope of the stakeholders required to comply with regulations on the advertising of medicinal products.

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Navigating the digital age: A comparative approach to pharmaceutical advertising on social media (continued)

In Germany, advertising – whether intentional or not – of a pharmaceutical company or third parties by use of social media is not specifically regulated but falls, as any other pharmaceutical advertising, within the application of the German Healthcare Advertising Act *(Heilmittelwerbegesetz, HWG)* and the general rules of the German Unfair Competition Act *(Gesetz gegen den Unlauteren Wettbewerb, HWG)*. While some provisions of those acts also apply to other forms of advertisement, the ban on advertisements involving influencers and other celebrities and the prohibition of disguised advertisements is particularly important in the social media context.

In Belgium, there are no specific rules regulating the promotion of medicinal products on social media. The general rules for advertising of medicinal products, as provided in Article 9 of the Belgian Law of 25 March 1964 on medicinal products for human use and the Royal Decree of 7 April 1995 regarding information and advertising of medicinal products for human use, apply. In addition, the Federal Agency for Medicines and Health Products (FAMHP) provides key guidance on its website, outlining the mandatory information that must be included in online advertising. In Belgium, only non-prescription medicinal products may be advertised to the public. Advertisements broadcast by other media than radio and television, must be notified to the FAMHP at least 30 days before they are broadcast.

In Spain, there are no specific rules regulating the advertising of medicinal products on digital and social media – the general rules for advertising of medicinal products apply. In addition, various authorities have published guidelines on the advertising of medicinal products in digital and social media that should be reviewed before launching an advertising or information campaign. In general terms, digital and social media could be used for (1) institutional advertising, (2) projecting the company's image, (3) providing health-related links or information, or (iv) in some cases, advertising and/or information on prescription medicinal products in restricted environments. Conversely, digital and social media should not be used for (1) advertising and/or information on prescription medicinal products in non-restricted environments, (2) providing information on treatments of prescription medicinal products, (3) publishing content that may create unnecessary social alarm, or (4) adding the 'link' icons on websites where advertising and/or information on prescription medicinal products aimed at health care professionals (HCPs) is displayed.

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Navigating the digital age: A comparative approach to pharmaceutical advertising on social media (continued)

In the Netherlands, direct-to-consumer promotion of over-the-counter (OTC) medicinal products through social media is permitted. It should comply with both the Code for Promotion to the Public of Medicinal Products and the Advertising Code Social Media and Influencer Marketing, both self-regulatory industry codes of conduct. For prescription-only medicinal products, any communications on social media should not be promotional, in order to steer clear from the prohibition of direct-to-consumer promotion. Not only pharmaceutical companies should pay attention. Individual employees of pharmaceutical companies in the Netherlands have also been held to violate the advertising rules due to posts, likes, or shares on social media.

In the UK, the promotion of medicines on social media platforms is permitted and is subject to the same legal framework that applies to the promotion of medicines generally. The open and transitory nature of social media platforms makes compliance with this framework, and in particular the prohibitions on the promotion of prescription only medicines to the public and the promotion of unlicensed medicines or indications, challenging. To assist, the Prescription Medicines Code of Practice Authority (PMCPA) published social media guidance in 2023 that provides practical guidance to pharmaceutical companies on this issue. A growing risk area for pharmaceutical companies in the UK is responsibility for the posts/activities of employees on social media platforms where there is an overlap between employees' personal use of social media and their "professional responsibilities or the interests of the company". Pharmaceutical companies should have in place comprehensive social media policies that extend to employees' personal social media accounts and provide training to employees on these policies and issues, to help mitigate this risk.

In the U.S., FDA's Office of Prescription Drug Promotion (OPDP) appears to be ramping up activities in the advertising/promotion enforcement space, including by issuing several new guidance documents. OPDP issued enforcement letters against Instagram "influencer" advertisements in 2015 and 2021. However, OPDP has not updated its June 2014 draft guidance on Internet and social media platforms with character space limitations, despite the rise of several new platforms in the past decade. It remains to be seen if there will be an uptick in enforcement against social media activities by pharmaceutical companies.

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Navigating the digital age: A comparative approach to pharmaceutical advertising on social media (continued)

In Japan, there is no difference between social media communications and other types of communications. As such, social media communications in respect of medicinal products would typically be subject to the general legal framework applicable to communications about such drugs, in particular the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (PMD Act) and the Standards for Appropriate Advertisement of Drugs, etc. (Appropriate Advertisement Standards). According to the PMD Act, advertisement or promotion of unapproved drugs is prohibited. Furthermore, advertisement or promotion of prescription-only-drugs to the general public (excluding HCPs) is not permissible under the Appropriate Advertisement Standards. In contrast, advertisement of OTC drugs to the general public is permissible, but this remains subject to strict regulations, including the PMD Act and Appropriate Advertisement Standards; misleading or exaggerated advertisements are prohibited, for instance. The definition of product advertisement or promotion is interpreted rather broadly in practice in Japan, which makes it even more important for companies to establish and enforce clear internal policies about the sharing of information about medicinal products via social media and to continue to educate and monitor accordingly.

Since the dissemination of advertising messages through social media networks knows no boundaries and the possibility of reposting messages from countries different from those in which the message was created, published, or intended can impact the applicable law, identifying the applicable regulations, and adopting safeguards to reduce the risk of violating various regulations in the countries where the message might be spread is one of the most significant challenges for pharmaceutical companies. Furthermore, considering that the risks of breaches for pharmaceutical companies can also arise from employees publishing and sharing activities on their personal accounts, to mitigate these risks it is essential to establish comprehensive social media policies that cover employees' personal social media accounts and provide training about these policies and related issues.

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Organizational means to efficiently handle social media, apps, and website projects in the legal department

Legal departments in pharmaceutical or medical device companies are often confronted with new media projects of their internal clients. Such projects may be the establishing of a social media platform or a new website, introducing apps for health care professionals (HCPs) or patients as well as use of influencers. Usually, several departments within a company are involved in such projects, since they touch upon various aspects like promotional compliance, HCP compliance, public relations, IT, privacy, pharmacovigilance – and legal. Often, the project management by the responsible department is poor or non-existing and such projects need to be handled under time pressure. In an effort to get a project legally right, a legal department often finds itself being pushed into the undesired role of the project lead, collecting information required, checking involvement of various stakeholders concerned, etc. – in order to grant approval for a project to go live.

However, there are means to handle these situations. The key solutions are organizational and procedural means which the legal department would implement. The overarching aim would be to provide the key stakeholders with means to be able to take their responsibilities. Hereby the legal department would achieve not being pushed into the driver's seat.

- Once the request to approve a new project comes in, the legal team should have a questionnaire which is handed over to the project lead. Therein, the questions on the objectives of the project, target groups, the timelines and other relevant aspects would need to be clarified; the project would need to be clearly described taking all relevant aspects into account. The project lead would need to be defined.
- Based on that questionnaire, initial advice by the legal department could be provided.
- The questionnaire would then be supplemented by a checklist which the project lead would need to process.
  - The checklist would force the project lead to consider which departments in the company need to be involved and whether this has already happened.
  - Further, the checklist would request the project lead to tick-box of aspects including: terms of use, privacy, cybersecurity, pharmacovigilance, third-party-vendor due diligence, third party content and copyrights, trademark use, confidentiality of company information, HCP, and promotional compliance, handling inappropriate content, etc.
- Only once the checklist is properly processed would the legal department get more closely involved in legally assessing the project and eventually approving the project.

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Possibly significant changes to U.S. and EU orphan drug regulation may be looming

Events over the past year suggest 2024 will bring heightened attention – and perhaps meaningful changes – to the orphan drug regulatory schemes in the U.S. and the EU. Authorities seem to be seeking to adjust the balance between creating incentives for orphan drug development and allowing competing products to come to market. Recent events that may signal upcoming significant changes include:

U.S.

- in December 2023, FDA finalized a guidance document providing additional flexibility in the regulatory standards for drugs intended for subsets of rare diseases, including with regard to nonclinical data and programs for expediting development.
- a recent FDA decision – being challenged in court – suggests the agency is changing the standard for breaking a competitor's orphan exclusivity and awarding a new exclusivity period by a finding of clinical superiority by way of a major contribution to patient care. A number of core FDA and administrative law issues are at play here.
- in denying a rare pediatric disease priority review voucher for a gene therapy product, FDA took an approach to defining sameness of active ingredient that seems difficult to reconcile with views on the topic expressed in a relatively recent guidance.
- a provision in the Inflation Reduction Act (IRA) that exempts certain orphan products from being subject to price negotiations is leading some companies to rethink strategies for product development. The provision, which would seem intended to create incentives for orphan drug development, may actually be leading companies to stop investigating products for second orphan uses.

EU

- The European Commission published proposed legislation that would reduce the availability and benefits of orphan market exclusivity. Proposed changes include:
  - reducing the standard orphan exclusivity period to nine years (from 10, which would be reserved for products addressing a high unmet need).
  - limiting applicants to a maximum of two one-year extensions of exclusivity for subsequent orphan approvals (rather than the full additional period of exclusivity currently available with each such approval).
  - allowing competitors to apply for marketing authorization during the exclusivity period (rather than waiting until the end of exclusivity before submission).
  - dropping the two-year extension of exclusivity for completing pediatric studies.

Especially because the nature, extent, and timing of any changes are uncertain, the strategic implications can be important for products in all stages of development, and merit attention.

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Seismic shifts in drug pricing

The policy and regulatory frameworks for drug pricing in the U.S. and UK are undergoing significant changes, setting a precedent which regulators in other markets are likely to follow.

In the U.S., all eyes are on the implementation of the drug price negotiation provisions of the Inflation Reduction Act (IRA), with "negotiations" currently being underway for the first ten drugs and the resulting "maximum fair prices" (MFP) set to be announced by 1 September. The MFP for each drug will be scrutinized by the market in an effort to divine the Centers for Medicare and Medicaid Services' (CMS) reasoning, and the impact of those prices on commercial markets and generic/biosimilar launches will be closely tracked. Finally, the IRA's impact on industry investments will continue to be monitored. Proposed legislation to address the "small molecule penalty", by lengthening the nine-year negotiation timeline for small molecules to the same 13-year period as biologics, is a priority for industry but that doesn't mean Congress will act on it, particularly in an election year where President Biden has made drug pricing a central pillar of his campaign.

Activity at the state level has the potential to be as impactful. In the spotlight are state prescription drug affordability boards, (PDABs), and in particular those with authority to set upper payment limits (UPLs) on drugs deemed "unaffordable". Colorado is the first state out of the blocks to move toward the setting of UPLs on brand products, which effectively cap the price at which a manufacturer can sell a product to anyone in the state and are expected to be lower than commercial prices. Due to a requirement that manufacturers extend their lowest or "best price" for a drug to all state Medicaid programs, these UPLs are likely to end up impacting prices nationwide. As with manufacturer court challenges to the IRA, expect litigation challenging these laws as well, particularly as they proliferate across the country.

In the UK, drug pricing is controlled indirectly through rebates payable on sales of branded medicines to the National Health Service (NHS), the largest single customer in the UK. The rebates are set out in a voluntary scheme negotiated between the UK government and industry, or in the default statutory scheme that applies to companies not in the voluntary scheme.

The voluntary scheme has recently been renegotiated, with the new Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG) in place from 1 January 2024. For the first time ever, the voluntary scheme now differentiates between "newer" and "older" medicines, with similar changes to the statutory scheme expected in the coming months.

Under the previous voluntary scheme, all companies paid the same fixed percentage rebate on their in-scope sales. Under VPAG, the rebate percentage will now vary by product, meaning each company will pay a different overall rebate percentage based on their specific product portfolio.

The rebate percentage payable for "newer" medicines, being for the first 12 years after marketing authorization grant or until the expiry of any applicable Supplementary Protection Certificate (SPC), will be a single rate that varies from year to year calculated on the difference between the allowed NHS growth in sales and actual NHS spending. The percentage rebate for "older" medicines will be a basic rate plus a "top-up" rate based on a sliding scale determined by observed price decline.

The U.S. and UK examples represent fundamental shifts in national policy on regulating the pricing of innovator, generic, and biosimilar medicines – a shift that is likely to influence drug pricing policy and regulation globally.

Band one for Life Sciences & Pharmaceutical Sector (International & Cross Border), *Chambers USA-Nationwide*, 2024

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11 Europe

Digital and circular economy: EU updates common liability rules

To adapt Europe's product liability landscape to the digital age and the circular economy, the European Commission proposed new rules in September 2022 to deal with liability claims for defective products, including life sciences and health care products, product updates, and AI systems:

- a revised **Product Liability Directive,** building on the strict liability rules for defective products known since 1985 while modernizing their scope to encompass digital products, circular economy business models and global supply chains
- a first of its kind **Artificial Intelligence Civil Liability Directive,** targeting harmonization of the member states' national fault-based liability rules for AI-enabled products and services which will be closely related to the recently adapted European AI-Act.

In the course of the EU legislative process, the EU Council adopted its common position on the **Product Liability Directive** proposal in June 2023 and the EU Parliament adopted its report in October 2023. Lastly, in the so-called "trilogue", the EU co-legislators reached a political agreement on the revision of the Product Liability Directive on 13 December 2023. The agreed final text is not publicly available yet. It still needs to be formally adapted by the EU Parliament and the EU Counsel, before being published in the EU's Official Journal.

The EU legislative process for the **Artificial Intelligence Civil Liability Directive** is still underway but could also be concluded shortly, possibly in Q1 2024.

Once the final texts have been adapted at EU level, the new rules will have to be transposed into the national liability systems of the Member States.

To better protect consumers from damages caused by defective products the current common product liability rules will be updated in many ways, including:

- the definition of product will be extended to include digital manufacturing files and software (excluding free-of-charge open-source software);
- the definition of damage will be extended to included medically recognized damage to psychological health, destruction of data as well as non-material losses;
- the new rules shall ensure that there is always an EU-based business, such as a manufacturer, importer, or their authorized representative that can be held liable for a product that caused damage, even if the product was not bought in the EU;
- additional economic operators substantially modifying and then marketing or putting into service the product (circular economy) may also face liability; and
- the longstop for product liability claims shall be extended to 25 years in exceptional cases.

With the declared aim of putting consumers on an equal footing with defendants and to ease their burden of proof – in particular in cases where discharging it would be excessively difficult according to the European legislator (as arguably in most life sciences and health care cases) – both Directives introduce novel procedural mechanisms, as in particular:

- member states must ensure that their national court's ruling on compensation claims have procedural mechanisms at hand to grant consumers access to necessary and proportionate evidence at businesses' disposal;
- national courts shall allow claimants to rely on rebuttable presumptions:
  - for the defectiveness of the product or for the causal link between the alleged defect and damage; and
  - for the causal link between non-compliance with a duty of care and damage,

  when discharging their respective burden of proof.

For the European legislator, the reform aims at reducing legal uncertainty and fragmentation of the product liability regime across Europe. However, the proposed changes, including the novel procedural mechanisms to be introduced, may well first have an opposite effect. They could result in:

- forum shopping in Member States where judges are known to have a more pro-plaintiff approach;
- more complex and burdensome disputes, both procedurally and on the merits; and
- shifting the battlefield from defect, fault, and causation to the application and rebuttal of corresponding presumptions.

Businesses operating in the EU life sciences and health care sectors should be prepared for the entry into force of these Directives and the respective changes they will likely bring to the existing Member States' national civil liability rules.

Hogan Lovells' Product Liability Team will continue to monitor this update of the EU's common liability rules, both at EU level and regarding their implementation by Member States' after entry into force. Check out our regular updates on Hogan Lovells Engage.

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Early access in Europe: New schemes and trends for compassionate provision of unapproved product

There is an increased number of medicinal products for unmet medical needs in late stage clinical development or under pending marketing approval in the European Union. Some of these products may already be author in the U.S., but not yet in Europe. These are the situations where increasingly informed patients seek for access to these products – and treating physicians requesting compassionate supply by the respective pharma and biotech companies. We see an increased trend at our companies to affirmatively address these requests for ethical reasons but also, where possible, to generate early revenue.

In each of the European jurisdictions there are schemes to make product available prior to marketing approval. Often, patients can even receive reimbursement for the costs of such products. While the approach of companies may be to make the product available across Europe or even beyond, each jurisdiction has its own schemes which vary significantly. Taking two examples, Germany and France:

In Germany, early access via importing commercial product from countries where the product is already authorised, often the U.S., allows companies to generate revenue and patients a chance to receive reimbursement. The other scheme for wider compassionate use programs for patient cohorts, however, stipulates that the product has to be provided by the company free of charge. However, it may still be ethical and commercially viable, also considering a later commercial launch in Germany, to supply product under this scheme.

In France, the situation is different and two categories of early access programs are available: (1) “compassionate access”, designed for a specific patient at the request of a prescriber; originally, the “compassionate access” was intended for products at an early stage of development in Europe (often authorized in the U.S.) but is now authorized much more widely by the French authorities. The second is “early access”, which allows a cohort of patients to be treated even before marketing authorization. The distinctive feature of these two systems compared to other European schemes is that they allow companies to set a temporary sales price, subject to substantial clawbacks once the reimbursement price has been negotiated. In the case of “early access", the company also undertakes to finance the collection of data to be used in the scientific evaluation of the product.

In other jurisdictions, again, the situation is different.

We have done research on the different schemes applicable in many jurisdictions. Further, we conducted audits with clients on the compliant implementation of early access throughout the world. In this regard, please refer to the article on “Compliance and overarching recommendations for early access” in our brochure “Early access to pharmaceutical products in major European markets”.

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EU regulatory data exclusivity under the EU Pharmaceutical Law Package

In an effort to make medicinal products in the European Union more accessible, affordable and innovative, the European Commission published a proposal to reform the EU's pharmaceutical legislation (Pharmaceutical Law Package). The proposal, which was published on 26 April 2023, is expected to drastically change a number of topics within pharmaceutical law. One of the main topics being regulatory exclusivity rights – more specifically – regulatory data protection (RDP) and orphan market exclusivity (OME).

RDP: The current standard period of RDP of eight years will be reduced to six years. Extensions would be possible if:

- the product is launched and continuous supplied in all 27 EU Member States (two year extension);
- the product addresses an unmet medical need (six months extension); and/or
- comparative clinical trials are conducted (six months extension).

A further extension, on top of the baseline and possible additional protection period, could be available if:

- a new therapeutic indication with significant clinical benefit compared to existing therapies is approved (one year extension).

OME: The current baseline of ten years is reduced under the proposal to nine years for most orphan medicinal products. This market exclusivity period can also be extended under certain conditions. Under the proposal, there will not be any separate 10 year orphan market exclusivity periods for new orphan indications: those would only result in a one year extension.

Concerns have been raised that the conditions for obtaining any of these extensions are uncertain and complex. For example, the extension for the launch in all EU Member States within two years after marketing authorization is controversial, due to hurdles in opportunity for effective launch, also due to different and time-consuming procedures for pricing and reimbursement in the various EU Member States.

For 2024, it is expected that political debate and policy advocacy around the Pharmaceutical Law Package will continue, resulting perhaps in amendments to the proposal. If and when adopted, there will be a transition period. Nevertheless, the new protection periods for regulatory exclusivity rights could potentially affect protection of current pipeline products. When developing and investing in novel products, it is recommended to already take into account the potential modifications and reductions in EU regulatory exclusivity rights.

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France implements stringent measures to address medicinal product shortages: Impacts on pharmaceutical industry

The legal and regulatory framework aiming at addressing medicinal product shortages in France has been recently completed with a particularly stringent measure impacting the pharmaceutical industry. Since the adoption of a law dated 26 December 2023, pharmaceutical companies marketing mature medicinal products of major therapeutic interest (MITMs) may be forced to find a buyer if they wish to suspend or cease the marketing of such MITM, under specific conditions. This requirement applies when available alternatives do not permanently cover the medical needs.

In addition to the current declaration of suspension or ceasing of MITM marketing, companies will now need to submit an analysis of the foreseeable impact on the French population's needs in case of such suspension or cease. If the French National Agency for Medicines' and Health Products' Safety (ANSM) considers the available alternatives insufficient, the marketing authorization holder (MAH) must notify potential buyers for taking over the marketing of the concerned medicinal products, respond to each offers received, and provide necessary information to enable the buyer to acquire and market the MITM. The marketing authorization holder has a nine month timeline for notifying the ANSM of the offer it intends to accept.

This new obligation is particularly challenging for pharmaceutical companies for the following reasons:

- the timeline is particularly short considering the timing usually required in the context of a business transfer;
- companies targeted by this new regime are often facing economic difficulties, are in an unfavorable competitive context, and would therefore be weakened by this new procedure as their power of negotiation with potential buyers would be particularly decreased. Such system could potentially benefit companies interested in acquiring MITMs at lower prices;
- this new procedure seems better suited for long-term sales rather than temporary suspensions;
- the ANSM's discretionary attributions limits companies' visibility and ability to plan;
- disclosing strategic information during negotiations may weaken companies or compromise sensitive data;
- if no buyer is found, companies may have to provide the medicinal product for the French market, free of charge, to a public entity for up to two years, with financial penalties for non-compliance;

In addition, the ANSM can unilaterally categorize medicinal products as MITMs, adding unpredictability and complexity for companies.

An implementing decree is awaited and will provide for detailed criteria and conditions under which this new procedure will be applied.

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France's new 2024 security finance bill for 2024 comes into force: Between promoting therapeutic innovation and budgetary constraints...

One of the most controversial aspects of the new law concerns the so-called “safeguard clause”, the mechanism for financial regulation of the pharmaceutical product market, which in recent years has reached record levels in terms of the financial burden imposed on French pharmaceutical companies. This mechanism has been thoroughly overhauled to correct one of its main criticisms, namely its opacity. From now on, it will be based on the amounts reimbursed by health insurance for pharmaceutical products, rather than sales. However, this reform is only a superficial solution to the imperfections of the system, and the litigation initiated several years ago by pharmaceutical companies against the Ministry of health will continue.

Several measures have also been introduced in line with one of the French government's priorities: the security of supply for all patients. These include the obligation to find a buyer in the event of end of the marketing of a product of major therapeutic interest having lost its patent, and measures in favor of hospital preparations, which are open to challenge.

Substitution of biosimilars is also to be extended, with a new system of “automatic” substitution at the end of a two-year period during which the biosimilar is marketed. However, this automaticity is relative, and the complexities and administrative authorizations remain.

As for early access, this has been strengthened, with an obligation for pharmaceutical companies that sign up to this attractive system to supply all patients. Pharmaceutical companies must therefore be sure of their production capacity before applying for early access.

The mechanism for setting the price of innovative therapies had also been extended to include the collection of real-life data, but the French Constitutional Council censured this measure, which will therefore not come into force.

Finally, “anti-waste” measures have been introduced, with the welcome inclusion in the criteria for setting the price of innovative medical devices of the health authorities’ assessment of their ecological performance - a future-oriented subject in line with the French government's roadmap.

In short, innovation in health care products is still at the heart of the French government's concerns, albeit with severe budgetary constraints and funding obstacles.

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New European Commission's proposal amending the MDR and IVDR

In January 2024, the European Commission (Commission) published a proposal for a Regulation extending the transitional periods for certain In Vitro Diagnostics (IVDs), providing for the gradual roll-out of the European database on medical devices (EUDAMED) platform and also laying down certain information obligations for manufacturers in case of interruption of supply.

Extension of the transitional periods for IVDs

Under the proposed Regulation manufacturers will have additional time to bring their IVDs into compliance with the IVD Regulation (IVDR). The new timelines, similar to what is currently provided in the IVDR, will depend on the IVDs' risk class:

- Class D IVDs: transition period until 31 December 2027;
- Class C IVDs: transition period until 31 December 2028;
- Class B IVDs and sterile Class A IVDs: transition period until 31 December 2029.

As regards "in-house IVDs", health institutions will now have until 31 December 2030 (instead of 26 May 2028) to demonstrate that there is no alternative and equivalent commercial device on the market to address the target patient group's specific needs.

EUDAMED

Under the current rules, the use of EUDAMED will only be mandatory once all modules are functional. The proposed Regulation intends to accelerate the launch of the parts of EUDAMED that are already finalized, allowing the mandatory use of several modules as of late 2025.

Information obligation in case of interruption of supply of certain medical devices and IVDs

The proposed Regulation intends to amend the Medical Devices Regulation (MDR) and IVDR and include a new article (Article 10a) requiring that when manufacturers anticipate an interruption of the supply of a medical device or IVD and where it is reasonably foreseeable that this interruption may result in serious harm or a risk of serious harm to patients or public health in one or more EU Member States, manufacturers shall notify the anticipated interruption (at least six months in advance) to the competent authority of the EU Member State where they are located, as well as to the economic operators, health institutions and health care professionals (HCPs) to whom they directly supply the device or IVD. Economic operators (including importers and distributors) who have been notified by the manufacturer shall also inform any other economic operators, health institutions and HCPs to whom they directly supply the device or IVD.

The proposed Regulation will now be put forward to the European Parliament and Council for adoption.

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UK CMA guidance on collaborations facilitating provision of combination therapies

On 17 November 2023, the UK Competition and Markets Authority (CMA) published a statement confirming that, provided certain conditions are met, it will not prioritize the investigation of commercial negotiations and agreements between medicine manufacturers which aim to make life-saving combination therapies available to the National Health Service (NHS).

The issue

There are typically two prices for a patented medicine available on the NHS: a public list price determined by the manufacturer, and a confidential discounted price agreed between the manufacturer and the NHS which meets a 'cost-effectiveness' threshold. Combination therapies (involving two or more separate therapeutic agents used together) must meet this 'cost-effectiveness' threshold in the same way as monotherapy treatments.

Complications arise with this pricing structure where the confidential price of the existing 'backbone' treatment is already at or near the 'cost-effectiveness' limit, leaving little room to accommodate the cost of the 'add on' treatment of the combination therapy. The manufacturer of the 'add on' treatment may therefore be required to lower the price of its own medicine in some cases to the point of commercial nonviability.

A commercial agreement on pricing between the respective medicine suppliers is therefore often the only means by which the parties can reach a satisfactory solution. However, the perceived risks of competition law infringement have to date acted as barriers to these commercial discussions.

The CMA's guidance

The Association of the British Pharmaceutical Industry (ABPI) has developed a negotiation framework for the purpose of these arrangements. So long as this is followed, the CMA will not prioritize investigation of any required exchanges of information during negotiations or subsequent agreements whereby the manufacturer of the already-supplied medicine agrees to pay to the manufacturer of the 'add-on' medicine an amount per patient to compensate for the necessarily low price at which it must supply the NHS.

While competition law is only one challenge faced by manufacturers attempting to bring combination therapies to market, the CMA's statement provides much-needed guidance and clarity on this key issue for the industry. It is the first of its kind worldwide and opens the door for more NHS treatments for cancer and other serious health conditions. It will be interesting to see whether other competition authorities follow suit, and whether the CMA decides to extend a similar self-assessment framework for the private sector.

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UK: Delivering on regulatory flexibility

The UK Government committed in its Life Science Vision to deliver a progressive regulatory environment in the UK post-Brexit to support innovation and accelerated access to new medicines and medical technologies.

In line with this, the UK regulatory environment for medicines and medical devices is undergoing significant changes, providing new opportunities such as enabling companies to apply for UK authorization based on a product authorization from another trusted market, allowing medical devices companies with additional time to transition to the future requirements, and providing more detailed guidance to support compliance of AI and software medical devices.

The regulatory measures introduced in the UK include:

- the International Recognition Procedure (IRP): From 1 January 2024, an expedited pathway to obtain a marketing authorization is available for medicines that have already been approved by a "Recognised Regulator" in Australia, Canada, the European Union, Japan, Singapore, Switzerland or the United States. Approvals will be granted in accordance with a 60-day or 110-day timetable, depending on the product type and the time since its approval by the relevant Recognised Regulator. The IRP can be used for innovator, generic and biosimilar applications as well as line extensions and variations;
- a shorter standard marketing authorization process which has a 150-day application timetable rather than 210-day;
- a rolling review (RR) process for marketing authorizations involving a phased approach where the applicant can submit modules of the electronic Common Technical Document (eCTD) dossier in separate parts for pre-assessment rather than waiting to make a full consolidated submission;
- the Innovative Licensing and Access Pathway (ILAP): Under ILAP, medicines in pre-clinical or clinical development that qualify for an "Innovation Passport" benefit from an accelerated pathway to market. The UK medicine regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), and partners including the National Institute for Health and Care Excellence (NICE), create a "Target Development Profile" that sets out a product-specific licensing and access plan;
- participation in Project Orbis which is a program co-ordinated by FDA to improve the efficiency of regulatory submissions and assessment of promising new oncology products;
- as well as procedural changes to better align the submission of clinical trial authorization with ethics committee approvals and marketing authorizations with the health technology assessment (HTA) process.

There are also significant changes in relation to the regulation of medical devices, with the Innovative Devices Access Pathway (IDAP) offering a supported research and access route for innovative medical devices through the creation of a Target Development Profile (TDP) and a roadmap for reforming UK medical device legislation to more closely align with current EU medical device legislation, but with greater flexibility and more detailed guidance for software and artificial intelligence as a medical device.

A key question over the coming years will be how the UK responds to regulatory changes in other markets, in particular to the proposed revision of data and market regulatory exclusivity periods in the EU's pharmaceutical legislation. UK regulatory exclusivities currently remain aligned with the existing EU position and any decision to change or not to change these in the UK will need to balance the stated aims of supporting innovation and accelerating access for patients.

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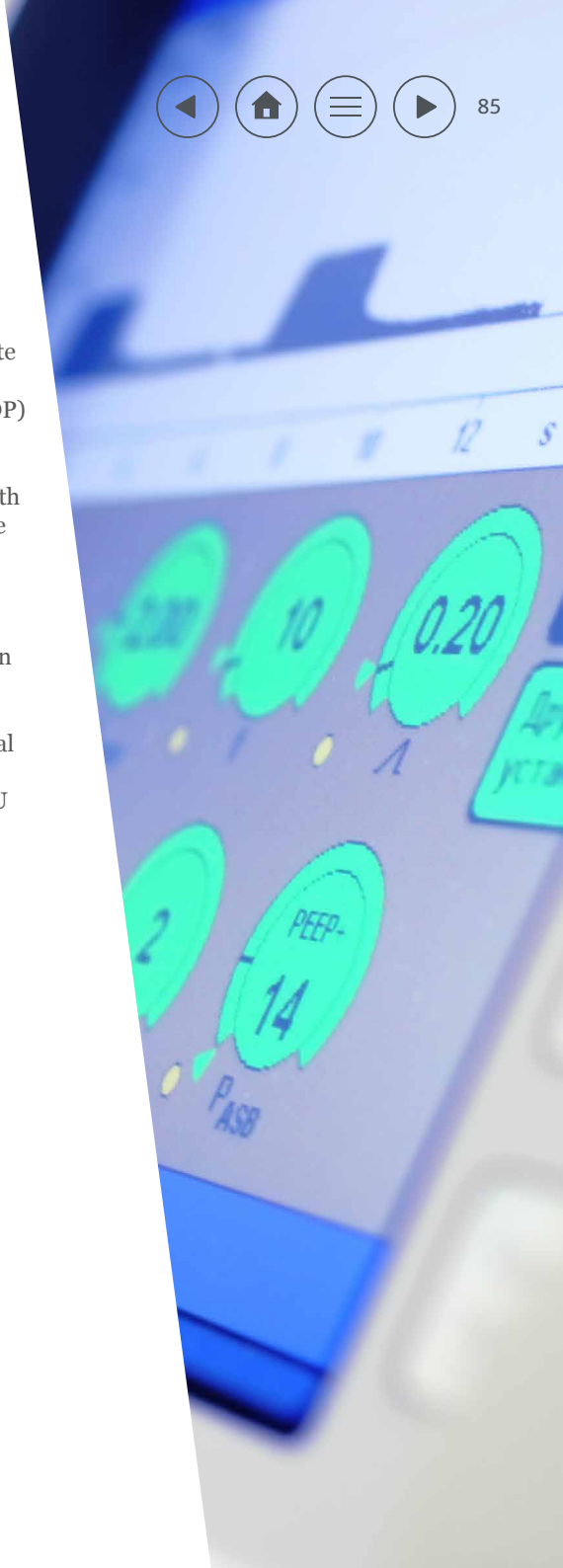

Updates on the conflict between medical device companies and Italian Public Administration over the implementation of the payback legislation: Is it worth challenging unjust administrative measures in Italy?

On 15 September 2022, the Italian Government implemented the payback mechanism for medical devices (Mechanism) through the Ministry of Health's Decree. According to the Mechanism, companies supplying medical devices to the National Health Service (NHS) were required to pay about 45% of the amount exceeding the spending cap by Italian Regions for the purchase of medical devices from 2015 to 2018.

Although the Mechanism was introduced in 2015, it was activated with very little notice and without clear parameters for quantifying the spending cap's exceeding. Moreover, the Mechanism failed to take into account that prices of medical devices are determined based on public procurement tenders, thus resulting in an unjustified and excessive burden on companies that participated in these tenders. On top of that, the Mechanism was activated retroactively, without any predictability for economic operators, affecting profits accrued in previous years, without any guarantee that a minimum reasonable margin of profitability would remain.

In response, affected companies filed hundreds of appeals to the competent administrative court (TAR Lazio) against the payback implementation provisions.

As a significant outcome of the aforesaid legal actions, the initial payment deadline scheduled for mid-January 2023 was extended multiple times, finally reaching 30 November 2023. Additionally, the Italian Government introduced a 'legislative settlement' mechanism, offering a 52% discount on the amount due for companies that chose not to pursue legal action.

For companies resisting the settlement temptation, TAR Lazio, acknowledging the potential validity of their contentions, issued a precautionary suspension of payback in July 2023 for the appealing companies. In November 2023, TAR Lazio elevated the issue of the constitutional legitimacy of payback legislation to the Constitutional Court, confirming the suspended payment obligations for the years 2015-2018.

Meanwhile, the Ministry of Health has instructed Italian Regions to calculate payback amounts for 2019. The stance of the Italian Government on this matter remains unclear for the time being. While it has shown a willingness to accommodate companies' demands, it is also mindful that canceling the measure could jeopardize revenue crucial for the entire NHS.

Regardless of the final outcome of this conflict, legal initiatives have brought immediate benefits for companies taking advantage of the 52% discount and extended payment deadlines. Furthermore, these initiatives serve as a warning against the issuance of manifestly unjust administrative measures in the future.

Let's stay connected for the next episodes of this ongoing saga!

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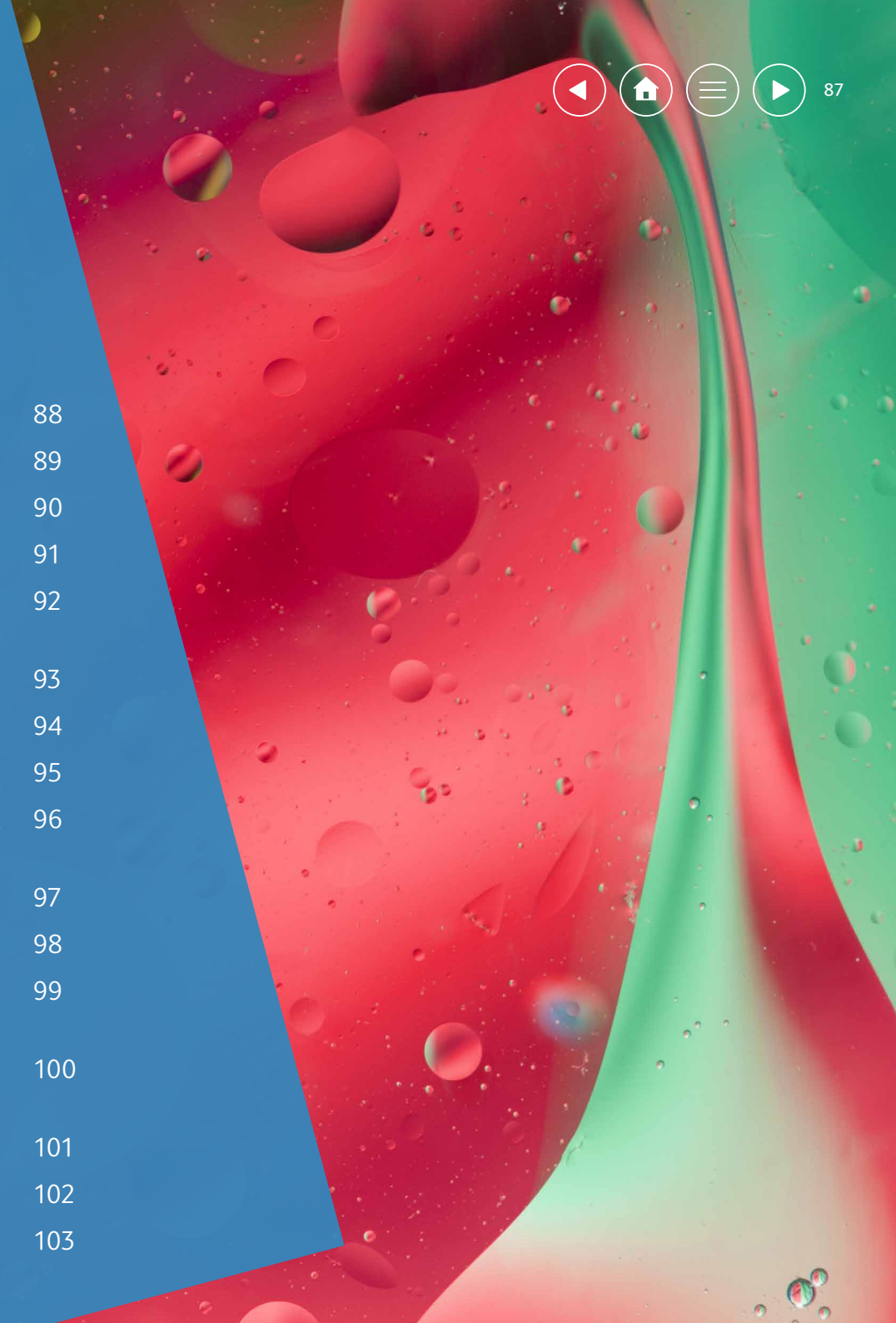
Read our Life Science Law Update for key developments for pharma & device companies in the EU

12 United States



A new age of psychedelics

Industry innovators are looking forward to an expanding class of FDA-approved drugs: psychedelics. Over the past few decades, researchers have demonstrated the great promise of these new therapies, particularly for psychiatric conditions.

FDA is gearing up, too. In 2023, the agency issued a landmark draft guidance providing recommendations for the development of and clinical trials for psychedelic drugs. FDA Draft Guidance for Industry, Psychedelic Drugs: Considerations for Clinical Investigations (June 2023). The guidance also highlights key challenges in designing effective clinical trials, developing effective chemistry, manufacturing, and controls (CMC) information for botanicals, assessing abuse potential, and monitoring safety, among other topics.

The pioneers aiming to develop, gain approval and commercialize these treatments will also face practical challenges in marketing these formerly taboo drugs.

- **REMS:** FDA may impose restrictions on the approval through a Risk Evaluation and Mitigation Strategy (REMS). A REMS could come in many forms, such as a provider and/or pharmacy certification program, restrictions on the distribution, patient monitoring and additional safety measures and reporting obligations. Although REMS are intended to ensure that the benefits of the drug outweigh its risks, these restrictions can hinder patient access, perpetuate stigma about the product, and have outsized impacts on commercial prospects.
- **DEA scheduling:** Many, if not all, psychedelic substances under development for or consideration for pharmaceutical use are currently controlled in Schedule I of the federal Controlled Substances Act (CSA) and similarly controlled at the state level. While there is a path through federal and state law for research and approval of Schedule I products, manufacturers will not be able to distribute and sell their products immediately upon FDA approval and must wait for the U.S. Drug Enforcement Administration (DEA) to reschedule the product. Prior to commercial launch, DEA must issue an interim final rule rescheduling the substance or product under the CSA. Similar rescheduling at the state level is also necessary. At the federal level, DEA's interim final rule is expected within 90 days of the later of (1) the date DEA receives the U.S. Department of Health and Human Services scheduling recommendation or (2) the date DEA receives notice of drug approval.
- **DEA registration and state licensing:** Manufacturers and their distributors will also need to assess the need for and obtain any necessary federal and state controlled substances registrations (in addition to other required state licenses). These assessments are fact-specific and often hinge on the structure of the supply chain.

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A regulatory paradigm shift for OTC drugs under the ACNU rule

Over-the-counter (OTC) products have historically been intended primarily for acute, self-limiting conditions. Over the past decade, however, FDA has been considering ways to expand access to OTC medications for chronic conditions, such as diabetes, hypertension, and high cholesterol. This year may mark a momentous shift in the agency's formerly dichotomous OTC/prescription (Rx) drug regulatory paradigm. FDA's submission to the Fall 2023 Unified Regulatory Agenda indicates that the agency has assigned a high priority to finalizing its 2022 proposed rule entitled *Nonprescription Drug Product With an Additional Condition for Nonprescription Use* (ACNU).

The 2022 proposed rule aims to expand consumer access to a wider range of OTC drugs by making it easier for sponsors to "switch" products from Rx-only to OTC. Specifically, the proposed rule would allow more drugs to be marketed OTC even when the labeling, by itself, is insufficient for independent self-selection and/or actual use, by requiring applicants to implement an ACNU that would allow for safe use without the supervision of a health care practitioner. The proposed rule would also, in some cases, permit the simultaneous marketing of Rx and OTC products with the same active ingredient, dosage form, strength, route of administration, and indication, in part, to ensure access for patients who may be unable to use self-selection platforms.

FDA embraces the use of modern technologies for an ACNU, including digital self-selection channels such as a questionnaire on a mobile app or via an automated telephone system intended to help consumers determine if they should use the drug. Although FDA will not require generics to have the exact same ACNU system, the use of patented digital technologies as an ACNU for OTC drugs may challenge a generic drug's ability to demonstrate "sameness". ANDA applicants would be required to demonstrate that the operationalization of the ACNU is the same as the reference listed drug (RLD) (*e.g.*, both use mobile apps) or show that a different operationalization of the ACNU achieves the same purpose as the ACNU for its RLD and such differences are otherwise acceptable.

Whether FDA will make any substantive changes to address concerns raised in comments on the proposed rule is yet to be seen. Three important issues identified in comments include:

1. the requirement that sponsors "fail first" by providing data from failed self-selection and label comprehension studies rather than allowing sponsors to incorporate an ACNU into their original switch programs;
2. the patentability of ACNU systems; and
3. the exclusion of the majority of OTC drugs – OTC monograph drugs – with limited justification.

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Complex generics

As a part of its stated goal to encourage market competition, FDA continues to provide support for the development of complex generics, *i.e.*, products that are difficult to copy given their use of complex active ingredients (peptides, nucleic acids, nanoparticles, macromolecular entities), complex formulations (liposomes, micelles, microspheres, copolymers), complex routes of delivery and dosage forms, innovative devices, or digital systems.

Complex generics have gained attention from high-end generic sponsors, who see an opportunity to enter as a lone generic where the norm for most generics is to enter as one of many in a crowded field. Or when the generic system fails to accommodate, spons ors increasingly look to the more flexible 505(b)(2) pathway and attempt to obtain an "A" therapeutic equivalence rating.

FDA continues to provide substantive guidance and recommendations for complex generic manufacturers on overcoming development and manufacturing challenges and demonstrating therapeutic equivalence. In 2024, FDA plans to publish over 30 new product-specific guidances for complex products. And in March, FDA will co-host a workshop with the Center for Research on Complex Generics (CRCG) to unpack demonstrating generic substitutability for drug-device combination products. We will monitor these developments to identify trends and the evolving standards for generic versions of innovator products.

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Drug pricing as potential basis for Bayh-Dole march-in

In December 2023, the Biden Administration announced its "Draft Interagency Guidance Framework for Considering the Exercise of March-in Rights". The U.S. Government generally retains "march-in" rights in "subject inventions" under federally funded agreements. Under this construct, the Government may, in limited circumstances, license federally funded intellectual property to third parties to ensure that an invention is made available to the public. Notably, to date the Government has never exercised it march-in rights. The announcement signals renewed interest and potentially a more aggressive stance by the U.S. Government in exercising these rights going forward. We expect additional agency action on this draft framework in 2024, after the administration considers comments due in February.

The "march-in" construct stems from the Bayh-Dole Act, a cornerstone of the Government's management of federally funded inventions since 1980. Bayh-Dole preserves the rights of contractors and grantees to own their "subject inventions" but also provides the government with the extraordinary—and to date, never exercised—right to grant a license to third parties under specific circumstances. The circumstances for "march-in" set forth in the statute include when (1) subject inventions are not developed in a reasonable time; (2) health or safety needs are not reasonably satisfied; (3) federal regulations deem requirements for public use are not satisfied; and (4) contractors are in breach of the obligation to substantially manufacture in the U.S.

The draft framework would impose a three-step analysis for agencies to apply that focuses on whether a funded technology has been offered to the public in a way that does not "unreasonably limit availability". It introduces the consideration of excessive pricing as a potential factor to be considered in the reasonableness analysis.

The Biden Administration has been explicit in pointing out its intention to use the new draft framework as a tool to address drug pricing. Indeed, there has been increased attention to march-in rights in recent years as a means to increase access to federally funded medical technologies created in response to the COVID-19 pandemic.

Given the renewed focus on march-in and the linkage with drug pricing, it is clear that the possibility of march-in will continue to be a point of contention, and we are monitoring developments in this area. Any government exercise of march-in rights on the basis of drug pricing is almost sure to be the subject of litigation.

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Medicare and HCT/P skin substitute products: Uncertainty persists as the Medicare agency eyes sweeping changes to coverage and reimbursement

The Medicare program continues to explore comprehensive changes to its policies surrounding human cells, tissues, and cellular and tissue-based (HCT/P) skin substitute products. In recent years, the Centers for Medicare & Medicaid Services (CMS) and its Medicare contractors have considered (but ultimately not finalized) sweeping changes both to coverage and reimbursement for this class of regenerative medicines.

Most recently, this past summer, three Medicare contractors issued Local Coverage Determinations (LCDs) that would have imposed dramatic coverage restrictions on skin substitutes—including limiting the frequency with which they could be administered. Further, in policy articles associated with the LCDs, the contractors designated certain HCT/Ps as categorically non-covered, while permitting coverage of other, similarly situated products.

These LCDs and their associated coverage restrictions had originally been scheduled to take effect on 1 October 2023, but were ultimately withdrawn following widespread criticism from industry and patients. In addition to procedural irregularities, the LCDs included restrictions that appeared inconsistent with the scientific principles under which these products function, as well as the FDA regulatory framework surrounding HCT/Ps. For example, the LCDs drew a seemingly arbitrary distinction between similarly situated HCT/P skin substitute products based on whether a given product acted as "scaffolding", while failing to recognize that all appropriately applied, sheet-based HCT/Ps necessarily act as a form of scaffold. Likewise, the contractors' LCDs appeared to misunderstand the purpose and function of the advisory letters issued by the FDA's Tissue Reference Group for HCT/Ps.

Although these most recent coverage restrictions are currently withdrawn, there continues to be great uncertainty surrounding how HCT/P skin substitute products will be covered and paid in future years. Even following the withdrawal of the recent LCDs, CMS and its contractors have continued to signal strong interest in reworking the policies governing these products. Following the withdrawal of the summer LCDs, the Medicare contractors have stated they intend to publish new proposed LCDs "in the near future". Similarly, CMS has—for multiple years—solicited comment on potentially sweeping changes to the payment policies surrounding skin substitutes, including ending separate payment for skin substitute products furnished in physician offices.

Industry should continue closely to monitor for new developments impacting Medicare coverage and reimbursement of skin substitutes. Scrutiny surrounding skin substitutes has dramatically increased in recent years, and the agency has a strong interest in rethinking its approaches to how these technologies are covered and paid.

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Navigating listed chemicals compliance requirements

The U.S. Federal Controlled Substances Act (CSA) establishes a closed distribution system to regulate and monitor substances that pose a risk of abuse and dependence. Drugs designated as controlled substances (*i.e.*, substances subject to regulation) often garner the most attention from the Drug Enforcement Administration (DEA) and the general public. However, less well known, but also within the DEA's purview, are chemicals that can be used to manufacture controlled substances, known as "listed chemicals".

Like controlled substances, listed chemicals are subject to compliance requirements. The primary compliance requirement for listed chemicals is registration with the DEA. Unless a statutory exemption exists, companies engaged in the manufacture, import, export, or distribution of listed chemicals must register with federal and many state regulatory authorities. Registrants may engage only in specific activities within the scope of their registrations.

Registrants must also comply with regular reporting and recordkeeping obligations. Registrants may be required to report its inventory, changes in production volumes and usage patterns, and transactions involving a listed chemical. Authorities may also require registrants to submit customer data to confirm the customer's identity and the purpose for which the chemical is being used.

Nonetheless, inherent to the CSA is the notion that listed chemicals have an overall lower risk of contributing to abuse and diversion than controlled substances, and the degree of risk varies by the extent to which the chemical can be used for lawful purposes unrelated to controlled substances. Many listed chemicals are integral to legitimate industrial processes, including use in pharmaceutical manufacturing, industrial solvents, and food flavoring agents. Accordingly, the CSA assigns listed chemicals to two tiers, List I and List II, based on the significance of the listed chemical to controlled substances manufacturing. List I chemicals are subject to stricter requirements than List II chemicals. Additional exemptions exist for chemical mixtures containing listed chemicals at or below established thresholds.

Compliance with listed chemical requirements is not merely a legal obligation; it is a critical aspect of responsible business practices. Companies must conduct regular reviews of their inventories to ensure any activities involving listed chemicals are within the scope of their registration, and have robust monitoring processes in place to ensure that their operations are compliant with federal and state requirements.

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OIG's General Compliance Program Guidance

In November 2023, the U.S. Department of Health & Human Services Office of Inspector General (OIG) released its first ever General Compliance Program Guidance (GCPG). The GCPG is a high-level amalgamation of OIG's existing guidance and applies to all individuals and entities involved in the U.S. health care sector.

While much of the information contained in the GCPG is not new, there are a few key highlights.

- The GCPG provides prescriptive guidance on compliance program resources and common functions and activities, such as policies and procedures, training, annual risk assessments, and the use of data analytics. One particularly noteworthy statement in the GCPG is that OIG recommends including quality and patient safety considerations within the compliance function.
- In another noteworthy statement, the GCPG speaks directly to OIG's concerns "about the impact of ownership incentives (*e.g.*, return on investment) on the delivery of high quality, efficient health care" and clearly states that private equity firms and other investors are responsible for understanding the laws applicable to the health care industry and the role of an effective compliance program, particularly for those investors "that provide management services or a significant amount of operational oversight for and control in a health care entity".
- The GCPC includes specific recommendations for the role of the Compliance Officer, the corporate Compliance Committee, and the Board. It reemphasizes the OIG's emphasis on "tone at the top" and the need for well-informed, active oversight for an effective compliance program.
- The GCPG encourages both "sticks" and "carrots" to encourage compliance. The "sticks" include well-documented disciplinary protocols and requiring compliance program participation (*e.g.*, training, absence of discipline) in annual performance evaluations. The "carrots" align with the Department of Justice's (DOJ's) 2023 Pilot Program Regarding Compensation Incentives and Clawbacks by encouraging the integration of compensation with compliance.

OIG acknowledges that compliance programs are not one-size-fits-all, and advises on adjustments that may be needed for larger or smaller corporations, as well as the U.S. subsidiaries of large international organizations. In addition to reviewing their compliance program against the GCPG, companies operating on the U.S. should be on the lookout for forthcoming industry-sector-specific compliance guidance from OIG.

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Pediatric exclusivity and the Pediatric Research Equity Act

FDA's pediatric framework, most notably including the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), has played a pivotal role in incentivizing and regulating pediatric drug development. The BPCA, enacted in 2002, offers exclusivity (*i.e.*, six additional months for some patents/exclusivities) in exchange for conducting pediatric studies based on a written request (WR). PREA, enacted in 2003, mandates pediatric studies for certain pharmaceuticals and biologics. The BPCA incentives and the PREA mandates are sometimes referred to as the "carrot" and the "stick". In May 2023, FDA issued two draft guidance documents outlining recommendations for sponsors investigating products for pediatric indications. In these guidances, FDA proposed significant changes, particularly regarding the issuance of WRs for pediatric exclusivity.

Historically, despite the critical roles the two statutes play in pediatric drug development, FDA had provided little comprehensive guidance on the interplay between BPCA and PREA. The new draft guidances seek to assist industry in (1) complying with PREA and qualifying for pediatric exclusivity, and (2) developing data and obtaining information needed to support approval of drug products in pediatric populations.

The most consequential change is FDA's newly proposed policy on issuing WRs. The draft guidance generally explains that a sponsor must be in receipt of a WR from FDA to qualify for exclusivity, how FDA determines whether studies "fairly respond" to the WR such that exclusivity would be granted, and the scope of the exclusivity once granted. However, the agency has proposed to limit the issuance of WRs to only sponsors who conduct additional pediatric studies beyond what is required under PREA. Previously, a sponsor could benefit from pediatric exclusivity even though it was doing solely what was already required under PREA. The WR would often mirror PREA-required studies, allowing the sponsor to benefit from the "carrot" while at the same time satisfying requirements under the "stick".

The result of the new proposed policy, which the agency states will only go into effect upon finalization of the guidance, would be an expansion of studies required for pediatric exclusivity beyond what has historically been required. This may result in more expansive WRs and may lead to fewer opportunities for pediatric exclusivity.

We continuously monitor FDA's actions in this area, and are keeping a close eye on FDA's proposed approach to advise clients on how to engage with FDA on WRs.

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Pharmaceutical patents in an era of increasing interagency scrutiny: Trends, cross-currents and policies at the cross-section

Last year saw signs of increasing interagency collaboration between the U.S. Food and Drug Administration (FDA), the U.S. Federal Trade Commission (FTC), and the U.S. Patent and Trademark Office (USPTO). 2024 promises more. These issues have important implications for pharmaceutical and biotechnology companies, impacting the development, prosecution, and enforcement of patents. There are new initiatives afoot, interagency cooperation, information sharing, and new roles being played by FDA, USPTO and FTC affecting the way patents will be prosecuted, how and what information will be listed by FDA in the Orange Book, and enforcement risks.

These are not happenstance developments. In July 2021, the White House issued an Executive Order (EO) on Promoting Competition in the American Economy, charging FDA to work with the FTC and USPTO to "identify and address any efforts to impede generic drug and biosimilar competition" and "to help ensure that the patent system, while incentivizing innovation, does not also unjustifiably delay generic drug and biosimilar competition beyond that reasonably contemplated by applicable law".

To further this, FDA and USPTO set a goal to create a formal mechanism of collaboration, to include topics such as consistency in representations made by drug sponsors to both agencies, overlap in the agencies' authorities and responsibilities with respect to labeling carve-outs, the connection between method of use patents and associated use codes, and to reach some accord on practices referred to as "patent thickets", "evergreening", and "product hopping".

And last year saw a new front emerge for Orange Book patent listings, with FTC taking the helm. FTC issued a policy statement, warning that it would crack down on allegedly "improper" Orange Book patent listings, and then issued a spate of warning letters, challenging the listing of certain patents, using FDA's own patent listing dispute regulations and procedures. In response, some sponsors delisted patents, while others have stood firm. This is likely to lead to further developments in 2024.

These initiatives hold the potential to deeply influence how patents are and can be used to protect innovation and drive pharmaceutical development. Like the agencies, we are combining our expertise across practice areas to respond to these new regulatory trends, to ensure our clients protect their technology to the full extent the law allows.

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Responding to the discovery of controlled substances in your facility

Imagine that an unknown substance is discovered at your manufacturing facility or laboratory. Upon testing, you learn that the substance is a Schedule II controlled substance, but your U.S. Drug Enforcement Administration (DEA) registration permits you to handle Schedule III-V controlled substances only. Or, perhaps this is the first time that a controlled substance has ever appeared at your facility and you are not a DEA registrant. This is not an infrequent occurrence for entities that engage in research and development. What do you do?

Navigating the discovery of controlled substances at your facility can be challenging. Whether the substances were inadvertently brought in, created in the lab, or are remnants of previous activities, it is crucial to take immediate action. Importantly, the disposal of controlled substances is a highly regulated activity and can be challenging for a facility without the appropriate DEA and state license.

The moment controlled substances are discovered, prioritize identifying the type and quantity of substances found and store them in a secure location. Consider conducting a thorough sweep of the facility to assess whether other unknown substances are present.

It is critical to understanding the regulations governing controlled substances at the federal level and in your state. This step is vital to ensuring that all subsequent actions meet regulatory requirements. Prompt and organized cooperation with local law enforcement and regulatory authorities, such as the DEA and similar agencies in your jurisdiction, is key and can help demonstrate your commitment to compliance and abate agency concerns of wrongdoing.

Identifying how the controlled substances entered the facility is paramount as well. To that end, evaluate current policies and procedures to determine what safeguards need to be put into place to prevent the reoccurrence of this issue. This may also be a good opportunity to update internal policies related to ordering chemicals and controlled substances, inventory management, and employee training. If you are a DEA registrant, every employee handling controlled substances should be familiar with the scope of the facility's registration.

Throughout this review, maintain thorough records of everything discovered and actions taken, any corrective measures implemented, and correspondence with authorities. Following the outlined steps will help your company navigate the situation responsibly, mitigate potential legal consequences, and work towards preventing such incidents in the future.

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State of affairs: Medical device licensing enforcement is on the rise!

In addition to federal requirements for medical device manufacturers and distributors, a large number of U.S. states license entities involved in the supply chain of prescription (and sometimes over-the-counter) medical devices that enter their jurisdiction. However, many companies operate unaware of these requirements until they receive a letter from the state Board of Pharmacy, or similar state agency, alerting them to a possible violation.

State requirements for who must be licensed and what type of license is required depend upon a number of different factors, such as the type of device, prescription status, facility location(s), and the licensee's specific activities. Among other things, states may license companies that ship devices to end users or other third parties in the state, that sell the devices into the state (but have another company do the actual shipping), or even companies that only manufacture a device that ultimately enters the state's stream of commerce, whether or not the manufacturer undertook any distribution activities whatsoever. In each case, and for each specific state, different license types may be implicated and certain exceptions to the license requirement may apply.

Whether because of the difficulty in determining which, if any, state license is required, or simply a lack of awareness as to the requirement generally, many companies have left state licensing unaddressed. At the same time, many states are paying an increasing level of attention to licensing compliance.

This attention can take the form of requiring immediate remediation of any licensing gap along with, in many cases, an order to temporarily cease operations within the state and the potential for civil monetary or, though rare, criminal penalties. When assessing monetary penalties, states will often perform a look-back of past product distribution into the state and may set penalties on a "per violation basis"; where a "violation" may be based upon the number of shipment days, number of shipments, or even number of individual products shipped. Although some states cap the amount of any such fine, many others do not and, consequently, the dollar amounts at issue can become very large. Moreover, Board disciplinary action disclosure requirements may lead to potential follow-on enforcement in other states. Accordingly, the threat of business disruption and hefty fines has made state licensing a topic of renewed interest in the medical device industry.

So what should companies do? Get into compliance! First, determine what license, if any, is required in the states in which you operate. Where the company has been operating without a license, remedy the situation immediately. If the state has contacted you regarding potential discipline, it is highly advisable to seek legal counsel when crafting your response in order to mitigate both the initial and downstream effects of the enforcement. Whatever you do, don't ignore your state level compliance responsibilities!

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Unpacking FDA's new draft guidance on scientific information on unapproved uses of approved products

In late 2023, FDA issued draft guidance on drug manufacturer communications to health care providers (HCPs) regarding scientific information on unapproved uses of approved/cleared medical products (SIUU). Although positioned as a revision to an existing guidance from 2014 on permissible dissemination of certain publications about unapproved uses (commonly referred to as the "reprints guidance"), this new guidance threw industry for a loop as it seems to reinterpret the "rules of the road" for drug manufacturer communications to HCPs after nearly a decade of very little change in the agency's approach to HCP communications. However, agency officials have publicly described the changes as important, but "narrow" in scope, and limited to specific categories of information.

Unlike the old reprints guidance, the new guidance permits drug manufacturers to disseminate "firm-generated presentations" of SIUU, in addition to traditional materials covered by the reprints guidance (*e.g.*, scientific publications, reference texts, clinical practice guidelines). The shift seems to reflect the agency's endorsement or tacit acknowledgement of increasingly common industry activities, including availability of SIUU information on company-sponsored websites.

The new guidance also introduces a new standard for evaluating information being presented: the information and analyses should be "scientifically sound" and provide "clinically relevant" information. Like other evidentiary standards set forth by FDA related to medical product advertising and promotion (*e.g.*, "competent and reliable scientific evidence" and "scientifically appropriate and statistically sound"), this latest standard is defined broadly and presents both challenges and leeway in interpretation.

Ultimately, the draft guidance raises as many questions as it purports to answer. For example, FDA recommends that SIUU communications should not use "persuasive marketing techniques" in firm-generated presentations, but does not fully explain the scope of such techniques. The draft guidance is also agnostic as to who may engage in SIUU communications, leaving open to interpretation whether Commercial and/or Medical functions may be involved in such discussions.

The SIUU draft guidance adds to a constellation of guidance documents related to appropriate communications to HCPs and payors. Whether it also portends increased enforcement activity by the Office of Prescription Drug Products or other agencies remains to be seen. We will monitor for developments in this area as we continue to counsel clients on effective and compliant communications to HCPs, patients, and payors.

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U.S. cosmetics industry faces new facility registration and product listing requirements

The regulatory requirements for cosmetics are becoming more like drug requirements. On 29 December 2023, new requirements for registration of cosmetic product manufacturing establishments and listing cosmetic products came into effect. These new requirements were enacted as part of the Modernization of Cosmetics Regulation Act (MoCRA), along with requirements for reporting serious adverse events, compliance with forthcoming good manufacturing practice regulations, and substantiation of cosmetic product safety, among other requirements. Although the cosmetic registration and listing requirements went into effect last December, FDA announced it would not begin enforcing the requirements until 1 July 2024, to provide more time for the U.S. cosmetics industry to submit registration and listing information.

Under the new requirements, owners and operators of facilities that engage in the manufacturing or processing of a cosmetic product for distribution in the U.S. will be required to register the facility with FDA. The registration information includes the brand names and product categories for cosmetic products manufactured or processed at the facility. While FDA previously had a voluntary cosmetics registration program, FDA has discontinued the voluntary program and stated that registration information under the prior voluntary program will not carry over into the new system.

In addition, "responsible persons" – defined as the manufacturer, packer, or distributor of a cosmetic product whose name appears in accordance with certain labeling provisions – will be required to list their cosmetic products with FDA. The required listing information includes the facility where the cosmetic was manufactured and a list of all ingredients in the cosmetic product, including fragrances, flavors, and colors, among other information about the cosmetic.

For cosmetics that are also regulated as over-the-counter (OTC) drugs – and hence are subject to the registration and listing requirements for drugs – MoCRA provides an exemption to the cosmetic registration and listing requirements. MoCRA also includes an exemption to the registration and listing requirements for small businesses, defined as businesses whose average gross annual sales in the U.S. of cosmetic products for the previous three-year period is less than $1,000,000, adjusted for inflation, and who do not engage in the manufacturing or processing of certain types of cosmetic products described in the statute.

To submit facility registration and product listing information, FDA has established a new online portal, Cosmetics Direct. Submissions to Cosmetics Direct use the Structured Product Labeling standard, similar to submissions of registration and listing information for drugs.

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Increased scrutiny of the accelerated approval program

In recent years, FDA's accelerated approval program, which permits the agency to approve certain drugs that treat serious or life-threatening diseases before confirmatory trials are completed, has come under intense public scrutiny. There have been increasing concerns about the rising number of drugs approved under this pathway and the perceived delays in drug sponsors completing confirmatory trials. Congress recently enacted program reforms aimed to reduce delays in confirmatory trials and increase transparency, and the U.S. Department of Health and Human Services (HHS) could take additional steps to penalize lags in confirmatory trials.

Increased FDA authority: The Consolidated Appropriations Act of 2023 included several new tools for FDA to exert more power over the accelerated approval pathway, including by:

- allowing the agency to require a post-approval study to be underway prior to granting accelerated approval;
- permitting FDA to pursue the expedited withdrawal procedures if a sponsor fails to conduct any required post-approval study of the product with due diligence; and
- requiring sponsors to submit periodic progress reports on post-approval studies at least every 180 days.

Potential pricing penalties: To identify strategies to address prescription drug affordability, HHS recently examined a pricing model to reduce Medicare Part B payments for some drugs approved through the accelerated approval program when sponsors fail to timely complete their post-approval studies. For now, HHS appears to have set aside this proposal, reporting that it will "continue to monitor" developments in the accelerated approval program. HHS, Centers for Medicare & Medicaid Services Innovation Center's One-Year Update on the Executive Order to Lower Prescription Drug Costs for Americans (11 October 2023). If, however, there is more public outcry over controversial approvals, delays in confirmatory trials, or delayed product withdrawals, HHS may revisit pricing strategies to penalize delays in confirmatory trials.

Tips for innovators: For innovator sponsors pursuing the accelerated approval pathway, we recommend the following:

- communicate early and often with the agency about both scientific and practical challenges in designing and completing confirmatory trial(s);
- assume that the agency will require one or more confirmatory trials to be underway prior to approval;
- reach alignment with the agency on the adequacy of the confirmatory trial(s) design prior to submission of the new drug application; and
- manage timing expectations for confirmatory approval with key stakeholders, including the public, following accelerated approval.

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New approach to accelerated approval withdrawals in 2024

FDA's accelerated approval pathway is designed to allow earlier access to promising drugs that treat serious or life-threatening disease. The pathway permits approval based on early clinical endpoints (*i.e.*, interim clinical or surrogate endpoints), but requires a post-marketing confirmatory trial with an established clinical endpoint to confirm the product's clinical benefit. If clinical benefit is not confirmed by the confirmatory trial or if the trial is not conducted in a timely manner, the indication may be withdrawn. Originally enacted to help address the HIV-AIDS epidemic, the majority of accelerated approvals in recent years have been in the oncology space.

Over the past several years, FDA has focused on addressing increasing numbers of "dangling" approvals where the confirmatory trials had failed, been delayed, or were never completed. FDORA, signed into law in December 2022, made several changes to facilitate the timely completion of confirmatory trials and included provisions intended to expedited withdrawal procedures for sponsors that fail to conduct any confirmatory trial with "due diligence." Prior to FDORA, the withdrawal process, set forth in regulation and intended to provide an abbreviated process, could drag on for years before an advisory committee was convened and the approval was withdrawn.

Under FDORA, sponsors are not eligible for a second advisory committee if a committee was previously convened with respect to withdrawal. While the intent is to further streamline the withdrawal process, the amended statute provides the sponsor with additional opportunities to engage with the agency prior to an advisory committee, including opportunities to meet with the Commissioner and for public comment. The exact sequencing of steps remains unclear, as FDA has not yet updated its regulations to align with the statutory language. A July 2023 Notice of Proposed Withdrawal of Approval for Pepaxto (melphalan flufenamide) suggests sponsors will first have an opportunity to meet with the Commissioner, followed by opportunities to appeal and for public comment on the proposed withdrawal.

The changes also raise questions regarding how aggressive FDA will be in seeking withdrawal of indications, and how long sponsors will have before an indication will be subjected to the process. Recent agency statements in the oncology space suggest confirmatory trials should be completed in two to four years, but exactly how FDA will exercise its authority to initiate the withdrawal process both in oncology and in other disease areas is unclear.

We continuously monitor new developments in this evolving area and advise clients on how to engage with FDA on these issues.

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Spotlight on single-trial approvals

In general, standalone marketing applications must present substantial evidence of effectiveness (or safety, purity, and potency) to support a New Drug Application (NDA) or Biologics License Application (BLA). FDA has interpreted this to mean two or more adequate and well-controlled trials (AWCTs), albeit with notable exceptions (for drugs and biologics with well-known, longstanding uses). Since 1997, FDA has had the statutory authority to accept one AWCT plus confirmatory evidence as sufficient for approval. FDA has issued several guidance documents intended to clarify the characteristics of a single AWCT and the amount and type of data required for confirmatory evidence.

The most recent draft guidance, issued in September 2023, outlines the quality and quantity of evidence required for an application supported by a single AWCT, plus confirmatory evidence. It introduces the concept of a sliding scale for the amount of confirmatory evidence needed to support approval, based on the features and results of the AWCT. The guidance also provides examples of categories of confirmatory evidence. These categories include clinical evidence from a related indication, mechanistic or pharmacodynamic evidence, evidence from a relevant animal model, evidence from drugs in the same pharmacological class, natural history evidence, real-world data/evidence, and evidence from expanded access use of an investigational drug.

One important consideration, particularly for BLA sponsors, is whether the confirmatory evidence intended to support a single-study application relies on data that the sponsor does not own or to which the sponsor does not have a right of reference. FDA specifically notes in the draft guidance that use of certain sources of information may not be permitted under certain regulatory pathways. This likely refers to the fact that, unlike for NDAs, there is no "hybrid" 505(b)(2) pathway available for a standalone BLA submitted under section 351(a) of the Public Health Service Act to rely on data not owned by the sponsor. BLA sponsors must therefore be cautious about submitting confirmatory evidence that the agency may view as impermissible for a standalone application.

Relatedly, FDA draft guidance from May 2023 describes the extent to which an application may rely on "generally accepted scientific knowledge" for certain non-clinical data requirements.

We expect that questions regarding the sufficiency of the clinical and non-clinical data package for both BLAs and NDAs will continue to be of significant focus in 2024. We look forward to continuing to assist our clients in crafting strong scientific and legal arguments to bring critical therapies to market.

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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 the authors in this publication, or one of the partners with whom you regularly work.

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